A QUANTITATIVE STUDY OF THERMAL SENSATION IN MAN

by

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To

My dear wife Vian, baby Lazia and

my wonderful parents

DECLARATION

The work reported in this thesis was carried out by myself under the supervision of Professor J A Simpson.

The technical aspects of the work were carried out in close collaboration with Dr Stig Hansen PhD, of the Department of Clinical Physics and Bioengineering, West of Scotland Health Boards, Glasgow.

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SUMMARY

Clinical tests of thermal sensation are poorly quantified and not strictly modality-specific. This thesis traces the rationale and the development of a relatively rapid in vivo method for the clinical and non-invasive assessment of thermal thresholds in normal human subjects and in groups of patients with various neurological disorders.

The method uses a microprocessor driven Peltier element thermode, standardises all the factors and sources of error and uses the forced-choice paradigm of psychophysical analysis to eliminate the subject's response bias and the up-and-down transform rule to determine the threshold levels to readily controlled relatively small preset steps of thermal stimuli. In this method, the application of the thermode is standardised, the basic skin temperature (on the top of which the thermal stimuli are applied) is controlled, the rate of change of the stimulating temperature is fixed and the thermode is calibrated at each site before each test to measure the amount of power needed to obtain the specific rate and to reduce errors encountered due to differences in thermal properties of the skin.

A consideration of the present knowledge of the anatomical basis of thermal sensation including peripheral and central pathways and leading through to the various levels of increasing complexity to the cerebral cortex is presented in Chapter 1. In Chapter 2, the present concept of the physiological, physical and biochemical mechanisms underlying thermal sensation is outlined including the transmission of thermal energy through human skin, the transduction of this energy by the specific thermal receptors into electrical pulses and coding of this information in the peripheral structures and their modification in the central structures of the thermal system. Methods applied in the investigation of thermal

sensation both in clinical practice and in research are reviewed in Chapter 3. The principles underlying the method and the design of the technique are presented in Chapter 4. In Chapter 5, the effect of various factors influential in producing variability of thermal thresholds are studied and the results of the application of the method to a large group of normal subjects are presented including analysis of these results in terms of inter- and intra-individual reproducibility on repeated measurements. The method is compared with contemporary methods and its superiority over these techniques in terms of sensitivity and reproducibility is discussed in Chapter 6.

In Chapter 7, the results of the application of the Glasgow method to 143 patients with generalised peripheral neuropathy of diverse aetiologies, to 25 patients with selective small fibre neuropathy and to 10 patients with selective large fibre abnormality (Friedreich's ataxia) are presented and its sensitivity in detecting subtle changes of thermal sensation is demonstrated. The findings suggest that this method has considerable value in the documentation of small nerve fibre dysfunction in the context of generalised neuropathy. The sensitivity of the method in detecting mild abnormalities of thermal sensation due to central nervous system pathology is also demonstrated in five patients. Application of the technique to 24 patients with acromegaly demonstrated the presence of subclinical abnormality of thermal sensation in 2/3 of the patients. Simultaneous application of other neurophysiological techniques suggested the presence of a generalised peripheral nerve dysfunction in these patients. The indices of peripheral nerve dysfunction and thermal threshold values correlated significantly with total body exchangeable sodium, a measure of disease activity in these patients.

Comparison of the results of the application of the Glasgow method in 40 patients with definite motor neurone disease (MND) and 40 age and sex-matched controls showed the presence of a significant abnormality of

thermal sensation in 80% of the patients with MND. Application of the method to 24 patients with myotonic dystrophy provided unequivocal evidence of thermal sensation abnormality in 83% of these patients. Concomitant application of other three independent neurophysiological tests pointed to the presence of a significant dysfunction of peripheral nerves. These results are presented and discussed in view of other reports in the literature in Chapter 8.

Under the title of 'prospects for future work' in Chapter 9, studies which are still in progress using the Glasgow method and those planned to be carried out in the near future are outlined. Preliminary data are also presented about a method for the detection of cortical responses to pure thermal stimulation of the hand of normal humans. Chapter 10 contains the conclusions of this study.

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INTRODUCTION

The integrity of the thermal sensation system in the human being is extremely important as efficient temperature regulation is only possible with normal functioning neurones comprising this system. The thermal system consistently senses the ambient temperature and sudden deviations from the adapting basic skin temperature through the initiation of extra activity in the system to code for these changes so that the organism attempts to keep the balance by appropriate counter measures. The term 'thermoreception' is, therefore, suggested by some authors (Hensel 1974) to account for the fact that thermal senses are not only involved in conscious temperature sensation but also play an important role in the autonomic regulation of body temperature and the behavioural responses of the organism to thermal environment.

The scale of human temperature sensation differs from the physical temperature scale. The latter is based on an arbitrary definition where it has a monotonic structure with an absolute zero point while the phenomenal scale of temperature in man has a dual character, heat and cold, separated by a null point (the physiological zero) which is surrounded by an indifferent zone of temperature values of 30-36^{o}C to which thermal sensors quickly adapt both phenomenally and physiologically and which is termed the adaptation zone. In this thesis the words heat and warm are used synonymously as there is no evidence that these two descriptions indicate separate sensations but rather represent intensities of the same sensation. In the French language and in the author's own language (Kurdish) there is no special distinction between the words heat and warm. On both sides of the extreme ranges of heat and cold sensation, the sensation becomes painful. Neurophysiological and morphological studies indicate that the sensations of heat pain and cold pain are carried by a different neuronal system and, therefore, they represent a different modality of pain rather than thermal sensation.

Thermal sensation has its own distinct anatomical pathway and has a known range of pathologies affecting it. Accurate assessment of this sensation in clinical neurology is of paramount importance. The methods currently used for this purpose are inaccurate, unquantitated, insensitive and inadequately reproducible and the stimuli used are not strictly modality specific. These methods provide evidence for the presence of dysfunction of severe degree only. There is, therefore, an increasing demand for the introduction of an objective, sensitive, not time consuming, reproducible and practical method to apply in the context of clinical examination to evaluate this sensation.

This thesis reports an attempt to produce a method of testing thermal sensation in man through the reproducible estimation of thermal thresholds using readily controlled small steps of thermal stimuli while keeping all the identified factors of variability under control. The method uses a psychophysical technique which eliminates patients' response bias. The method reported here has a reproducibility and sensitivity unrivalled by contemporary methods.

It is able to detect qualitatively similar changes of thermal sensation too small to be detected by other methods. The application of the reported method to pathologies likely to involve thermal sensation provided an increased rate of detection of abnormalities of thermal sensation in these disorders. It was also able to detect significant abnormalities of thermal sensation in other neurological disorders currently thought to spare the sensory system. By detecting smaller true changes in the function of a thermal system, the method is of value in assessing the response of neurological illnesses to treatment.

The reported technique has been adopted for incorporation as a module in the neurophysiological laboratory by Medelec Ltd. A large part of the work in this thesis has been published, accepted or submitted for publication (see References List and Appendices).

CHAPTER 1

THE ANATOMICAL BASIS FOR THERMAL SENSATION

Sensing changes of temperature, the thermal sensation, is a subjective experience arising from activity within the brain in response to the specific physical stimulation. Knowledge is incomplete of the anatomical structures and pathways, especially in the central nervous system (CNS), along which the impulses giving rise to thermal sensation travel.

The purpose of this chapter is to outline the current views about these pathways in human beings. The current knowledge concerning the structure and characters of thermoreceptors 'the specific transducers', the fibre population responsible for conducting the action potentials from these receptors to the first relay station, the spinal cord and brain stem and finally the centrally conducting pathways, of these impulses, to neurones in the thalamus and the cerebral cortex is presented.

Many types of experiments, necessary to acquire knowledge about these structures, are only possible in animals since the procedures involved are destructive to tissues or demand certain approaches unacceptable ethically when a human being is the subject. On the other hand, sensation is a phenomenon only reportable by man. As a consequence, there is a gap between the objective measurements that can be obtained in animals and the sensory experience of man.

In this chapter, therefore, where information from the human being is missing or limited, it is supplemented with data and observations from similar sensory elements of experimental animals. Priority in this context will be given to those from primates and, if such information is inadequate, to observations from other mammals.

PERIPHERAL PATHWAYS

Thermal sensation arises from the stimulation of specific thermal receptors in the skin. These distinct structures act as transducers, which change the thermal energy into electrical impulses. These impulses reach the CNS by passage along the peripheral nerves. The receptor and the peripheral nerve are parts of the first order neurone the cell body of which lies in the dorsal root ganglia. This is a bipolar cell with an axon process directed centrally to the spinal cord. The major sensory innervation of the head is through the trigeminal nerve with similar arrangement to spinal nerves. It was demonstrated recently in primates, that approximately one-third of all afferent small diameter C fibres enter the spinal cord through its anterior roots and travel to the dorsal horn to join C fibres which entered via the posterior root (Coggeshall et al, 1974; Clifton et al, 1976). Their cell bodies also lie in the dorsal root ganglia (Clifton et al, 1976). Their fu_nctional role or whether they contribute in the convey of thermal or pain sensation or whether there is a similar analogue in man, has not yet been established.

Cutaneous Thermoreceptors

The first evidence for the existence of specific thermoreceptors came from the discovery of 'sensory spots' by Blix (1882), Goldscheider (1884) and Donaldson (1885) and the description of the warm and cold spots in human skin. This original work was followed by a series of more detailed studies which confirmed and reproduced Blix's observations (Rein 1925b; Strughold and Porz 1931; Skramlik 1937; Hensel 1952a; Geldard 1972). From these spots adequate thermal or electrical stimuli elicit warm or cold sensation depending on the type of spot stimulated. Since these psychophysical studies the existence of two types of specific thermoreceptors is strongly argued for (Iggo 1982a,b). Some workers,

however, have maintained that they could not reproduce the location of these spots (Dallenbach 1927) and others have questioned their specificity (Jenkins 1940,1941a,b; Kilber and Nathan 1960; Melzack et al, 1962; Stevens et al, 1974). Under more controlled conditions, others have found their number and location to be constant (Braun and Meier 1944; Bing and Skouby 1949). Braun and Meier (1944) also demonstrated that after application of a local anaesthetic, no warm sensation could be elicited from the warm spots on proper stimulation, whereas the sensation could still be elicited from the surrounding tissue. Mertin (1947) demonstrated a similar finding for the cold spots.

The introduction by Adrian and Zotterman (Adrian 1926; Adrian and Zotterman 1926a,b) of the technique of electrophysiological recording of action potentials from a single somatosensory unit evoked by adequate stimulation of its receptive field was very influential in the advance of our knowledge about the sensory systems. The technique had to await further refinement before recording from the small thermally sensitive single units was possible (Hensel and Zotterman 1951a). In 1960 the first recording was made from disected human nerve fibres by Hensel and Boman (1960) and this was followed by many other recordings from intact human nerves by special intraneural needles in wakeful subjects from both warm and cold units (Konietzny and Hensel 1975,1977,1978,1980; Jarvilehto and Hamalainen 1980; Konietzny 1981).

These single unit electrophysiological studies in man have convincingly established the existence, in the skin, of specific thermoreceptors (Iggo 1982a,1984). This review, therefore, accepts the existence of specific thermoreceptors of two types, one specific for cooling, the other for warming.

Structure and identification of thermal receptors

The abundance of recent information about the function of thermal receptors following the single unit studies has not been accompanied by any significant increase in knowledge of their morphological structure.

Following the discovery of specific warm and cold spots (Blix 1882) and the speculation of von Frey (Frey 1895,1910) about the corpuscular structure of thermoreceptor nerve endings, many attempts to identify these have failed (Dallenbach 1927,1929; Hensel 1952b; Hagen et al, 1953; Weddell et al, 1955; Weddell and Miller 1962). In these studies subjectively identified cutaneous spots were excised and examined for encapsulated or corpuscular nerve terminals without success. More recently, however, using a more precise approach, Hensel and his associates (Hensel et al, 1974) were able to identify individual cold receptors from their spots. After accurately mapping the receptive fields of single cold units in the cat's face using electrophysiological methods, the overlying skin was excised and examined ultrastructurally and the existence of distinctive nerve terminals in each identified receptive field was established. The nerve fibres, which were found to be of the thinly myelinated A_{δ} type, were found to branch in the dermis just to the depth of the basement membrane of the epidermis, to lose their myelin sheath and be enveloped only by Schwann cells, and finally to terminate in close apposition to the deepest epidermal cells immediately beneath the identified cold spot. Receptors of warm fibres in animals or of cold or warm fibres in humans have not yet been identified using this method.

Recent electron microscopic examinations of the nerve endings of the thinly myelinated (A_{δ}) and the unmyelinated (C) fibres, which include the thermal fibres, showed that they are non-encapsulated (Cauna 1980). It was shown that even the finest terminals of these fibres are sheathed to their tips with Schwann cell, although very small areas of these terminals may be open to the interstitial fluid space.

The failure to identify the thermal receptors morphologically does not disprove the functional and morphological specialisation of these receptors (Hensel 1981).

Localisation of thermal receptors

The difficulty in localising thermoreceptors morphologically led many workers to seek physiological methods for the purpose of determination of the depth in the skin at which these receptors lie. The first experimenters used the reaction time of the subject to a thermal stimulus, utilising the rate of transmission of heat/cold through the skin, calculated from the thermal diffusion coefficient and intracutaneous measurement of temperature changes by thermistors (Bazzett and McGlone 1930; Bazzett et al, 1930,1932). The average depth of cold receptors in human skin was found to be 0.15 - 0.17 mm, immediately beneath the epidermis, while that of heat receptors was 0.3 - 0.6 mm, in the upper layer of corium. This method, however, included the subjective reaction time to thermal stimuli and many other uncontrollable factors (Zotterman 1959). By the use of electrophysiological recording from the unit stimulated (instead of subject's reaction time), of rapidly rising thermal stimuli with precise onset, of the calculated rate of transmission of heat/cold stimuli through the skin and of intracutaneous recording of temperature changes, more accurate estimation of the depth of thermal receptors in cats was obtained (Hensel et al, 1951). This measurement closely correlated with histological measurement of depth of the receptors in the same area. This method has not been applied to human beings yet.

Topography of thermal receptors

The warm and cold spots are distributed over the skin in varying density and on the whole they are less numerous than the touch points of the mechanoreceptor system (Hensel 1981). A comprehensive review of these

spots with topographical charts in human body is found in Goldscheider's paper (1926).

A comparison of the densities of cold and warm spots in the skin has shown that there are clearly more of the former than the latter in general, but the relation between the two kinds varies in different areas. The highest density of thermosensitive spots is in the most temperature-sensitive region of the skin, the face, especially the lips and eyelids. here there are 16-19 cold spots/cm^2, whereas the warm spots are so numerous that they cannot be resolved into individual points and forms a sensory continuum (Rein 1925a). The forehead is very cold sensitive but only moderately sensitive to warm (Strughold and Porz 1931), the hand surfaces have 1-5 cold spots/cm^2 but only 0.4 warm spots/cm^2 and the conjunctival sac and the periphery of the cornea were found to possess cold but not warm sensitivity (Strughold and Karbe 1925; Strughold and Porz 1931).

The specificity of thermal receptors

The concept of specific thermal receptors was introduced only after the discovery of specific warm and cold spots which not only respond to warm and cold stimuli, respectively, but also to electrical stimuli producing warm and cold sensation (Blix 1882). The existence of specific receptors in these spots in the skin was first proposed by von Frey in 1926.

The recording of spike activity of single thermal nerve fibres in mammals (Hensel and Zotterman 1951a,b,c; Dodt and Zotterman 1952) including monkeys (Perl 1968; Iggo 1969; Hensel and Iggo 1971; Sumino et al, 1973; Darian-Smith et al, 1975,1979; Duclaux and Kenshalo 1980) and, most importantly, in conscious humans using the technique of microneurography (Hensel and Boman 1960; Konietzny and Hensel 1975,1977,1980; Jarvilehto and Hamalainen 1980; Konietzny 1981) leaves no doubt about the existence of specific thermal receptors in lower mammals and the human. From these

works, it was found that the cutaneous thermal receptors could be divided,by the criteria of their response, into two well defined classes of heat and cold receptors (Hensel and Bowman 1960; Konietzny and Hensel 1975,1977,1980; Jarvilehto and Hamalainen 1980; Konietzny 1981). Irrespective of the initial temperature, a heat receptor will always respond with an overshoot of its discharge on sudden warming and a transient inhibition on cooling, while a cold receptor will respond in the opposite way. In the resting state, the temperature during which maximum discharge occurs is much lower for cold than for heat receptor. The special properties mentioned above are summed up in the term 'specificity' which can be considered from two points of view. The first assesses the specificity of the sensation produced in human subjects in response to the stimulus, ie the arousal of a specific phenomenon from the stimulation of these receptors and this is referred to as the 'phenomenal specificity'. The second takes account of the differential response of the receptor to a specific physical cutaneous stimulus and is termed the 'physical specificity' and here the criterion is the quality of the stimulus applied, irrespective of whether the excitation of the receptor is or is not accompanied by temperature sensation or, as in the case of animals, conscious experience is difficult to establish (Hensel 1981). These two definitions of specificity, though closely related, are not identical and a clear distinction is necessary, in particular when a receptor responds to more than one kind of physical stimulus, but may be unimodal in terms of the quality of sensation produced. Another situation is when two different types of receptors respond to the same type of physical stimulation with different kinds of sensation produced as in the case of heat and polymodal pain receptors (Iggo 1969). The sensation produced in the latter is pain rather than heat.

The specificity of thermal receptors is defined usually in terms of phenomenal specificity, as established by psychophysical 'phenophysical'

experiments (Hensel 1981). Recent neurographic recordings, however, from single peripheral thermal units had made it possible to investigate the question of physical specificity of these receptors. The physical specificity of thermal receptors has been proven in the work of Hensel and his associates (Hensel and Boman 1960; Konietzny and Hensel 1975,1977,1978,1980; Jarvilehto and Hamalinen 1980; Konietzny 1981). It was noted that this physical specificity is not absolute, and that other forms of strong stimulation may also excite the nerve endings, though not to the same degree as the proper physical stimulus. This is also true with most kinds of cutaneous receptors. In the non-proper stimulus, however, there is no direct comparison between the intensity of stimulation and the frequency of the discharge of the unit. Cold receptors, for example, fire maximally at 150 s^{-1} during rapid cooling, while very few spikes or almost no response is produced to severe mechanical stimulation (Iggo 1982b). The phenomenal specificity, therefore, is the central issue. The combination of electrophysiological and psychophysical studies, in the recent work of Torebjork and Ochoa (1980) provides some evidence to further suggest that this is the case in the sensory receptors.

In primates, including man, therefore, the specificity of thermal receptors has been conclusively established. In neurophysiological terms, the general properties of these receptors can be described as follows:

1. They have a maintained discharge at constant skin temperatures with the discharge rate being proportional to the temperature.
2. They show a dynamic response to changes in temperature of the skin by a rise or fall of the rate of discharge depending on the direction of the change of temperature.
3. Their range of activity is in the non-painful range of temperature.
4. They are relatively insensitive to mechanical, chemical and other non-thermal stimuli.

5. The cold receptors are excited by a fall and the heat receptors by a rise of skin temperature.
6. Over the particular range of temperature, they discharge at a rate that depends on the intensity of thermal stimulation.

Fields of thermal receptors

Both kinds of receptors have spot-like fields, corresponding to the warm and cold spots in the skin found when using fine-tipped thermal stimulators in psychophysical studies (Hensel 1981). The fields are usually smaller than 1 mm^2 (Iggo 1969; Hensel and Kenshalo 1969; Sumino et al, 1973; La Motte and Campbell 1978; Darian-Smith et al, 1979) and a single nerve fibre innervates a single spot. In one investigation, however, single cold fibres were reported to innervate up to 8 spots, the whole field amounting to 1.7 cm^2 (Kenshalo and Gallegos 1967). Spot-like receptive fields of about 1 mm^2 were also found for single warm and cold fibres in humans (Konietzny and Hensel 1975,1977,1978,1980; Jarvilehto and Hamalainen 1980).

Unspecific thermal receptors

There are other cutaneous receptors which might respond to changes of temperature in the skin, but are not involved in thermal sensation and are not to be considered as specific thermal receptors (Hensel 1981).

Certain slowly adapting (SA) mechanoreceptors type I and type II in cats were found to respond not only to mechanical stimulation but also to intense cooling (Duclaux and Kenshalo 1972). In man, about one-third of type II SA mechanoreceptors were found to have this character (Hensel and Boman 1960; Konietzny 1981). It was also demonstrated that sudden warming of these receptors caused a transient decrease in their discharge (Konietzny 1981). These receptors, however, were found to require strong

cooling stimuli to excite. When so stimulated, their activity persisted for short time, and they did not show the characteristic 'burst discharges' of the specific cold receptors (see Chapter 2) (Hensel and Bowman 1960; Konietzny and Hensel 1980; Konietzny 1981). These type II SA mechano-receptors were found to be served by thinly myelinated Aδ fibres (Konietzny 1981). In monkeys, these receptors were found to be at least 20 times less sensitive than the specific cold receptors (Darian-Smith et al, 1973). The quality of the sensation associated with activity of these receptors is as yet unknown (Hensel and Konietzny 1980). Their contribution to the sensation of cold and whether they have any 'phenomenal specificity', therefore, is unknown, though some assume that these are pressure rather than cold receptors (Hensel and Konietzny 1980).

Another example of other cutaneous receptors in man responding to thermal stimuli is the 'nociceptors'. Various investigations described these receptors' response to temperature stimuli in the noxious range, where the stimulation results in the sensation of pain (Torebjork and Hallin 1972,1974,1976; Torebjork 1974; Konietzny and Hensel 1980; Konietzny 1981). These receptors, however, are not only excited by intense heat stimulation, but also by strong mechanical (eg squeezing by forceps), chemical and pin-pricking stimuli and hence the description of 'polymodal nociceptors' (Torebjork and Hallin 1974; Konietzny and Hensel 1980; Konietzny 1981). Polymodal nociceptors have also been described in monkeys (Bessou and Perl 1969; Burgess and Perl 1973; Perl 1976; Beitel and Dubner 1976; Croze et al, 1976; Kumazawa and Perl 1977; La Motte and Campbell 1978) and other mammals (Burgess and Perl 1973; Kumazawa and Perl 1977; La Motte and Campbell 1978). In the human, these receptors exhibited no response to temperature stimulation in the non-painful range, and started to respond to heat stimulation at 45^{o}C with few irregular discharges which increased in frequency with stimulation at higher temperature (Torebjork and Hallin 1974; Konietzny and Hensel 1980; Konietzny 1981). The nerve

fibres subserving these receptors were unmyelinated (C) fibres (Konietzny 1981). Another group of nociceptors responded to intense cooling, below 20°C, in addition to intense mechanical stimulation (Torebjork and Hallin 1974). Cooling and mechanical responsive nociceptors have been found in animals (Burgess and Perl 1973; Kumazawa and Perl 1977; La Motte and Campbell 1978). These receptors, therefore, do not possess 'physical specificity'. If they are involved in pain sensation, they may then have 'phenomenal specificity'.

Peripheral nerve fibres serving thermal sensation

Particular afferent functions or sensory qualities have been assigned to nerve fibre groups determined by diameters or conduction velocities by combination of techniques for restricting activity to part of these fibres. Such correlations supplied indirect evidences in this context (Collins et al, 1960). More recently, with the introduction of single unit recording in conscious human beings, conduction velocities of fibres connected with specific cold receptors were found to fall in the range of thinly myelinated (AΔ) group (Hensel and Boman 1960; Konietzny 1981; Hensel 1981). Similar conduction velocities to those of humans were found for primate cold fibres (Hensel and Iggo 1971; Darian-Smith et al, 1973; Long 1973,1977; Kumazawa and Perl 1978; Duclaux and Kenshalo 1980). In primates, few of the cold fibres, however, were found to be unmyelinated (Iggo 1980).

Conduction velocities of fibres subserving human specific warm receptors within the radial nerve suggested that they were unmyelinated C fibres of less than 1 /um diameter (Konietzny and Hensel 1975; Torebjork and Hallin 1976b; Konietzny 1981). Similarly most of the fibres subserving warm receptors in primates were found to be unmyelinated (Perl 1968; Iggo 1969; Hensel and Iggo 1971; Darian-Smith et al, 1973,1975,1979;

Sumino et al, 1973; Duclaux and Kenshalo 1980). A few heat receptors, however, have been reported for the monkey's facial skin to have conduction velocities greater than 2.5 ms^{-1}, indicating that they possibly are thinly myelinated (Dubner et al, 1975).

In their work on differential blockings of cutaneous sensations with local anaesthetics, Fruhstorfer and co-workers (1974) demonstrated that warm and cold sensations could be dissociated and that warm sensibility was lost significantly earlier than cold sensibility. They also demonstrated that both these sensibilities were completely lost when touch sensation was still perceived. These authors estimated the conductivity of the afferent fibres from measurements of the reaction time and found that reaction times to warm stimuli were on average twice those to cold stimuli. They concluded that the sensation of cold is served by the $A\delta$ and heat by the C fibre groups. Other workers have also demonstrated differential blocking of warm and cold sensations using selective nerve blocking methods (compression or local anaesthetics) (Glasgow and Sinclair 1962a,b). Using the technique of microneurography and correlating changes in the evoked intrafascicular neurogram to electrical stimulation, during selective neural blocking procedures, with changes in the perception of standardised sensory stimuli, Mackenzie etal (1975) showed that loss of cold sensibility accompanied disappearance of the $A\delta$ potential while loss of warm sensibility accompanied abnormalities in the C fibre potential.

The afferent fibres serving warm and cold sensations are either thinly myelinated (1-3 μm in diameter) or unmyelinated (< 1 μm in diameter). It is generally accepted that fibres from cold receptors are thinly myelinated while warm receptors have unmyelinated afferent fibres.

CENTRAL PATHWAYS

Progress in knowledge and understanding of the relevant central neural events and the central pathways involved in thermal sensation in humans has been slow compared to the peripheral processes. Most progress has been made concerning the transmission of the thermal receptor inputs within the dorsal horn of the spinal cord and the brain stem trigeminal complex. Knowledge of the subsequent processing of this input in the thalamus and cerebral cortex remains inadequate and fragmentary.

There are three main sources of information concerning the central structures, pathways and mechanisms of thermal sensations.

1. Clinical observations and pathophysiological correlations of diseases, lesions and injuries, encountered in humans, in the spinal cord, brainstem and forebrain.
2. Electrophysiological single unit recording from thermosensitive afferents in the CNS which is almost exclusively performed on animals.
3. The introduction and development of new techniques of mapping axonal pathways by the intra-axonal injection of labelled amino-acids (anterograde axonal studies) or of horseradish peroxidase (HRP) (retrograde axonal studies). These have proved to be a powerful method for the investigation of the central connections of the thermal pathways.

An excellent knowledge concerning the organisation of various tracts in the spinal cord came from the careful description, by Brown Sequard in 1868 in a series of lectures in 'Lancet', of the effects of a hemisection of the spinal cord. He described the involvement of thermal sensation and pain appreciation on the opposite side below the lesion and of touch, sense of position and paralysis on the same side as the lesion. He also observed that in some patients thermal sensation alone, without impairment of pain,w as lost on the opposite side. These descriptions closely correspond with

findings of spinal cordotomy for the treatment of intractable pain (Spiller and Martin 1912; Spiller 1915). It was found that the neurosurgical interruption of the antero-lateral tract will cut off the transmission of thermal and pain stimuli opposite and below the lesion leaving the sensation of touch unaffected. Similar observations were reported for the brainstem trigeminal complex. Hun (1897) observed that following posterior inferior cerebellar artery occlusion in man, which destroys along with other medullary structures, the nucleus caudalis and interpolaris of the brainstem trigeminal complex, a pattern of sensory dissociation is produced. The patient is unable to appreciate pain and thermal stimuli in the face on the ipsilateral side of the lesion, with preservation of light touch, suggesting that these nuclei of the brainstem trigeminal complex are the sites of relay of the facial pain and thermal pathways. These suggestions were reinforced by the introduction of trigeminal tractotomy in 1938 for the treatment of trigeminal neuralgia (Sjoqvist 1938) and the clinical studies performed on these patients (Grant et al 1940; Kunc 1966,1970).

Clinical observations from lesions of the cerebral cortex have provided very few clues about the regions likely to be relevant to the appreciation of thermal sensation. No simple correlation has been established between the impairment of cutaneous thermal sensibility and the location of cortical injury. Many patients with extensive cortical injuries have been noted to retain their thermal sensibility (Head and Holmes 1911; Head 1918). On the other hand, there have been well documented reports of patients with focal lesions of the post central gyrus and with good evidence that the lesions were limited to the cortex in whom pain and temperature sensibility on the contralateral side were substantially lost (Russel and Horsley 1906; Russel 1945,1947; Marshall 1951). The contribution of the cortex to thermal and pain sensation remains a mystery.

Electrophysiological recording from thermosensitive afferents in the CNS, almost exclusively performed in laboratory animals, is generally difficult for many reasons. CNS afferent fibres are divergent (each neurone has excitatory synapses with many neurones) and convergent (each neurone receives contacts from many neurones) (Burton 1975; Iggo and Ramsay 1976). The other factor is that sensory central neurones, in addition to the excitatory synapses, receive inhibitory synapses of two types; afferent inhibition and descending inhibition (Brown 1973; Tapper et al, 1973; Towe 1973; Burton 1975; Carsten et al, 1979). Both of these control and modulate the afferent influx. The previous difficulties do not exist in the peripheral neurones making interpretation of single unit studies a straightforward matter (Hensel 1981). In spite of these difficulties, there are some indications from these single unit electrophysiological studies that the specificity of the peripheral system is shared by the central neurones. Afferent fibres from receptors which are functionally specific for a particular modality of sensation connect to anatomically discrete regions in the CNS (Werner and Whitel 1973).

The relatively recent introduction of the method of retrogradely labelling neurones by the intra-axonal injection of horseradish peroxidase (HRP) (Kristensson and Olsson 1971) has provided a technique with several advantages to map the projections and pathways of sensory neurones (Light et al, 1979). A large injection of HRP into the caudal thalamus of the animal was found to label neurones retrogradely throughout the spinal cord (Trevino and Carstens 1975; Willis et al 1979). Information from these studies is still coming.

Spinal Cord

The transfer of thermal stimuli in the spinal cord is still inadequately understood. The new mapping techniques have been used for direct visualisation of the termination of single pain and various mechano-

receptor peripheral units in the spinal cord (Light and Perl 1979a,1979b; Brown 1981) but not yet of single heat and cold fibres. The termination of the specific peripheral heat and cold fibre is tentatively attributed to that of the unmyelinated (C) and thinly myelinated (AΔ) fibre populations respectively. The connections of these two populations to and their destinations in the spinal cord have fortunately been intensively investigated in the monkey (La Motte 1977; Ralston and Ralston 1979; Brown 1981) and in other mammals (Light and Perl 1979a,b; Rethelyi 1977; Willis and Coggeshall 1978; Rethelyi et al, 1979). The large diameter myelinated afferent fibres enter the spinal cord medially while the smaller AΔ and C fibres enter more laterally within the dorsal spinal roots (Ranson 1913; Szentagothai 1964). The AΔ and C fibres make their synaptic contacts with neurones within one or two segments of the ipsilateral dorsal horn of the cord, the first synapse in the pathway (Kumazawa et al, 1975; Iggo and Ramsay 1976; Light and Perl 1977,1979a,b; Light et al, 1979; Rethelyi et al, 1979). It is believed that all primary afferent fibres entering the spinal cord probably make excitatory synaptic contacts with the second order neurones there (Hugon 1971; Handwerker et al, 1975) as evidenced from electrophysiological analysis in mammals.

The dorsal horn of the spinal cord, in which the second order neurones, are located, runs the full length of the cord and is divided into specific sheets or laminae over its entire extent (Rexed 1952). According to anatomic and integrative properties and types of afferent and efferent connections, Rexed (1952) has divided it into six layers named by Roman numbers I to VI. The unmyelinated axons in primates were found to terminate mainly in lamina II of Rexed, also called the substantia gelatinosa, while the small thinly-myelinated fibres terminate mainly in lamina I of Rexed, also called the marginal zone (Kumazawa and Perl 1977; La Motte 1977; Light and Perl 1979a,b; Ralston 1979; Ralston and Ralston 1979). The reverse pattern of termination of these fibre populations,

however, has been described by other workers (Beal and Fox 1976) who reported that unmyelinated fibres terminate in lamina I and the thinly-myelinated fibres terminate within the superficial layers of substantia gelatinosa (lamina II of Rexed). The important point is that this distribution implies that cold and heat fibres terminate within lamina I and II of the spinal cord. The large myelinated fibres of the medial division of the dorsal root terminates in the deeper lamina IV, the nucleus proprius, with no direct input to laminae I and II of the dorsal horn (Hugon 1971; Brown 1981). This segmental neuronal system of the spinal cord which separates input due to innoxious mechanical and proprioceptive input (lamina IV) from signals due to noxious and thermal stimulation (laminae I and II) is in keeping with the specificity theory (Hugon 1971). It is also possible that laminae I and II differentiate between different kinds of stimuli through the presence of a projection system highly specific to that type of receptive unit.

Few studies have been published on the transmission of thermal stimuli in the spinal cord of the monkey (Christensen and Perl 1970; Iggo and Ramsay 1974,1976; Burton 1975; Kumazawa et al, 1975; Kumazawa and Perl 1976,1978). In lamina I of the monkey's spinal cord specific neurones responsive to moderate cooling of their receptive fields in the foot and lower leg of the same side were identified (Christensen and Perl 1970; Kumazawa et al, 1975; Iggo and Ramsay 1976; Kumazawa and Perl 1976,1978). These neurones were not responsive to mechanical and noxious thermal stimulation. Their response to cooling was less than the response of peripheral units, irregular with the absence of the typical 'burst' discharges observed in peripheral cold units (see Chapter 2) and their activity was suppressed by the application of a warm stimulus to their receptive fields. As expected, the input to these cells was from thinly-myelinated peripheral units. Their receptive fields were on average larger

than those of peripheral cold units (Kumazawa and Perl 1978). Their larger receptive fields and peculiar response to cold stimuli might be explained on the basis of the 'convergence' of many peripheral cold units, possibly as many as 100, on a single second order neurone (Hensel 1981).

Christensen and Perl (1970) and Burton (1975) in their studies on Squirrel monkeys, found few dorsal horn neurones in laminae I, II and IV of the spinal cord responding not only to moderate cooling but also to innoxious mechanical stimulation to their receptive fields. This activity is thought to be possibly due to the excitation of cold sensitive SA mechanoreceptor types I and II and Burton (1975) doubted that their activity reflects transmission from specific cold receptors. Other neurones were found to respond to cooling, mechanical and noxious heat stimulations, or to innoxious heat and mechanical, or to heat and cold stimulations (Burton 1975). Our knowledge in relation to the transmission of non-painful heat stimulation is particularly limited (Hensel 1981).

After modifications associated with their transfer to the second order neurones in the dorsal horn of the spinal cord, the data concerning thermal stimulation are transmitted to higher centres by the contralateral spinothalamic tract and the spinoreticular systems (Hugon 1971; Hensel 1981). The latter is connected, as its name implies, to the reticular formation of the brain stem which is an important station in the ascending non-specific system (Brown 1981). There may also be projections through the ipsilateral dorso-lateral (spino-cervical) tract, which terminates in the thalamus and includes predominantly afferent cutaneous fibres from the forelimb (Brown 1973; Iggo and Ramsay 1976; Cervero et al, 1977). The function of this tract and whether it plays any role clinically in man is still unknown (Hensel 1981).

Through the contralateral spinothalamic tract which is located antero-laterally in the cord, the thermosensitive pathways for spinal cord project to a third order neurone in the ventrobasal complex of the thalamus

(Landgren 1970; Kumazawa and Perl 1978). Although the specific thermoreceptive neurones in the monkey's spinal cord were visualised to project to the upper cervical cord (Kumazawa and Perl 1978), strong indirect evidence of their termination, among other neurones contributing to the spinothalamic tract, in the ventrobasal complex of the thalamus comes from the work of Willis and his co-workers (Applebaum et al, 1979; Willis et al, 1979). They demonstrated clearly, through the use of the retrograde mapping technique, that cells from lamina I of the dorsal horn project directly to the contralateral ventrobasal complex of the thalamus. They also demonstrated that some ipsilateral projection also occurs but is uncommon. These findings were also reproduced in the work of Berkeley (1980) from his studies of terminal degeneration following anterolateral tractotomy in the monkey.

Thermal sensation of the face

Sensation from the face is carried by the trigeminal nerve which enters the brain at the pons. The trigeminal (gasserian) ganglion, the spinal nucleus and the main sensory nucleus are analogues, respectively, of the spinal dorsal root ganglia, the dorsal horn of the spinal cord and the dorsal column nuclei of the spinal large fibre afferents. This analogy also extends to the tracts leaving these nuclei. In the spinal nucleus, afferents from nociceptors, thermal receptors and some mechanoreceptors synapse with neurones sending axons to the reticular formation and the thalamus, similar to the spinal spinoreticular and spinothalamic tracts. Only afferents from mechanoreceptors terminate in the main sensory nucleus and the post-synaptic axons join the medial lemniscus.

This anatomical arrangement of the trigeminal pathway is consistent with clinical and pathophysiological studies of brain stem lesions (Hun 1897; Gerard 1923) and with findings following trigeminal tractotomy

(Spiller and Martin 1912; Spiller 1915; Sjoqvist 1938; Smyth 1939; Grant et al, 1940). Gerard (1923) argued from clinical and experimental studies, that only the caudal part of the brain stem trigeminal complex (the nucleus caudalis, with input from the spinal trigeminal tract) subserves pain and temperature sensibilities. Clinical studies on patients having trigeminal tractotomy as a treatment for trigeminal neuralgia (Grant et al, 1940; Kunc 1966,1970) supported this. From partial dissociation of pain and thermal sensations observed in patients having occlusion of the posterior inferior cerebellar artery or trigeminal tractotomy (Smyth 1939), it was suggested that thermal sensation might be mediated by nuclei rostral to what is called nucleus caudalis (Spiller 1915; Smyth 1939).

Dostrovsky and Hellon (1978) and Poulos and Molt and their coworkers (Poulos and Molt 1976; Poulos et al,1979) expanded earlier observations of single units in the trigeminal brain stem complex responding to moderate cooling of the facial skin (Poulos et al, 1970; Mosso and Kruger 1972; Fruhstorfer and Hensel 1973; Schmidt 1976). In a large sample of nucleus caudalis thermoreceptive neurones, Dostrovsky and Hellon (1978) found most cells to be excited by cooling and only a few by innoxious heating of the skin of the face in cats. More than half of each of the two types were found to respond exclusively to innoxious temperature changes in the appropriate direction. The rest were in addition excitable by low intensity mechanical deformation of the skin. The cell bodies of most of these neurones were found to be in the marginal zone of nucleus caudalis, the trigeminal analogue of Rexed's lamina I in the spinal dorsal horn (Gobel 1978; Hockfield and Gobel 1978; Dowson et al, 1980; Arvidsson and Gobel 1981). The activity of these trigeminal neurones closely resembled primary warm and cold fibres innervating the face (Hensel and Huopaniemi 1969; Hensel and Kenshalo 1969; Poulos and Lende 1970a,b). The receptive fields of these thermoreceptive neurones were found, like those of spinal dorsal horn neurones, to be larger than the peripheral ones, strictly

ipsilateral, and mainly concentrated on the nose, lips, lower eyelids and the pinna (Schmidt 1976; Dostrovsky and Hellon 1978). The trigeminal neurone receptive fields were smaller (10-100mm^2 mostly) than those on the limbs (200-500mm^2) (Dostrovsky and Hellon 1978).

Dostrovsky and Hellon (1978) suggested that the thermosensitive neurones in the trigeminal nuclei project to the contralateral ventrobasal complex of the thalamus. They found that these neurones could be antidromically activated by electrical stimulation of the contralateral posterior thalamus in the region of the ventrobasal nucleus. This finding supported the results of the earlier histological studies of Burton et al (1979) who traced the trigemino-thalamic projections using retrograde and antegrade axonal transport methods and the recording of thermosensitive neurones in the trigeminal nucleus caudalis. According to these workers, the marginal zone of the nucleus caudalis projects bilaterally to the nucleus ventralis posteromedialis and contralaterally to the medial part of the posterior nucleus of the thalamus.

The Thalamus

Spinal and trigeminal thermoreceptive pathways most probably project to third order neurones in the ventrobasal complex of the thalamus which plays a key role in transforming information that reaches the cerebral cortex (Poulos and Binjamin 1968; Landgren 1970; Poulos 1975; Dostrovsky and Hellon 1978; Burton et al, 1979). A similar somatotopic representation to that of the primary sensory cortex is present in the thalamic ventrobasal complex.

Single unit recording in the thalamic ventrobasal complex demonstrated the presence of neurones responding to cooling of the mucosa of the cat's tongue (Landgren 1960,1970; Poulos and Binjamin 1968). About one-third of these cold responsive neurones were specific in their response and were not

responsive to low intensity mechanical, noxious and gustatory stimuli to their receptive fields. The intensity of the stimulus applied to their fields was coded in the mean discharge rate of the neurone, similar to the cold peripheral unit (Darian-Smith 1973; Arvidsson and Gobel 1981). The remaining two-thirds of the thermosensitive thalamic neurones responded to other qualities of stimuli (eg low intensity mechanical stimulation) in addition to the cold stimulation. It is possible that the response of at least some of these thalamic neurones to mechanical and cold stimuli is due to converging input to these neurones from both cold and SA mechanoreceptor fibres (Hensel 1981). Specific cold responsive neurones similar to those observed in cats have been described in the thalamic ventrobasal complex of monkeys (Burton et al, 1970; Poulos and Molt 1976). There is relatively little information on thalamic response to cold stimulation of the skin of limbs (Burton et al, 1970). Likewise, much less success has been encountered in attempts to isolate specifically responding thalamic neurones to innoxious heat stimuli in animals (Landgren 1970). Martin and Manning (1971) found some neurones in the ventrobasal complex of the thalamus of cats which were excited by innoxious heat, but also by cooling and light tactile stimulation of their receptive fields in the skin.

In their experiments on rats, Hellon and colleagues (Hellon and Misra 1973; Hellon et al, 1973; Hellon and Mitchell 1975) were more successful in studying larger numbers of thermosensitive thalamic innervation from the scrotum. They demonstrated the presence of specific heat and cold responsive units in the ventrobasal complex of the thalamus.

The receptive fields of thalamic neurones in cats, on the contralateral body surface, ranged in area from 6-96cm^2 indicating the presence of convergence (Poulos and Binjamin 1968). They were smaller in size on the distal extremities and the face and larger on the proximal parts of the extremities and largest on the trunk.

The Cerebral Cortex

Despite the observation that many patients with extensive cortical injuries have been noted to retain their thermal sensibility (Head and Holmes 1911, Head 1918), the general consensus is that the cerebral cortex is necessary for the sensation and perception of thermal stimuli (Hensel 1981). All the sensory information required for these functions reaches the cerebral cortex from thalamus (Jones and Powell 1970; Werner and Whitsel 1973).

Three main areas in the cortex are believed to be involved with somatic sensation; the primary sensory cortex (SI), the secondary sensory cortex (SII) and the sensory association area (Marshall et al, 1937; Woolsey 1952,1958; Jones and Powell 1973). The primary sensory sensory area (SI) was identified before SII and hence the names primary and secondary do not indicate order of processing of sensory information (Adrian 1941; Woolsey 1984). SI is located on the postcentral gyrus just behind the central sulcus while SII is on the upper wall of the lateral sulcus which separates the parietal and temporal lobes (Sylvian fissure) (Woolsey 1952,1958,1984). A well ordered, though distorted map of the body surface is represented on SI, somatopic organisation, where regions of high sensory acuity, such as the fingers and lips, have larger representation than those of lower sensory acuity such as the posterior surface of the trunk (Woolsey 1952,1958,1984; Jones and Powell 1973). This is believed to reflect the higher densities of receptors in these regions which project to large populations of neurones in the SI. The somatotopic organisation of SII is much less precise with a far greater degree of overlap than SI (Celesia 1963; Whitsel et al 1969). The projection in SI is contralateral, while in SII it is bilateral, ie both sides of the body are represented in each hemisphere in SII (Woolsey 1952,1958). A third cortical region believed to receive somatic sensory input is located in the posterior parietal cortex

(Broadmann's area 5 and 7), referred to as the somatic sensory association area, in which complex associations between different sensory modalities are thought to be made (Jones and Powell 1973). Based on electrical recording by electrodes at different depths in the cortex, it was hypothesised that the functional organisation in the somatosensory cortex is believed to be a column of cells arranged perpendicular to the surface and extending through all the layers of the cortex (Mountcastle 1957; Powell and Mountcastle 1959). Though originally described for various types of mechanical stimuli, this columnar arrangement appears to be a general design principle of cortical organisation in the visual, auditary and motor areas (Hubel and Wiesel 1969; Werner and Whitsel 1973). The existence of cortical columns of neurones that process only temperature stimuli, however, has not yet been established.

A single column contains cells which are activated by one modality of stimulation (ie one type of receptor) and similar topographical representations so that their receptive fields are adjacent and considerably overlap (Mountcastle 1957; Powell and Mountcastle 1959; Webster 1977). This columnar arrangement of the functional units may be important for the orderly representation of particular stimulus features (Werner and Whitsel 1973).

Despite many attempts to investigate the role of these sensory cortical areas in thermal sensation, their contribution remains a mystery. Experimental studies of cutaneous thermal sensory capacities in the monkey following ablation of the somatosensory cortex have, like the clinical studies, yielded equivocal results. Removal of SI and SII, separately and in combination, in one experiment, did not have any effect on resolving small changes in the skin temperature by the animal (Peele 1944; Cragg and Downer 1967; Porter and Semmes 1974). The learned ability by the monkey to resolve changes in skin temperature was not transferred from one hand to the other on sectioning the corpus callosum (Porter and Semmes 1974).

Sectioning of the corpus callosum, therefore, appears to prevent transfer of a learned temperature discrimination from the trained hemisphere to the opposite one. This finding was argued by the authors to point to the involvement of the cerebral cortex in some way in the sensing of changes in the skin temperature. Electrical stimulation of the sensorimotor and posterior parietal cortex in conscious patients has provided some support for this concept (Penfield and Boldrey 1937; Libet 1973). Many patients reported 'coldness' or 'warmth' in response to electrical timulation of the cortex. These appeared to the subjects to be qualitatively similar to the natural sensations.

Electrophysiological single unit studies of sensory cortical neurones in cats showed that the specificity of peripheral thermosensitive inputs are preserved even at this level. In his single unit studies on cats, Landgren 1957a,b,1960,1970) was able to record from single cortical sensory neurones in the lingual projection area with specific response to cooling and heating of the tongue. There were also other cortical neurones with high degree of convergence between various combinations of other sensory modalities like mechanical, noxious and gustatory stimuli. There is little information on the response of cortical sensory neurones to thermal stimulation of the extremities. Kreisman and Zimmerman (1971,1973) isolated only three such units in monkeys, responding to innoxious cooling and heating of the skin,but also to mechanical deformation of the receptive fields in the skin. In view of the high thermal discriminative abilities and the large thermoreceptive fibre populations innervating the hand of the monkey, these findings were puzzling to the authors. However, similar to their success with the thalamus, Hellon and Misra (1973) and Hellon et al (1973) were able to isolate units in the primary somatosensory cortex of the rat (SI) which specifically responded to cooling or warming of the scrotal skin.

In conclusion, the thalamo-cortical projection of thermal afferents is still inadequately defined but there is little doubt that it exists, with bilateral SII and contralateral SI representation, the latter being the more definitely somatotopic as for other sensory modalities.

Thermal Afferents to the Hypothalamus

Since the cutaneous thermal receptors are not only involved in conscious thermal perception, but also in autonomic thermal regulation (Hensel 1981), it must be assumed that thermal afferents reach the thermo-regulatory centres in the hypothalamus. At present relatively little is known about these connections (Hensel 1981) and the evidence for this is solely from experiments performed on laboratory animals (Weiss and Aghajanian 1971; Gilbert and Blatteis 1977). Human beings most probably also possess 'internal' thermosensitive units (Hensel 1981). These have been demonstrated by various electrophysiological methods to be present in various CNS areas (eg the hypothalamus, the midbrain, the medulla oblongata and the spinal cord) and in deep body sites outside the CNS (veins and abdominal cavity). It is possible that these internal thermoreceptors are involved in temperature regulation. Expansion on these aspects is not intended as it is not relevant to this thesis which concerns only consciously perceived thermal stimulation.

CHAPTER 2

PHYSICAL, PHYSIOLOGICAL AND BIOCHEMICAL MECHANISMS OF THERMAL SENSATION

The distinct sensations produced by localised changes in the skin temperature are virtually specified by the direction of the change of temperature, by their intensity, temporal profile and their extent and location. These thermal stimuli, after being transduced by the thermal receptors into electrical impulses, are mediated to the central nervous system through the peripheral nerves serving thermal sensation with utmost precision and economy.

Results of single and population thermosensitive unit studies reinforce the view that cutaneous thermal stimuli are represented with specificity not only in the peripheral but also in the central units. The evidence to date is that sensory analysis begins with the specific receptors in the skin which are the first sites where parameters of the thermal stimulus are coded. Subsequently, this information is preserved in specific pathways leading through the spinal cord and thalamus to the cerebral cortex. A reinforcement of this concept of specific peripheral and central pathways for various sensations has come from the recent modification of the technique of microneurography (Torebjork and Ochoa 1980) which has established that distinct and consistent sensations can be aroused by the activation of individual afferent fibres and bypassing the specific receptors.

Of the peripheral thermal mechanisms, the least understood is the process of transduction in the thermal receptors that initiate them. The events in the receptor membrane resulting from changes in the temperature of the skin remain obscure. Many modifications of the impulses initiated at these receptors and transmitted by the peripheral nerves are believed to occur as they pass through the central pathways. Although most evidence indicates that the central processing of information about thermal

sensation is efficiently handled, the current knowledge of this processing is both inadequate and fragmentary.

Stimulus events which lead to the stimulation of thermal receptors

The particular aspects of the thermal stimulus that give rise to the stimulation of the thermal receptors in skin have been in dispute for a long time. The first widely accepted view on this, following the 'law of specific energies' of Muller (1838), was that of Weber (1846) which was progressively modified and supported by others (von Skramlik 1937). This view held that a change in the temperature of the receptor is required to arouse a thermal sensation and that the direction of the temperature change determines the quality of the sensation, that is, a rise in temperature results in warm and a fall in temperature results in cold sensation. Many authors, however, objected to this view. The main objections were that warm and cold sensation, even if initially caused by a direction of temperature change, persist after the stimulus is removed while the direction of temperature change is reversed (Vierordt 1871). Furthermore, Vierordt (1871) pointed out that warm and cold sensations are present at extreme high or low skin temperatures even when the skin surface temperature is maintained.

In an attempt to explain these findigns and to identify the stimulus events evoking thermal sensation, Ebbecke (1917) introduced the 'gradient hypothesis'. This theory proposes that the immediate factor of receptor stimulation is an alteration of the spatial temperature gradient that exists between the skin surface and the layer of cutaneous vascular plexuses. The inadequacy of this theory to explain experimental findings of other authors led to successive modifications of this hypothesis (Bazett and McGlone 1932; Bernhard and Grant 1946; Lele et al, 1954). Findings of subsequent studies weighed heavily against the spatial gradient theory and its modifications (Hensel and Zotterman 1951a; Vendrik and Vos 1958;

Hensel and Witt 1959). Comparison of the infra-red and ultrahigh frequency microwave stimulation techniques showed that for the same change of skin surface temperature, the quantity of sensations produced is comparable for the two methods despite the fact that using microwave technique, the temperature uniformly changed throughout the cutaneous and subcutaneous tissues with no spatial gradient changes (Vendrik and Vos 1958). Hendler and Hardy (1960) also disagreed with the theory of spatial gradient and stated "... the warmth sensation evidently persisted in spite of what must have been a radical reversal of the spatial temperature gradient". The results of electrophysiological studies of thermosensitive receptors also opposed the spatial temperature gradient theory (Hensel and Zotterman 1951a; Hensel and Witt 1959). These authors identified the receptive field of a cold receptor on the upper surface of the cat's tongue and then cooled it from both sides of the tongue. Stimulation from either side was found to produce an uninterrupted increase in the frequency of their discharge in spite of the reversal of the spatial gradient.

Weber's theory (1846) that a change in skin temperature is required to excite thermal receptors continued to be accepted by most authors. Hering (1877), a proponent of the theory, proposed that the amount of energy conducted to the receptor zone is the most important stimulus condition in the arousal of a thermal sensation. This suggestion, he believed, accounts for the persisting thermal sensation at skin temperatures outside the zone of complete adaptation (see next chapter) as well as for the sensation produced by changes in temperature. Hensel (1950b) pointed out that a temperature change and its direction are correlated with thermal sensation produced only within the temperature zone of complete adaptation (30-36^{o}C) and when the skin is maintained at temperatures outside this zone, the change in temperature is correlated with an increase or a decrease of the persisting thermal sensation. The temperature of the tissue at the

receptor level is, therefore, accepted as the principal factor that governs the occurrence of thermal sensation (Hensel 1950b,1952a,b; Kenshalo 1970,1972).

Conduction of Thermal Stimuli in Human Skin

The degree to which thermal energy is transferred or is employed to change the skin temperature is determined by the thermal properties of the skin and of the material in contact with the skin (Stoll 1977). The information currently available about the thermal properties of the skin and their variation with body sites, skin colour and human age is quite limited (Cohen 1977). An important parameter to determine in this context. is the thermal conductivity (TC) of the skin (units are cal/cm/s/^{o}C). It is defined as the quantity of heat transmitted in skin for a unit distance (cm) due to the application of a unit temperature gradient (1^{o}C) in unit time (s) under steady conditions in a direction normal to the surface of a unit area of the skin (cm^{2}), when the heat transfer is dependent solely on the temperature gradient (Kaye and Laby 1959). This thermal conductivity (TC) of the skin depends on many other factors shown in the equation:

$$TC = tdc\ (cm^2/s) \times density\ (g/cm^2) \times Sh\ (cal/g/^{o}C).$$

where Sh (specific heat) is the quantity of heat that raises the temperature of 1g of the skin by 1^{o}C and is synonymous with the heat capacity of 1g of the skin.

tdc (thermal diffusion coefficient) is a determining constant.

Determination of both of these and the density of the skin which is necessary to calculate the TC of the skin, is difficult.

Many attempts to quantitatively measure the conduction of heat energy in the excised human skin were done. The earliest of these were reported by Klug (1874) and Lefevre (1901). Their values of about 5 x 10^{-4} cal/cm/s/^{o}C were based on the assumption that the thermal gradient extended from the surface of the skin inwards for 20 mm, including the subcutaneous

tissues. However, the same value of 5 x 10^{-4} (cal/cm/s/^{o}C) was obtained for the epidermis of porcine k_{skin} by Henriques and Moritz (1947). Their calculated TC value for the dermis was 9 x 10^{-4} (cal/cm/s/^{o}C). Values of TC for human dermis of excised skin ranged between 7-8 x 10^{-4} (cal/cm/s/^{o}C) in various studies (Roeder 1952; Lipkin and Hardy 1954).

Some authors, however, had maintained that many biological changes might take place in the excised skin which might change its TC and that measurements should be performed on unexcised skin, that is in vivo measurements (Burton and Edholm 1955; Vaendrik and Vos 1957). In unexcised skin, there is also an added effect of the blood flow on the resultant measurements (Buettner 1936). Buettner in 1951 measured the TC for the upper 2mm of living human skin, the depth within which the thermal receptors lie, the value of which was 9 x 10^{-4} cal/cm/s/^{o}C. When he cooled the skin, this value changed to 13 x 10^{-4} and when the skin was "very warm" the value was 67 x 10^{-4}. Many other workers subsequently determined TC for the superficial layers of living human skin at ordinary temperatures and obtained values ranging from 7-9 x 10^{-4} cal/cm/s/^{o}C (Aschoff and Kaempffer 1947; Roeder 1952; Lipkin and Hardy 1954; Hensel and Bender 1956). More variability in the values of TC for the dermis is encountered and is probably due to changes in the blood flow (Aschoff and Wever 1959).

A method for the direct measurement of thermal diffusion coefficient (tdc) was described by Hensel (1950a,1952a). He recorded the intracutaneous temperature at different accurately determined skin depths by using very fine thermocouples following the application of rectangular temperature stimuli applied to 1 cm^2 area of the surface of the skin. The fine thermocouples he used were introduced intracutaneously through a thin cannula or through an intravenous punctured channel. Curves of these temperature changes against time were plotted and the tdc of the skin calculated. At a depth of 0.45 mm in the skin of human forearm, the tdc

was estimated to be 6 x 10^{-4} cm^2/s; at a depth of 0.9mm a value of 10 x 10^{-4} cm^2/s was obtained. These two depths are reasonably comparable to the estimated intracutaneous location of cold and heat receptors in human, respectively (Chapter 1).

By a different approach for measurement of the TC of human skin in vivo, Hensel and others (Fox and Solman 1971; Challoner 1975; van den Berg 1975) constructed a variety of flow contact-calorimeters. This method excludes the need to determine the specific heat, the tdc and the density of human skin. In these devices, heat from a contact thermode flows through the skin to an outer copper ring also in contact with the skin and a temperature differential between the thermode and the copper ring is established. This temperature differential depends upon the TC of the skin and the known conductance of the thermode. The TC of the skin is consequently determined from a special equation (Hensel 1952a). Calibration of the thermode against a material of known conductivity is necessary before measurements take place.

There is a marked variation in the thermal properties, in particular the TC, of the skin from site to site (Spells 1960; Cohen 1977). A few items, however, seem clear. An important factor is the thickness of the epidermal layer, which is primarily an inert and insulative material. Increased thickness of the epidermis decreases TC and lengthens the transfer pathway of the thermal stimulus to the receptor level (Stoll 1977). The TC was found to be nearly twice as efficient in the forearm as in the heel (Kraning 1973) and Stoll (1977) demonstrated that TC is slower in fingers that are calloused than in normal ones. The difference between the magnitude of thermal stimuli for painful heat threshold was found to be significant between regions of human skin with thin and thick epidermis (Stoll 1977). TC is also related to the water content and other physical and chemical properties of the skin (Kraning 1973; Cohen 1977). Kraning believed that, at least in part, the difference between TCs of the skin at

forearm and heel reflected the low water content of the thickened stratum corneum of the heel. The TC is also a function of the temperature of skin (Buettner 1951; Weaver and Stoll 1969). A variation of TC between 8 and 75 x 10^{-4} cal/cm/s/^{o}C was reported for skin temperatures between 35 and 60^{o}C (Weaver and Stoll 1969).

Transducer Mechanisms of Thermal Sensation

There is, as yet, no precise description of the sequence of the moleculo-biological events occurring in the thermal receptor membrane which underlie the process of transduction of the energy of thermal stimuli into a pattern of nerve impulses. The basis of excitation of receptors in general and the conduction of neurones is electrochemical in nature and this depends on the passage of Na^{+}, K^{+} and Cl^{-} ions across the semipermeable membrane which surrounds the central core of axoplasm. When the axon is electrically inactive, the concentration of K^{+} is greater within than without, while the reverse is true for Na^{+} and Cl^{-} ions. The difference in concentration depends on three factors; the diffusion of K^{+} and Cl^{-} ions is more easy than Na^{+} across the membrane, the Na^{+} pump actively transports Na^{+} from within the axon with active transport of K^{+} into the axoplasm. The arrangement of ions in this way gives the axon a resting potential with a voltage difference across the membrane where the interior of the axon is about 70 mV negative with respect to the exterior. When a chemical or electrical stimulation of sufficient strength to alter the permeability of the semipermeable membrane occurs, the distribution of ions changes. Na^{+} and Cl^{-} ions flow rapidly into the axon, so that the interior becomes less negative or even positive with respect to the exterior for a brief period, but very shortly afterwards K^{+} flow out. This change in electrical state is called depolarisation. This depolarisation only occurs if the stimulus is of sufficient strength, that is the axon gives an "all or none" response. Electrical activity ceases after a brief

period when the influx of Na^+ ions stops and the membrane becomes impermeable; the axon is then said to be in a refractory period. Once permeability is restored, the whole process is reversed with Na^+ and Cl^- ions being pumped out and K^+ moves in to restore the negative potential, a process called repolarisation. Immediate restoration of ion balance, however, is not necessary for the passage of further impulses, and indeed, it is only after the passage of many impulses that an axon reaches a state where conduction ceases. This sequence of chemical events probably underlies the initiation of an electrical impulse at a receptor and the conduction of such an impulse along the axon.

The initial response of any sensory receptor which is detectable electrophysiologically after the application of the proper stimulus is the receptor potential (RP) (Loewenstein 1961). An understanding of the genesis of this potential, which is a localised depolarisation restricted to the receptor membrane, is essential for the description of the transducer mechanism. It is believed that the RP is generated through an increase, in the receptor membrane, of the conductance of Na^+, K^+, Ca^{++} and Cl^- ions (Loewenstein 1961). The most important ion that can bring about depolarisation, however, is the Na^+ ion, for only this ion has an equilibrium potential in a depolarising direction with respect to the resting potential. Consequently Na^+ ion must be the chief ion in the production of the RP (Wareham et al, 1974). The change of conductance of the ions across the receptor membrane is in turn caused by a change in the permeability of this membrane to these ions, especially to Na^+ ions in most sensory receptors and it is expected that this is achieved by various sensory receptors in different ways (Loewenstein 1961; Wareham et al, 1974). It is believed that the common component of the transducer mechanism of sense organs is a divalent Ca^{+2}-ATPase-Mg^{+2} cation, capable of configurational changes which controls ion permeability in a graded fashion

(Duncan 1967; Jilka and Martonosi 1977). This permeability control system is very sensitive to potential changes across the membrane. The receptor of a particular sense organ must have specialised so that the stimulus energy to that receptor is coupled to the ATPase system regulating the permeability across the membrane (Duncan 1981). If the same events occur at the thermal receptors, it is then possible that this permeability control system is either directly or indirectly modulated by the thermal stimuli to produce changes in the conductance of ions across the thermal receptor membrane. The permeability control system could be modulated by Ca^{+2} which leads to the activation of the ATPase (Loewenstein 1961; Wareham et al, 1974). Active ionic pumps are believed to underly the discharge of primate cold receptors (Pierau et al 1975a). Indirect support to this hypothesis comes from the finding that excitability and pattern of discharge of primate cold receptors were found to be influenced by their metabolic state and in particular their oxygen supply (Iggo and Paintal 1977), where the availability of ATP, produced by the oxidative metabolism, could be a factor in determining the level of the electrogenic Na^{+}/K^{+} pump. Ca^{+2} has also been implicated in the transducer mechanism of thermal receptors (Braun et al, 1980; Hensel 1981).

Both the amplitude and rise time of the RP are dependent on and graded to the stimulus intensity and, when investigated, a simple linear relationship existed between the amplitude of the RP and the frequency of the impulses generated for most receptors (Katz 1950; Loewenstein 1961; Duncan 1981), that is, stimuli of larger amplitudes evoked greater RP. When the amplitude of the RP reaches the physiological threshold, an action potential (AP) is then generated. This AP then depolarises the adjacent axon and in effect, the AP proceeds along the nerve axon in a continuous fashion but only if the axon does not have a myelin sheath as in the unmyelinated C fibres. In the presence of myelin and nodes, electrical activity occurs only at nodal areas where the axon is not invested by

myelin and the depolarisation jumps from one node to another in a process called 'saltatory conduction', leading to a faster conduction. If an electrode is put near the nerve at a more proximal point, the passage of the AP is recorded and referred to as an 'impulse'. Greater suprathreshold stimuli lead to RPs of faster rates of rise and larger amplitudes and these RPs evoke trains of APs, recorded more proximally as impulses, of higher frequencies (Duncan 1981).

As the identification of specific thermal receptors morphologically is difficult, they are not accessible and no intracutaneous recording with microelectrodes is available from these receptors. In 1938 Sand presented a model for the response of ampullae of Lorenzini to thermal stimulation. He proposed that two processes, one excitatory and one inhibitory are operating in the same time in the cold sensitive receptors. The balance between these two processes determines the response of the receptor. Both of these systems have a positive correlation with temperature but with different rates of response. On sudden cooling of the cold responsive receptors, the excitatory process falls much slower than the inhibitory one, resulting in excitation of this receptor by cooling and a sudden dynamic overshoot in frequency of impulses followed by a decline to a new static level. On the application of a rapid heating stimulus, opposite events occur. A strong support for this model came from the intracellular recordings from the pacemaker neurones in molluscs (Aplysia and Helix) by Braun et al (1980). These neurones show a temperature dependent regular or bursting steady discharge. The intracellular recordings from these neurones were combined with recordings from cold fibres in cats. These workers suggested that the inhibitory process of the cold receptor may be the activity of an electrogenic Na^+ pump which would respond to changes in temperature so that the net result is a hyperpolarisation of the receptor membrane with increasing temperature and a depolarisation with a decreasing

temperature. The excitatory system was thought to be the Na^+/K^+ permeability ratio, an increase in which will depolarise the receptor membrane (ie an increase in the RP). The static and dynamic frequencies of impulses from the cold receptors will then depend on the difference between the two processes (Pierau et al, 1975). For the explanation of the 'burst' discharges in the cold receptors, the presence of an oscillating RP exceeding the threshold, with a rate equal to the frequency of the 'bursts' of cold receptors (while the amplitude of the RP will still determine the frequency and number of impulses within each burst), is proposed by many authors (Iggo and Young 1975; Pierau et al 1975a,b; Bade et al, 1979; Braun et al, 1980). This oscillation was proposed by these workers to arise from periodic changes in the Na^+/K^+ permeability ratio, while the Na^+ pump is determining more the resting potential (Bade et al 1979; Braun et al 1980). The Na^+/K^+ permeability ratio was assumed to be additionally affected by Ca^{+2} through its effect on K^+ permeability. The latter in turn is dependent on the voltage and the temperature of the receptor membrane. These workers also postulated that the RP had a negative feedback on the Na^+/K^+ permeability ratio so that with increasing RP, the excitatory effect of this ratio is diminished and the inhibitory effect of the Na^+ pump is increased causing a reduction in the RP and ending the burst (Braun et al, 1980). At high temperature, it was proposed that an increasing hyperpolarisation of the resting RP occurs due to the increased activity of the temperature-dependent Na^+ pump, the inhibitory system, so that the amplitude of the RP finally fails to reach the threshold for initiation of the AP. Support for this model comes from the fact that in cats, Ca^{+2} inhibits the static 'bursts' of lingual cold fibres whereas EDTA, which lowers Ca^{+2} level through its chelating effect, increases the number of impulses per burst and converts a non-bursting cold fibre into a bursting one (Pierau et al, 1977; Schafer et al, 1978,1979; Schafer 1981). This implies that the level of Ca^{+2} plays an important effect on the generation

of 'burst' discharges of cold receptors. It is also known that intravenous Ca^{+2} inhibits the activity of cold receptors and enhances that of warm receptors (Hensel and Schafer 1974; Schafer et al, 1978,1979).

Physiological Mechanisms of Thermal Peripheral Nerve Fibres

Single unit electrophysiological methods provide a convenient method for tapping off the sensory impulses in the sensory fibres proximal to the receptors. At present, correlation of thermal sensations and events in the thermosensitive fibres in man is limited as there are insufficient data available from a large population of these fibres (Iggo 1984). Wherever needed, therefore, analogies from animal studies are used to fill the gap, despite the risk that such analogies might not be representative of what happens in man.

Although recording from single sensory units in lower animals was started in 1926 by Adrian and Zotterman (Adrian 1926; Adrian and Zotterman 1926a,b), the first detailed recording of single thermal units, in cats, were made in the early fifties (Hensel and Zotterman 1951a,b,c) followed by studies in monkeys and other mammals (Iggo 1963; Hensel 1969,1973; Sumino et al, 1973). The first single unit electrophysiological recording in man from single afferent nerve fibres, including thermosensitive units of dissected radial nerve in the conscious subject, was performed by Hensel and Boman in 1960. In 1967, Hagbarth and Vallbo introduced the technique of microneurography whereby direct recordings from intact human sensory units, including thermosensitive fibres, became possible by the insertion of a special microelectrode into the nerve in situ. Through the combination of these microneurographic recordings and the use of quantitatively controlled natural stimulation of the proper receptors in the skin, large amount of useful data have been collected about receptor mechanisms in human (Vallbo et al, 1979).

Contrary to the voluminous data available on large myelinated fibres, the thermosensitive fibres have been relatively elusive in this technique, and useful but limited numbers of these fibres have been investigated to date (Hagbarth 1979; Vallbo et al, 1979; Hensel 1981). In his review, Jarvilehto (1977) pointed out the fact that the data from this method might be biased by fibre selection, in addition to other limitations of the technique. Despite these limitations, many specific heat and cold fibres from the hairy skin of man have been studied in detail by microneurography (Konietzny and Hensel 1975,1977,1978,1980; Jarvilehto and Hamalainen 1980; Hensel 1980; Konietzny 1981). Most of these workers used stimulators constructed from Peltier elements for the quantitative stimulation of the cold and heat receptors in the skin. Various sized stimulators could be made which were capable of precise control of the temperature of the skin between 5-45°C, of accurate application of heat or cold stimuli of up to 20°C, at the required rate of change of temperature between 0.05-2°C/s. The thermal stimuli were monitored on storage oscilloscopes and stored on FM magnetic tape together with the recorded afferent impulses (Hensel 1981). Testing for thermal specificity was performed (see Properties of Thermal Receptors, Chapter 1) before recordings were done.

Physiology of Thermal Fibres at Static Skin Temperatures

At the skin temperature of 30-36°C, many warm and cold fibres have been shown to discharge continuously at a low rate of 1-6 impulses per second (average 3) both in humans (Hensel and Boman 1960; Kanietzny and Hensel 1975,1977,1980) and in monkeys (Darian-Smith et al, 1973,1979; Kenshalo and Duclaux 1977; Duclaux and Kenshalo 1980). If the static temperature of the skin is changed to a higher or a lower temperature in the range of 25-45°C, the firing rate in the two groups of warm and cold fibres change reciprocally. Increasing the static temperature of the skin very slowly

from 36°C to 45°C increases the number of impulses in single warm units from 3 to 12 impulses per second on average (Konietzny and Hensel 1975,1978,1980). At the same time, as the static skin temperature goes higher, cold sensitive units firing gradually decrease before stopping completely (Hensen and Boman 1960). Konietzny and Hensel (1978,1980) noted that half of the heat specific fibres of human at static temperatures of 30-33°C showed this spontaneous activity. Their activity reached its maximum level at 7-9 impulses per second when the static skin temperature was raised to values of 40-43°C. The remaining half of the heat fibres started their static activity at skin temperatures between 35-38°C and they reached their maximum static activity of 8-12 impulses per second at skin temperature between 40-46°C. Above this temperature of 46°C the static discharge frequency falls and finally stops and a different group of fibres start responding in the painful range of static skin temperature. These fibres are called the 'polymodal nociceptors' as they respond not only to painful thermal but also to noxious mechanical and chemical stimuli (Konietzny and Hensel 1980). These findings in human beings have also been observed in monkeys (Hensel and Iggo 1971; Sumino et al, 1973; La Motte and Campbell 1978).

Activity of a few specific cold receptors has been recorded from the hairy skin of human hand (Hensel and Boman 1960; Hensel 1980; Jarvilehto and Hamalainen 1980; Konietzny 1981). From dissected radial nerve in conscious human, Hensel and Boman (1960) reported the details of responses of specific cold fibres. At constant skin temperatures between 29-32°C, a regular impulse frequency in the cold fibre was seen. Such a static frequency of the cold units, 1.5-3 impulses per second, increased on lowering the skin temperature. Half of the cold units reached their maximum static frequency at constant skin temperatures between 15-27°C. Meanwhile, decreasing the skin temperature caused a reduction in the static frequency of heat fibres (Konietzny and Hensel 1975,1977,1980). The maximum

static frequency was always lower in the cold than in the heat units (Jarvilehto and Hamalainen 1980). With decline in skin temperature to a static level of 20°C or below, the heat fibres completely cease to fire (Konietzny and Hensel 1980; Hensel 1981) and the cold fibre discharge also falls off (Hensel and Boman 1960). The total number of cold units investigated in humans, about 21 (Hensel and Bowman 1960; Hensel 1980,1981; Jarvilehto and Hamalainen 1980) is not large enough to draw firm conclusions on the behaviour of cold receptors in man. Dykes (1975) in his studies on cats and monkeys found the maximum static frequency of cold units discharge to be at skin temperatures between 25-30°C, but scattered over a temperature range of 0-40°C. In the monkey (Iggo 1969; Hensel and Iggo 1971; Dykes 1975) and in cats (Bade et al, 1979; Braun et al, 1980; Schafer 1981; Hensel and Schafer 1982), most of the cold units exhibited a typical pattern of discharge, the characteristic 'bursts'. This phenomenon was seen at static skin temperatures in the range of 20-30°C with a close relation to the steady skin temperature in this range. The characters of the bursts including the average number of impulses in and the duration of each burst, and the interval between successive bursts, were found to closely correlate with the static skin temperature in this range (Iggo 1969; Dykes 1975; Bade et al, 1979; Braun et al, 1980). At skin temperatures between 20-30°C, each burst was found to consist of 2-12 impulses (Iggo 1969; Bade et al, 1979). At lower skin temperatures, below 20°C, the burst discharges become irregular and then disappear. On increasing the static skin temperature again regular bursts are resumed which, if the static temperature is raised, are converted into regular single impulses with disappearance of the bursts. Further rise in static skin temperature causes the cold units to cease firing altogether (Iggo 1969). The constant skin temperatures at which these changes occur are variable for different cold units (Iggo 1969; Dykes 1975; Bade et al,

1979). In man, this phenomenon of burst discharge was not found and all the cold units tested were found to discharge impulses at regular frequency (Hensel and Boman 1960; Hensel 1980; Jarvilehto and Hamalainen 1980).

Physiology of Thermal Fibres with Dynamic* Changes of Skin Temperature

Heat and cold receptors are sensitive to rapid rather than slow changes of temperature (Hensel and Boman 1960; Darian-Smith et al, 1973,1979; Konietzny and Hensel 1975,1977,1980; Kenshalo and Duclaux 1977; Duclaux and Kenshalo 1980; Jarvilehto and Hamalainen 1980). Microneurographic recordings of single human heat units showed that starting from a constant adapting skin temperature of 30-36°C, linear temperature rises led to transient dynamic overshoot of impulse frequency in these units (Konietzny and Hensel 1975,1977, 1980). This was followed by adaptation to a new static frequency discharge after a certain period of time. When applying a linear heat stimulus of 5°C at a rate of 1•5°C/s to human skin with adapting temperature of 32-37°C, the new static frequency level was obtained after 30 seconds (Konietzny and Hensel 1977). The transient dynamic overshoot of any tested heat unit had a remarkable constancy when the same stimulus was repeated (Konietzny and Hensel 1975,1977; Hensel 1980,1981). Cooling of the receptive field of the heat unit caused a transient drop of the static frequency to a new level. Within the non-painful range of temperature, up to 46-48°C, the dynamic overshoot in the frequency of impulses of human heat units was found to be proportional to the magnitude of the heat stimulus in a linear pattern, when the rate of change of the heat stimulus and the adapting skin temperature were constant (Konietzny and Hensel 1975,1977,1980). This dynamic overshoot was also

* The word 'dynamic' is used to refer to the temporal and spatial distributions of the thermal stimulus (heat or cold) and its amount. For thermal units it refers to the temporal and spatial distributions of the impulse activity set in motion by these thermal stimuli.

found to be dependent on the adapting skin temperature, even when the magnitude or the rate of the change of the stimulating temperature stayed constant (Konietzny and Hensel 1977,1980; Hensel 1980,1981). The dynamic overshoot of heat units was also dependent on the rate of the change of stimulating temperature. When the temperature stimulus was linearly increased by different rates from the same adapting skin temperatures to equal final magnitudes, the dynamic overshoot in frequency of impulses of the heat units increased with higher rates of temperature changes (Konietzny and Hensel 1977). Slower rates of temperature change required a longer period to reach the human threshold of heat sensation and a larger total number of impulses, which were at slower frequency, than did faster rates of temperature change (Konietzny and Hensel 1977,1980). An analogous dependence of the dynamic response on the initial temperature, rate of change and magnitude of the stimulus has been found for warm receptors in animals (Hensel and Kenshalo 1969; Hensel and Huopaniemi 1969; Sumino et al 1973; Kenshalo 1976; Darian-Smith et al, 1979; Duclaux and Kenshalo 1980).

Sudden cooling of the receptive fields of human cold units resulted in a transient dynamic increase in the frequency of impulses in these units (Hensel and Boman 1960; Konietzny 1981). As with the heat units, the increase in dynamic frequency was dependent on the magnitude and rate of change of the cooling stimulus and on the adapting skin temperature (Hensel and Boman 1960; Hensel 1973,1982; Molinari and Kenshalo 1977; Konietzny 1981). When the receptor fields of these cold units were warmed, the discharge stopped and after some time reappeared with a gradual increase in frequency until a new static level was reached (Hensel and Boman 1960). On 10°C rapid cooling, a vigorous dynamic overshoot of impulse frequency to 80/second was seen, after which the discharge adapted gradually. In only few occasions (Iggo 1984) human specific cold units responded to rapid cooling by 'burst' discharges seen in monkeys (Iggo 1969; Kenshalo 1976)

and cats (Kenshalo 1975). Until larger number of human cold units are investigated, uncertainty remains as to whether or not 'burst' phenomenon is also a character of human cold units' response to dynamic cooling.

In conclusion, human heat and cold units exhibit a remarkable constancy in their dynamic responses to similar temperature pulses from similar adapting temperatures. There is a very good relation between the parameters of units response and the intensity of these thermal stimuli. All the responses in human units were found to be regular in nature and no burst phenomena were observed.

Thermal Receptor Coding of Intensity and Other Parameters of the Stimulus

The purpose of this section is to present, in a framework of operating principles, the way by which thermal receptors integrate and encode, in their signals, the characters of the stimuli to the central nervous system. In this context, coding of dynamic changes of skin temperature is considered in detail more than the less relevant, to this thesis, coding of static skin temperatures.

The physical measurable parameters of the thermal stimuli including intensity, location, spatial distribution and temporal dispersion in addition to the type of the stimuli are all items to be coded in the responses of the peripheral apparatus. To explain the code of 'what' kind of stimulus in the peripheral units, some authors have advocated a 'pattern theory' instead of the widely acceptable 'specificity theory'. The former assumes that production of each specific quality of somatic sensation depends on the presence of specific patterns of activation of the peripheral afferent units and on specific patterns of neural discharges evoked in these units. The patterning could comprise variations in the frequency and specific configurations of temporal and/or spatial distribution of these discharges in addition to the relative numbers of the peripheral units activated. Each of the peripheral afferent fibres,

therefore, is hypothesised to respond non-specifically to different physical stimuli at the periphery. The present evidence, however, overwhelmingly supports the concept of specificity of the response of the first order peripheral afferent units rather than their non-specificity to natural stimuli (Iggo 1965,1982a,1984; Perl 1968; Light and Perl 1984). In addition, recent single unit electrophysiological recordings of cortical responses to peripheral stimuli also suggest that each quality is represented in a separate type of vertical column of cells in the somatosensory cortex. Such a columnar arrangement has been demonstrated at least for different types of mechanoreceptors (Mountcastle 1957; Powell and Mountcastle 1959) and visual and auditory areas (Hubel and Wiesel 1969; Werner and Whitsel 1973) and is discernable histologically (Libet 1973). The 'specificity theory', therefore, assumes that different modalities of somatic sensation stem from the activation, by the specific stimuli, of specific types of receptors in the skin. This theory assumes that the central nervous system acts as though each receptor and the connected axon had a label; that the CNS 'knows' or 'assumes' that any signals arriving from a given afferent axon represent stimuli of special type within a certain receptive field. This peripheral unit (the receptor and the connected axon) is labelled to the CNS in terms of both the modality and the location of the stimulus. This is, however, the more modern name for the principles originally introduced for the first time by Johannes Muller in 1838 under 'the law of specific nerve energies' and advocated and modified by von Frey (1895). The labels for the optic and auditory sensations for example are unambiguous, but whether this concept of 'labelled lines' entirely applies to the somatosensory receptors is still in debate by proponents of the pattern theory. As reviewed in these two Chapters, although there may be some discreteness, more ambiguity and to some extent a multimodality in the labels of the somatosensory systems, the

recent studies on man and lower animals are entirely in favour of the specificity theory. Labels may partially overlap; many receptors and afferent fibres from them exhibit some overlap either in forms of stimuli which can excite them or in the topography of their receptive fields. This only means that there may be some degree of redundancy but this is incomplete and therefore there is at least a partial uniqueness for each peripheral unit in the nervous system.

In their early studies, Adrian and Zotterman (1926a,b) noted that the discharge frequency of the afferent fibres increases with increasing stimulus intensity. This is called the 'frequency code' for the stimulus intensity. Stimuli of greater intensity evoked larger generator potentials, which cause an increase in the total number and frequency of evoked action potentials (Loewenstein 1961; Duncan 1981). For most afferents, a graph of discharge frequency of the unit as a function of stimulus intensity is almost similar to the psychophysical magnitude estimation, that is the stimulus intensity is coded as a variable mean frequency of nerve impulses. A stimulus of increasing intensity also activates a greater number of receptors, 'the population code' for stimulus intensity. Therefore, as the intensity of the stimulus increases, it is coded in two ways; an increase in impulses in each afferent fibre and an increase in the number of activated afferent fibres of the same population. The afferent fibres act as information channels or lines of communication which carry the intensity code to the CNS.

An outstanding feature of thermal sensation in the human is his ability to discriminate rapid changes of skin temperature with high resolution (Johnson et al, 1973,1979). Coding of the intensity of thermal stimuli is believed to be on the same lines as for other somatosensory modalities, the principles of which were outlined above (Hensel 1980,1981). The quantitative features of the receptor mechanism remain the most important to account for coding of the stimulus from its origin. Among the

especially relevant features is the transfer function between the graded RP and the APs produced in the axons carrying thermal sensation in man and our knowledge of this is at present limited. From the investigation of specific heat and cold units in the human, it is clear that the general principle of frequency and population coding of stimulus intensity applies to the sensation provoked by changes of the temperature of the skin (Hensel and Boman 1960; Konietzny and Hensel 1975,1977,1980; Jarvilehto and Hamalainen 1980; Hensel 1981; Konietzny 1981). These authors, however, were able to investigate only a limited number of cold and heat units. It is, therefore, necessary to refer to analogous studies performed on higher mammals. In a series of studies, Darian-Smith, Johnson and colleagues correlated the human observers' measure of resolution of relatively small increments of stimulus intensity of cold (Johnson et al, 1973; Darian-Smith et al, 1975,1979; Darian-Smith 1980) and heat (Darian-Smith 1977; Johnson et al, 1979; Darian-Smith et al, 1979) to trains of impulses obtained from specific cold and heat fibres, respectively, of the monkey subjected to identical stimuli to those of the human. In their work, they analysed the neural response of single and populations of thermal units. In these studies and in others (Brearley and Kenshalo 1970; Cain 1973; Braun et al, 1980) it was found that many parameters for single heat and cold unit responses are closely correlated, and that the impulses are remarkably regular and the amplitude of the temperature stimuli applied has little effect on the profile of these responses. It was then assumed that peripheral thermal units' signals are, in general, similar and send little independent information about the stimulus from each other (Johnson et al, 1973,1979). On increasing the stimulus intensity, a larger number of peripheral units are activated (Johnson et al, 1973,1979; Konietzny and Hensel 1980). It must be assumed, therefore, that most of the information about the intensity of the temperature stimulus is signalled in the

peripheral units in terms of the rate of occurrence of these impulses during a specified unit time (Darian-Smith et al, 1975). Good correlation was found between the cumulative impulse count during three seconds from the onset of the cooling stimulus from monkeys' specific cold unit and the human judgement of intensity (Darian-Smith et al, 1973,1975; Johnson et al, 1973). The more recent work of Darian-Smith, Johnson and their coworkers, however, suggested that intensity resolution achieved by man requires more information than is supplied to the CNS by individual peripheral units and that input from a number of responding peripheral units must be used by the brain to account for the discrimination of the intensity of these stimuli (Darian-Smith et al, 1979; Johnson et al, 1979). Under most natural circumstances, thermal stimuli activate a population of primary afferent fibres (Hensel 1981). On the application of thermal stimuli of equal magnitude but of different rates of change of temperature between 0.4-5°C/s, to the skin at the same adapted temperature, it was found that the estimated amount of sensation was not linearly related to the rate of change of temperature (Molinari et al, 1977). The peak frequency of discharge clearly increases with an increase in the rate of change of temperature in humans (Konietzny and Hensel 1977). Kenshalo (1976), however, demonstrated the presence of very good linear correlation between the cumulative number of impulses in peripheral thermal units of the monkey during the period of change of temperature and the magnitude of the stimulus judged by human subjects. It is also possible that in addition to the frequency and fibre population codes of stimulus intensity, there are other codes which might be involved such as changes in the interval variance or a closely related microstructure code in which some fine graded temporal pattern may develop and convey information without changing the mean frequency of discharge. There is, however, no evidence as yet for the presence of such codes. It remains to be seen whether decoding in the CNS of man conforms to the presumed parameters of coding.

From several studies on the human (Hensel and Boman 1960; Konietzny and Hensel 1975,1977,1980; Beste 1977) and on cats and monkeys (Dykes 1975) it was found that the mean static frequency of cold or warm fibres is not closely correlated to the skin temperature. The maxima at which various cold as well as heat units discharge are scattered on a wide range of static skin temperatures (Hensel and Boman 1960; Dykes 1975; Beste 1977; Konietzny and Hensel 1980; Hensel 1981). In contrast, human judgement of static skin temperatures is good (Beste 1977). In 1973, Erickson and Poulos forwarded their theory of 'across fibre pattern' to explain the peripheral coding of the static skin temperatures, whereby the presence of a spectral distribution of the static neural discharge activity of single cold fibres (or warm fibres) leads to different across-fibre patterns for cold (or warm) fibre population at various low skin temperatures. The recent work of Hensel (1980) in which a calculated 'integrated frequency' of cold fibres correlated well with the static skin temperature of cat's nose for temperatures between 10-40°C, supplied some support for this theory. However, there is, as yet, no universally accepted experimentally supported coding system for static skin temperatures.

In conclusion, few important features characterise any thermal stimulus; the direction of the change of intracutaneous temperature and the amount and rate of this change, the area of the skin stimulated and the duration of the thermal stimulation. The excitation mechanism, therefore, can be represented by a three dimensional system of thermal-spatial-temporal factors which are dependent on each other and to a great deal are exchangeable. From the very beginning of electrophysiology, electrical recordings have suggested a general similarity in the recorded impulses of various nerve fibres. It is therefore reasonable to assume that functional differences in the messages transmitted by various afferents are probably derived from (1) the presence of specific 'labelled lines' which explain

the codes of 'what' and 'where' and (2) the frequency of activity and fibre population activation for the code of intensity or 'how much'. Another code might be derived from the processing of the impulses by the CNS, eg nature of the synaptic junctions, variation in the types and locations of the central neurones activated by these impulses etc.

Central Mechanisms of Thermal Sensation

The exact mechanism by which the brain combines, integrates and interprets all the stimulus information signalled by the specific thermal peripheral units is still a mystery (Hensel 1981). Whether the transport of impulses along the central pathways to the forebrain is accompanied by any degree of processing in the spinal cord, brainstem or thalamus, whether there is simple averaging process in the CNS of all the peripheral responses in 'the integration process' or whether the brain is selective and giving maximal 'consideration' to those fibres which are disproportionately stimulated stronger and relaying the most sensory information, is still unknown. The central thermal single unit studies showed that the higher the unit in the CNS, the larger the receptive field on the surface of skin was found to be (see Chapter 1). Such a finding indicates the presence of excitatory convergence on all levels in the CNS neurones (Darian-Smith et al, 1973; Iggo and Ramsay 1974,1976; Kumazawa and Perl 1978). By this process of convergence, the CNS may achieve the equivalent of simple summing of responses of various peripheral units. The selectiveness of the brain in giving disproportionate consideration to certain peripheral units with maximal input could be achieved through the interaction of various inhibitory processes and connections along the pathway of information transfer in the CNS. An example of such a process is the phenomenon of 'surround inhibition' demonstrated in the mechanoreceptors (Schmidt 1973). In this phenomenon there is inhibitory interaction in the CNS from the neurone connected to the maximally

stimulated peripheral unit to the adjacent neurones connected to adjacent peripheral units which are less intensely stimulated. The phenomenon of surround inhibition is, as yet, not demonstrated in thermosensitive neurones. In any sensory system, however, due to the presence of many divergent and convergent connections in the sensory pathway, a single stimulus might spread progressively in higher levels in the CNS causing the representation of the point stimulus to become enlarged, less precise in spatial distribution and more diffuse. Such a situation is not present in normal conditions. This is probably prevented through the presence of characteristic spatial organisation of inhibitory connections, similar to the description of lateral or surround inhibition, whereby the neurone with greatest afferent input imposes strong inhibition on its neighbours. This leads to a reduction of excitation at sites away from the centre of stimulation. This inhibition might exist at all levels of sensory systems, in the dorsal horn, in the brainstem, in the thalamus and perhaps in the cortex. This phenomenon results in an improvement and maintenance of the sharpness of localisation of the stimulus by the CNS.

All the sensory pathways, including thermal sensation, end in the cerebral cortex since conscious experience in man depends on the presence of cortex (Werner and Whitsel 1973). Electrophysiological analysis of the CNS has convincingly demonstrated the existence of special receiving areas in the cerebral cortex for somatovisceral sensory input (Werner and Whitsel 1973). The broad separation of the large myelinated sensory fibres, known to serve the mechanoreceptors in the skin which at segmental levels may send collaterals only into the deeper levels of the dorsal horn, from the smaller myelinated and unmyelinated fibres that end superficially in the dorsal horn, is now well documented (Chapter 1). The incoming sensory information excites the second order neurones in the dorsal horn (Chapter 1). The effectiveness of the input depends on the excitability of these

neurones and the enhancement or reduction of this excitation by excitatory or inhibitory synapses of either local (segmental) or remote (descending) origin (Wall 1973; Werner and Whitsel 1973). In addition there may be presynaptic actions that can reduce the effectiveness of a sensory input by lowering the synaptic potency (Schmidt 1973). It is, therefore, possible that at every station of the thermal pathway, the afferent inputs are subjected to excitation or inhibition of individual neurones as well as interaction among neurones or groups of neurones. The outcome of the various interactions may significantly modify the sensory input as it ascends in the central pathways. Single unit electrophysiological studies have shown that the specialisation in the peripheral thermal units is preserved at least to some degree in the higher neurones (Poulos and Benjamin 1968; Hellon and Misra 1973; Hellon et al, 1973; Hellon and Mitchell 1975; Dostrovsky and Hellon 1978). Thermosensitive neurones in the superficial layer of the spinal dorsal horn, exhibiting the same specialisation and responses as peripheral units, have been demonstrated (Christensen and Perl 1970; Kumazawa and Perl 1976,1978; Kumazawa et al, 1975; Iggo and Ramsay 1976). The cold responsive neurones of the dorsal horn which were excited only by moderate cooling, shown to have a sustained discharge at skin temperature of 27°C (a temperature at which peripheral cold units are very active), had a powerful burst of activity on dynamic cooling of the skin and stopped discharging when the skin was warmed to 40°C (Iggo and Ramsay 1976; Kumazawa and Perl 1978). There is, however, increasing evidence that a complex interaction can occur, involving some neurones upon which many different kinds of afferent neurones converge and also a large number of small interneurones in the substantia gelatinosa that have a modulating activity on the sensory output from the dorsal horn (Willis and Coggeshall 1978; Cervero and Iggo 1980).

More or less similar thermosensitive neurones to those found in the spinal dorsal horn are present in the brainstem trigeminal complex (Poulos

and Molt 1976; Poulos et al, 1979; Dostrovsky and Hellon 1978) and in thalamic and cortical centres (Burton et al, 1970; Landergen 1970; Hellon and Misra 1973; Hellon et al, 1973; Hellon and Mitchell 1975, Light and Perl 1979b). At its first appearance, the sensory input to the primary sensory cortex is believed to retain both its topographical and functional identity, but this is perhaps progressively lost and blurred in the surrounding cortical areas in which a great detail of interactive processing occur (Jones and Powell 1973; Werner and Whitsel 1973; Mountcastle 1974) which is possibly the site of the mysterious conversion of the nerve impulses into sensations.

How many impulses from the periphery correspond to conscious threshold thermal sensation? In electrophysiological studies, it was found that even when the skin temperature was between 30-36^{o}C, in the neutral zone where no thermal sensation is experienced, both cold and heat fibres discharged impulses (Hensel and Boman 1960; Konietzny and Hensel 1980; Konietzny 1981). Thus the presence of receptor activity alone, at least at low frequencies, does not necessarily give rise to subjective thermal sensation. It is also true that when small areas of skin are stimulated with small temperature changes, cold and heat units may be excited without conscious sensation (Konietzny and Hensel 1980). These facts led Hensel (1974) to introduce the concept of 'the central threshold'. This implies that conscious thermal sensation does not arise until a certain number of impulses, with certain spatial distribution, arrive in the CNS within a certain period of time. This central threshold is considerably larger than the threshold of single thermal receptor excitation. An attempt to determine this central threshold for a single peripheral cold unit in human was made by Jarvilehto (1973) by comparison with the activity of nasal cold fibres in the cat under identical stimulus conditions. The threshold of conscious cold sensation from a human cold spot corresponded with an

instantaneous frequency of 80 impulses per second or a total of 120 impulses in a single cold fibre of the cat. The cold sensation stayed for sometime after the drop in impulse frequency indicating that the central threshold depends not only on the instantaneous frequency but also on the number of impulses integrated over a certain period of time. Konietzny (1981) compared in humans single heat fibre activity to conscious thermal sensation. A single warm spot was stimulated with a small thermode starting from an adapting skin temperature of 35°C at a rate of 0.8°C/s. An instantaneous frequency of 9 impulses per second or a total number of 28 impulses in the single heat fibre corresponded to the first feeling of warm sensation. When the rate of change was slowed the total number of impulses needed before conscious sensation occurred was much higher. Similar results were found by Kenshalo (1976) in his experiments on man and monkey.

In conclusion, it is well known that activation of the peripheral thermal receptors is responsible for the occurrence of thermal sensation. The receptive activity, however, is reflected in conscious temperature sensation only after considerable CNS integration and processing of this activity from the periphery. Our knowledge of such CNS processing is at present extremely limited. There is accumulating evidence from single and population peripheral unit electrophysiological-psychophysical studies that a certain number of impulses with certain spatial configuration within a certain period of time should reach the CNS from the peripheral receptors for conscious sensation to occur.

The Response of Thermal Receptors to Noxious Thermal Stimuli

Most normal human subjects report pain when the skin temperature is raised higher than 45-48°C (La Motte and Campbell 1978; Hensel 1981) and this painful sensation increases as the skin temperature is further raised. Studies on monkeys have shown a similar finding (Beitel and Dubner 1976; Beitel et al, 1977). A decrease in the human skin temperature to below

20°C also becomes increasingly painful (Beste 1977) with similar findings observed in monkeys (Dykes 1975).

In the monkey a sudden rise in the temperature of skin from a basic value of 30°C to above 48°C was found to evoke only few heat fibres but mainly the nociceptor fibres (La Motte and Campbell 1978). The response of the warm fibres was found to increase linearly with the magnitude of the stimulus pulse when the skin temperature was raised to the value of 45-47°C. A sudden increase to 48-50°C caused the warm fibres to discharge vigorously at the start but they quickly stopped. Sudden heating pulse rises up to 50-51°C failed to elicit any response in the heat fibres (Sumino et al, 1973; Dubner et al, 1975; Beitel and Dubner 1976; La Motte and Campbell 1978; Darian-Smith et al, 1979). At skin temperature of 50°C only 15% of warm fibres were found to be responsive and at 53-54°C, even this 15% completely ceased to show activity (Beitel and Dubner 1976; La Motte and Campbell 1978). Above the temperature of 47-50°C, at which the activity of heat fibres cease, the quality of sensation enters into the painful range (La Motte and Campbell 1978). The nociceptor fibres, in contrast, are silent at temperatures below 45°C but begin to discharge above 45-47°C with their frequency increasing progressively with increasing intensity of stimulation (Perl 1968; Bessou and Perl 1969; La Motte and Campbell 1978).

In the cat, there are a number of cold fibres which possess some activity at temperatures as low as 5°C (Duclaux et al, 1980). It is not known, as yet, whether similar fibres exist in the human being. At temperatures below 20°C, nociceptive fibres especially responsive to noxious cooling show activity the amount of which increases with increasing intensity of cooling (Iggo and Ogawa 1971). Polymodal nociceptors similar to those of cats and monkeys have been found in human beings (Torebjork 1974; Torebjork and Hallin 1974).

CHAPTER 3

THE MEASUREMENT OF THERMAL SENSATION

The system of thermal sensation includes three main aspects; the phenomenon of perception of changes in skin temperature, the physical stimulus and the occurrence of neural events in the sensory pathways. The physiology of thermal sensation, therefore, includes not only the investigation of thermal stimuli and the accompanied changes in thermosensitive neurones, but also, and most important, the phenomenon of temperature sensation (Hensel 1974). Thermal sensation arises as a result of the stimulation of specific endorgans in the skin by thermal stimuli which initiate a series of activities and impulses in the neurones constituting the thermal pathway. This phenomenon of perception of sensation, though dependent on the occurrence of such neural activities in the thermal pathways is complex and its relationship with these neural activities is not straightforward. On the other hand, our knowledge of the neural events, especially in the central thermosensitive neurones, is fragmentary and studies of these physiological events alone even in the best circumstances, only offer a limited investigation of thermal sensation. The phenomenon of sensation and its correlation with the physical stimuli are more completely described, analysed and measured by the use of 'psychophysics'. Such studies include determination of threshold for detecting the thermal stimuli and various other aspects. Objective sensory physiology confined to the relationship between physical parameters and the neural events in the sensory pathway, without referring to the phenomenon of sensation is mainly carried out on laboratory animals. Because of the difficulty of recording from conscious human subjects, correlative study of the three aspects of thermal sensation has only been possible by using human subjects for the psychophysical observations while the afferent neurophysiological recordings were obtained from experimental

animals subjected to stimuli identical to those of the human subject (Darian-Smith et al, 1973,1979; Johnson et al 1973,1979; La Motte and Campbell 1978; Kenshalo et al, 1980). A direct combination in the study of all the three aspects is only possible in human beings through the recently introduced technique of microneurography (Hagbarth and Vallbo 1967; Knutsson and Widen 1967) or by microdissection of human nerves (Hensel and Boman 1960). Microneurography, in which recording is made from single afferent fibres in conscious human, has the advantage that the subject is able to communicate verbally concerning his sensory experience while simultaneously afferent fibre response patterns are assessed neurophysiologically (Vallbo et al, 1979). The technique of microneurography, however, has serious limitations especially for the small diameter nerve fibres (Jarvilehto 1977). Action potentials from small fibres are frequently masked by potentials from the larger fibres (Jarvilehto 1977; Vallbo et al, 1979). The technique is also too selective and what is recorded, even if successful, might not be representative of the whole (Jarvilehto 1977). The result, therefore, can be biased by preparation and recording techniques and it does not represent analysis of the activity of a statistically random sample of the population. It is difficult to decide whether the neurographic recordings give a true picture of the neural activity in a particular sensation. Limitation of the stimulus to the receptive field of a single afferent fibre might be difficult and additional fibres may be involved in the sensation, particularly in the range of higher intensities of the thermal stimuli. The technique is also very difficult, time consuming and needs special training and expertise which limits its application.

The somatic sensory systems including the thermal system, are not only remarkably sensitive in detecting the occurrence of a stimulus specific to that system, the threshold, but these systems also provide information

concerning the magnitude of the applied stimulus. Man is able to discriminate between stimuli of various intensities and to estimate such intensities accurately. These properties could be effectively utilised in the development of techniques which accurately measure the performance of the thermal sensory system.

Psychophysics of Thermal Sensation

A quantification of the correlation between the physical events of thermal stimuli and the sensory phenomenon of thermal perception is performed through psychophysical studies. Such investigations allow establishment of the limits of performance and the overall function of the neural machinery comprising the thermal sensory system and quantitate the response of such a system to the specific physical stimuli. Psychophysics also provides a powerful experimental tool for correlating behaviour with the physiological properties of the neurones comprising the sensory system by providing quantitative methods for investigating sensory phenomena (Kenshalo et al, 1980).

The early psychophysical investigations dealing with temperature sensation led to findings of cold and warm spots (Blix 1882,1884) and later refinement of these findings (Rein 1925a; Strughold and Porz 1931; Skramlik 1937). These studies, though very important at the time, did not quantitate the sensation of temperature. With the introduction of the electrophysiological identification, in experimental animals, of single cold (Zotterman 1953) and warm (Hensel 1952a; Iriuchijima and Zotterman 1960) fibres, little interest remained in the investigation of these warm and cold spots. More important quantitative psychophysical studies of temperature sensation were initiated by Hardy and Oppel who introduced for the first time means for controlling thermal stimuli from radiation sources to reasonable accuracy before their application (Hardy and Oppel 1937,1938; Oppel and Hardy 1937a,b). More sophisticated and accurate instruments for

the quantification of thermal stimuli were introduced later.

In quantitative psychophysical studies, two important criteria are measured and are closely correlated to the physiological properties of the specific afferent neurones; the absolute threshold and the suprathreshold magnitude-estimation of the sensation (Stevens 1957; Stevens and Galanter 1957; Galanter 1977). The absolute threshold is defined as the just noticeable sensation when starting from a zero level of this sensation. The magnitude-estimation is concerned with the quantification of intensity of the sensation, at suprathreshold levels and its correlation with the intensity of the stimuli to identify whether the resolving power of the system is maintained or defective. The magnitude-estimation of the sensation could be denoted by a subjectively estimated number on a scale or by a more complicated phenomenal scaling. One such method widely used in psychophysical studies is the differential threshold, defined as the just noticeable change in intensity (or quality) of an already existing sensation. Measurement of sequential differential thresholds provides useful information about the subject's capacity to resolve small differences in the intensity of the same quality of stimuli. Psychophysical experiments designed to measure this capacity do so in statistical terms as a function relating the actual increments in the stimulus intensity to the probability that the subject will judge the more intense of a pair of stimuli to be the larger, the classical psychometric function from which the sequential differential threshold may be derived (Johnson et al, 1973,1979). Darian-Smith and Dykes (1971) studied the relationship between subjective magnitude-estimation of the amplitude of stepwise cooling, applied to the human thenar eminence adapted to the temperature of 34°C, and the actual amplitudes of the cooling stimuli. The subjective magnitude was found to be linearly correlated with the actual amplitude of cooling stimuli over the range of 0-10°C. Below 10°C, cold

pain sensation starts, and the relation was no longer linear (Darian-Smith and Dykes 1971). The linearity of the correlation, in the range of 0-10°C, remained the same starting from adapting temperatures between 32-35°C.. The correlation between subjective sensory magnitude-estimation and intensity of warm-heat stimuli was also studied and the relation was also found to be linear, at adapting skin temperatures of 34-35°C, but only up to the skin temperature of 45°C (Darian-Smith and Dykes 1971; La Motte and Campbell 1978). At or above the latter temperature, pain rather than heat sensation is commonly reported and coincidently the form of the psychophysical function is no longer linear (La Motte and Campbell 1978). Spatial summation was found to be an important determinant not only for the detection, at threshold levels, but also for the scaling of sensation produced by thermal stimuli (Stevens et al, 1974). This effect of spatial summation is more apparent with low intensity stimuli at or just above threshold levels and it progressively falls off with stimuli of increasing intensity until it virtually disappears when the thermal stimulus becomes noxious (Stevens et al, 1974). In many studies of magnitude-estimation of thermal sensation in man, curves of subjective estimates of magnitude of sensation as a function of stimulus intensity closely parallel those curves plotting the afferent fibre discharges, representing intensity functions of these fibres, against the stimulus intensity (Darian-Smith and Dykes 1971; Darian-Smith et al, 1973,1979; Johnson et al, 1973,1979; La Motte and Campbell 1978). In these studies, therefore, a close correlation between the perceived magnitude of stimulus intensity and the rate of impulse firing in thermosensitive afferent fibres and their recruitment was usually present. The primary justification for the use of quantitative psychophysical studies of threshold and magnitude-estimation is that the data appear to be systematic, reproducible, easily interpretable and closely related to the amount of neural activity in the specific thermoreceptive fibres stimulated. The use of the absolute threshold

estimation in the clinical situation, therefore, continues to be a useful psychophysical method for the investigation of thermal or indeed any other somatic sensory system.

Psychophysical Methods of Threshold Detection in Clinical Practice

Measurement of the detection threshold is by far the most frequently used method in quantitative psychophysical studies in clinical practice to accurately test the performance, the overall function and the physiological properties of the neural complex comprising the thermal (and other somatic) sensory system (Lindblom 1981). An increasing interest of its use in clinical neurology has been evident in the recent years (Lindblom 1981; Dyck et al, 1984). The absolute threshold for a sensation is defined as the smallest stimulus that just produces a sensation. An important point in the measurement of sensory threshold is the presentation of a pure, effective and accurately quantified series of stimuli so that the experimental subject can reliably discriminate and detect such stimuli. Due to small fluctuations in the magnitude of the presented stimuli and changes in the subject over time, threshold determination is necessarily a statistical concept and is the average of responses to repeated presentation of these stimuli on predetermined formats. In this context, threshold is usually defined as that value of the stimulus that is reported correctly 50% (and in certain cases 75%) of the time.

Means of presenting stimuli vary in the psychophysical studies of thermal thresholds. Stimuli may be given as a continuously variable magnitude of either increasing or decreasing intensity. They could also be presented as a series of preset intensity levels and in this case they may be ordered sequentially in an incremental or decremental pattern, or randomly, or in a fixed relation to the subject's response to them. The selection of a particular format depends on the demands and aims of the

particular experiment.

There are many **methods of measuring the sensory threshold.** In the **Classical Method,** the threshold is measured by determining the stimulus intensity required for the sensation to be just detectable. That is, the examiner presents a series of stimuli to the experimental subject and estimates the intensity of stimulus just adequate to evoke a sensory experience in the subject, who compares the magnitude with an internal standard and he decides whether or not he has detected the stimulus. The stimuli could be presented in fixed sets of values selected to bracket the subject's threshold and presented in a random sequence. From the frequency or percentage of correct detections at each value a function is constructed and the threshold is usually indicated at the stimulus value corresponding to 50% correct detections and such depends on the subject's interal standard (Swets et al, 1961; Green and Swets 1966). This internal standard of the subject, however, is often variable and is known to be influenced by many non-sensory factors inherent in the psychological make-up of the subject, or peculiar to a testing situation (Swets et al, 1961; Green and Swets 1966; Coombs et al, 1970). The subject's timidity, anxiety over the test, or his general attitude towards the personnel involved in the assessment procedure may greatly influence the results and yet one must necessarily use the subject's report to make inferences about his sensation. This effectively means that a subject willing more than another to indicate the feeling of stimuli will appear more sensitive even in the absence of actual sensory differences between them. Moreover, in the same subject, his willingness to indicate the feeling of stimuli may vary from one area to another and it may vary with time. These variations make comparisons between body areas or longitudinal studies at various points in time inaccurate. The method is also relatively inefficient as only a small portion of the data collected is used in the calculation of the threshold.

Another method used for the measurement of sensory threshold in quantitative psychophysics is the **Method of Limits.** This method implies that there are boundaries or limits on a continuum of sensitivity at which a stimulus changes from being imperceptible to being perceptible and vice versa (Gescheider 1976). In this method stimuli are usually presented in alternate increasing and decreasing sequences. The increasing series starts well below threshold and the decreasing series well above threshold. In some measurements only the decreasing series may be presented (Gescheider 1976). The threshold is defined as the average stimulus value of the response transitions in the various series and it usually differs slightly between decreasing and increasing series. Starting points for the series are varied to prevent the subject from guessing or responding to a number in the sequence. The method of limits is relatively insufficient and inaccurate as it is subject to the same sources of variability as the previous method.

A modification of the method of limits is the **Tracking or Staircase Method** in which some improvement of the efficiency is accomplished. In this method, the stimulus changes in value on a preset scale as a consequence of the subject's response in the preceding trial.(Green and Swets 1966). For example, the stimulus intensity is decreased for the trial after a correct detection and increased for the trial following the one in which the subject has failed to report its presence. As in the method of limits, the threshold is determined from the region of response transition. Either the mid-point in stimulus intensity between correct detections and failure to report, or simply the stimulus value for 50% correct detections may be used. This modification permits rapid data collection around the threshold. It is, however, subject to the same inaccuracy stemming from subjective response-bias described previously.

A method of sensory threshold measurement associated with signal detection theory, **The Signal Detection Method,** has evolved in psychophysics to solve precisely most of the difficulties related to subjective variations and response bias (Green and Swets 1966). The signal detection theory assumes the constant presence, in sensory channels, of neural activity even in the absence of detectable sensation and uncorrelated with significant external stimulus. This random activity or 'noise' adds to the neural activity evoked by the stimulus (Swets et al, 1961; Eijkman and Vendrik 1963; Green and Swets 1966). Any level of activity in the system, therefore, may arise either from noise alone or from the combination of noise plus the effect of the stimulus. The observer's task is to decide within the limits of probability, whether the neural activity at any moment is sufficiently above the noise baseline to justify the belief that an external stimulus has made a contribution to that neural activity. To make such a decision the subject adopts a criterion and whenever the neural activity exceeds this criterion level he then reports the presence of a stimulus whereas when the resultant neural activity is below that level he reports the absence of a sensation. This subjective criterion level has been shown to vary with the subject's level of motivation (Swets et al, 1961; Green and Swets 1966; Coombs et al, 1970). The signal detection method, therefore, measures the threshold in terms of the likelihood of a subject having detected a stimulus and expresses the results as probability values which depend both on the 'background noise' and the subject's level of motivation. The standard experimental procedure of signal detection method of sensory threshold measurement is the yes/no procedure (Green and Swets 1966). On a sequence of trials, the subject is to decide whether a particular sensory signal is present or absent. If he decides that it is present, he is to say 'yes', whereas if he thinks it is absent he is to say 'no'. It is presumed that among 'yes' responses there may be possible ones independent of the presence of a sensation but dependent on response bias,

that is, the subject may not faithfully report his state of mind. Such responses are termed 'false alarms' while the 'yes' responses on the presence of actual stimuli are called 'hits'. This theory, having identified this problem, resolves it through the presentation of the signal to the subject on some fixed proportion of trials in some irregular order. If 50% of the trials do not contain a signal, then two independent measures of yes responses are made. One is the proportion of hits; the other is the proportion of false alarms. The first tells something about how the sensory system is operating, while the false alarms inform us of the subject's response bias, that is, his tendency to say "yes" regardless of the presence of the signal. The basic character of the signal detection method is that it incorporates this false alarm probability into its measure of the threshold. The method acknowledges that the subject's response or decision depends on both true sensory and non-sensory variables in the measurement and takes steps to get independent evaluation of both. Consequently, the method defines and determines threshold in a manner independent of non-sensory response bias, motivational and other variables. To accomplish this, many hundreds of stimuli must be given over a period of hours. Therefore, although this method is highly sensitive and accurate, it is time consuming and not suitable for routine clinical use.

Closely related to and successfully adapted from the signal detection theory is a psychophysical technique called **The Forced-Choice Method** of sensory threshold measurement (Green and Swets 1966; Wright 1974). In this method the subject is no longer required to establish or to use an absolute internal standard or criterion for the identification of applied signals. On each trial he is presented with both null and actual (non-null) stimuli, that is, two time intervals are clearly defined for him by a special indicator (a light or a tone ... etc) and only one of the two intervals is accompanied with presentation of the stimulus. The subject's duty is to

identify the interval in which the stimulus occurred. He/She accomplishes this task by comparing the neural activity present, in the sensory system under investigation, during each of the intervals and choosing the interval that had the greater level of neural activity. This method, therefore, clearly obviates the need for the subject to set a criterion for comparison. The interval, first or second, during which the stimulus is applied is varied randomly. The measure of sensitivity derived from a forced-choice procedure is a percentage of the correct answers. The forced-choice method, therefore, seems to be free of subject criteria and response-bias artefacts unlike all other methods used to measure sensory threshold (Green and Swets 1966). The great advantage of this method is that it permits and encourages the subject to use only the available sensory information following the stimulus application, a practice not encountered in any of the other methods of sensory threshold measurement (Eijkman and Vendrik 1963). The method is believed to be more sensitive and the threshold measurements to be reproducible and highly accurate (Green and Swets 1966; Wright 1974). These are the essential requirements of a clinical testing procedure for the detection of sensory threshold. the protocol of testing should be quick, not difficult or tiring to the subject. The forced-choice method seems to fulfil all these requirements and, therefore, is an ideal method to use for clinical situations.

Methods used in the Investigation of Thermal Sensation

The lack of instrumentation to control the conditions and characters of thermal stimuli has been one of the greatest difficulties in the psychophysical and neurophysiological investigation of thermal sensation. One of the earlier methods involved the use of water tanks which were maintained at "constant" temperatures in which the subject under investigation would dip the extremity to be tested. Weber in 1846 investigated the adaptation properties of thermal sensation using such

"stimulators". The thermostatically controlled waterbath improved considerably over the following years and was used by most subsequent investigators in the psychophysical studies of temperature sensation (Culler 1926). Despite these improvements, these studies were accompanied by many technical difficulties and inaccuracies. The most obvious was that the skin temperature changed because of the evaporative effects of the air when the extremity was moved from one water bath to another in addition to other difficulties in controlling the rate, extent and area of stimulation. These methodological difficulties made comparisons of the sensations resulting from exposure to water bath of different temperatures, at best, difficult.

Another approach to the study of cutaneous temperature sensations has been the mapping of the warm and cold spots of the skin pioneered by Blix (1882,1884) and later by Goldscheider (1884) and Donaldson (1885). The usual technique was to systematically map the skin of humans for points which gave rise to either warm or cold sensations through the use of a brass cylinder, with a pointed tip of about 1 mm diameter, after immersing it in baths of hot or cold water respectively, and drying its tip. Quantification of the temperature of these stimulators was difficult in the best circumstances as they returned to the room temperature once they were removed from the waterbaths. Many modifications of these point stimulators have been introduced most of which aimed at improving the control of the temperature at the stimulating tip and/or the pressure of its application (Dallenbach 1927; Jenkins 1937; von Skramlik 1937). In the various studies of warm and cold spots, the density of these for different sites of the body was determined (Strughold and Porz 1931). The relationship between spot density and temperature sensitivity, however, has not been established.

Holm (1903) and Gertz (1921) introduced relatively large contact thermodes for the study of thermal sensation. This thermode was later improved and modified by Hensel and coworkers (Hensel 1950b; Hensel et al, 1951). Circulated water from various thermostatically controlled water tanks, passed through the thermode, made of a conducting metal, in constant contact with the skin. The temperature of the thermode was changed by switching from one tank to another. The refinement of this technique by Hensel et al (1951) resulted in more precise control of rapid changes of skin temperature. In their method, two jets of water were directed at the thermode, one of which, the stimulating jet, was interrupted by a valve before reaching the thermode while the other jet, set at the desired resting skin temperature, circulates through the thermode. Rotating the scoop valve would result in the interruption of the second jet and the passage through the thermode of the first (stimulating) jet. This thermode was applied by other workers in the study of thermal sensation (Kenshalo et al, 1960). The chief difficulty of this technique was that it was cumbersome and only a limited not precisely controlled temperature stimulus could be employed (Kenshalo et al, 1960).

Hardy and Oppel in 1936 introduced the method of quantitative temperature stimulation of the skin by radiant energy. The method was capable of applying temperature stimuli to the skin surface with simultaneous measurement of the resulting temperature changes with a sensitivity of $0.01^{\circ}C$ and an accuracy of $\pm 0.01^{\circ}C$. Pure thermal stimuli, free from any other cues could be delivered to the skin. The method was also able to apply stimuli the intensity of which over the stimulated area was controlled with equal distribution. Morever, thermal stimuli of varied durations were easily applied. The method, however, also had many disadvantages. The apparatus is complicated, there is no direct way of transforming units of radiant flux energy into degrees centigrade change in the skin temperature and the method was unable to maintain skin temperature

for extended periods of time while applying thermal stimuli on the top of these new skin temperatures.

An important group of temperature-stimulating thermo-electric devices were introduced by Kenshalo in 1963. These operate on the Peltier principle. When a direct current of electricity is passed through the junction of two conductors of dissimilar material, the junction will warm or cool depending on the direction of the current flow. With the advent of electrical semi-conductors, it was possible to develop devices that effectively utilise the principle to produce efficient changes of temperature. In these devices, alternating series of two types of semi-conductor material (eg p and n types of bismuth telluride) are connected by copper bars. When a direct electric current flows through these junctions, one side of the block cools while the other side warms and when the polarity of the current is reversed, the temperature gradient at the junctions is reversed, as is the temperature of the sides of the block. The use of Peltier effect devices for investigations of temperature sensation had been suggested by several investigators prior to their introduction by Kenshalo (Isaakian et al, 1959; Jones et al, 1962; Lele 1962; Stuart et al, 1962). To his constructed thermode, Kenshalo applied automatic current circuits to regulate the amount and polarity of the current passed through the thermode and hence to apply heat or cold stimuli of precisely controlled magnitude through the same thermode (Kenshalo and Bergen 1975). Through the use of these thermodes a wide variety of experiments concerned with temperature sensation in human and subhuman organisms and electrophysiological studies of peripheral nerve activity associated with changes of skin temperature were performed (for review see Jamal et al, 1985a). The thermodes designed on the Peltier principle overcame many of the difficulties encountered in the preceding ones and had many advantages: (1) the temperature of the skin beneath the thermode could

be maintained at a constant predetermined value with an accuracy of ± 0.012°C; (2) the same thermode could be used for the application of heat or cold stimuli by changing the polarity of the current applied; (3) the intensities of the stimuli can be set into the apparatus before their presentation to the subject; (4) the accuracy of calculating the intensity of the thermal stimulus was significantly increased; (5) pure thermal stimuli, without tactile or any other component, can be delivered; (6) the rate of the change of temperature of the stimulus can be varied between 0.03 - 2°C/s; (7) thermodes with different contact surface area are possible. The Peltier effect thermode, therefore, incorporates all the advantages claimed for other methods and in the meantime it overcomes most of their disadvantages. It was also possible with the introduction of this thermode to combine the static and dynamic aspects of temperature sensitivity into a single procedure (Hensel and Boman 1960; Konietzny and Hensel 1975,1977,1978,1980; Jarvilehto and Hamalainen 1980; Konietzny 1981). For these reasons, Peltier-based thermodes have been utilised in some methods used for the estimation of thermal thresholds in humans (Fruhstorfer et al, 1976a; Dyck et al, 1978,1984; Bertelsmann et al 1985). Comparison between these methods and the method reported here is postponed until the current method is described.

Clinical Assessment of Thermal Sensation

Loss of cutaneous sensation is a common complaint in many diseases of the nervous system both the peripheral and the central parts. An examination of sensation generally consists of tests for the senses of light touch, pain, temperature and deep pressure as well as the measures of two-point discrimination and stimulus localisation. The assessment of thermal sensation in clinical neurology is important and necessary. If abnormality is present, it may imply disordered function of thermal sensory endorgans, afferent axons, central tracts, nuclei or the cerebral region

concerned with the sensation of temperature. Involvement of thermal sensation in a patient with features of peripheral neuropathy may indicate involvement of a specific group of nerve fibres which may be helpful in the differential diagnosis as some neurological diseases may affect sensations selectively. Special evaluation of thermal sensation, if involved, may help in appreciating, worsening or improvement of the sensory deficit and this is important in recognising the course of the disease or a therapeutic effect. However, though very important, the sensation of temperature is frequently neglected, forgotten or studied inaccurately in the context of clinical neurological examination. Instruments used at the bedside to test the sensation of temperature usually consist of two small glass containers one filled with hot and the other with ice cold water to test the sensation of heat and cold respectively. A variant of this approach is to heat or cool solid metal thermodes to known temperatures and to use these as stimulators. These methods are rough, insensitive and do not give the finely graded stimuli needed to properly evaluate and accurately measure the thermal sensation and threshold in healthy subjects or in patients with mild disorders of the thermal sensory system.

The protocol of the clinical testing is usually as follows. The test stimulus is first applied to a normal, uninvolved area of the body so that the patient may become familiar with the sensation evoked by the stimulus. The stimulus then is applied to the affected parts of the body at irregular intervals and the patient is instructed to say 'yes' or 'now' when he feels the stimulus. The patient is also asked to indicate whether he feels the stimulus abnormal and the nature of this abnormality. The same region of both sides of the body, adjacent regions and proximal and distal parts of the same side are all compared. Abnormality is recognised by either failure to report stimuli that should have been felt, based on the physician's notion as to what constitutes a normal response for that

patient, or by reporting regional differences of feeling elicited by the stimuli.

This method of testing thermal sensation is that most commonly followed by neurologists. It is inexpensive and provides some information about gross sensory loss, particularly when it has a sharp level or border, but it is so imprecise and inadequate that frequently only complete absence of thermal sensation can be determined reliably. The main drawbacks of this bedside method of examination of thermal sensation are that the physical characteristics of the thermal stimuli are undefined and variable and the stimuli are non-quantitiative and non-selective in nature, as they are mixed with tactile cues. Moreover, the patient's report of sensory events depends on such unmeasurable and variable parameters as suggestability, cooperation, motivation and attitude towards the examiner. The results of this method also depend on the experience of the examiner, his interest in the examination and the amount of time spent on it. They are, therefore, poorly reproducible, non-quantitated and subject to observer bias. It is inadequate for the clinical assessment of thermal sensation, for the detection of subtle and non-symptomatic sensory loss and for the evaluation of the response of these abnormalities to treatment. There is, therefore, increasing demand for more accurate objective methods for the evaluation of this sensation. The essential requirements for such a psychophysical method are, it should not be time consuming, easily performed, not difficult nor tiring for the patient, quantitative, sensitive and reproducible. The bedside clinical method and an appropriate psychophysical technique are each suited for different applications. The bedside clinicl approach provides a quick non-validated survey of sensation over the surface of the body and indicates the presence of gross abnormality while the new technique accurately quantifies the sensation and detects subtle and asymptomatic abnormalities of thermal sensation.

CHAPTER 4

A NEW TECHNIQUE FOR THE MEASUREMENT OF THERMAL THRESHOLDS

THE GLASGOW THERMAL SYSTEM

The increasing need for an objective and quantitative bedside method to investigate thermal sensation in man was pointed out in the previous chapter. Such a technique, through the use of quantitative psychophysical methods would be able to define dysfunction of the thermal system in terms of changes of perception threshold of thermal sensation. Measurement of sensory perception threshold is more convenient, less time consuming, less complicated, and more suited for clinical use with equal, if not more, accuracy than methods of sensory magnitude-estimation. The latter needs longer time and more complicated procedures for its measurement and, therefore, is unsuitable for clinical use.

Designs of techniques for the measurement of sensory thresholds have a few very important requirements. They must be reproducible so that they may be used for follow-up and longitudinal studies of patients. They should also be sensitive enough to detect subtle and asymptomatic abnormalities of the sensory system for early diagnosis of such abnormalities. Other important requirements are that the method should be quick to finish, preferably taking not longer than 10-20 minutes, easy to perform for the operator and not difficult or tiring for the patient. The lack of a suitable technique fulfilling all these criteria instigated my work for the development and construction of a new technique for the measurement of heat and cold thresholds in clinical practice.

Many relatively recent developments made such a technique feasible, (a) the availability of sophisticated technology for building the ideal thermode which is able to deliver modality-specific and finely graded thermal stimuli with many other required characters of these stimuli, (b) the introduction and modification of objective psychophysical methods which

are free from subject response-bias, (c) the increasing consolidation and expansion in the knowledge of thermal sensory physiology based on experimental studies on animals, especially the subhuman primates, and the confirmation of some of these findings by recent investigations of specific thermoreceptive neurones in conscious humans (Chapters 1 and 2) and (d) the accumulation of a large amount of data from various human psychophysical studies on temperature sensation providing useful information about the behaviour of temperature sensation in man.

Principles of the Technique

Prior to the design of the technique, several important facts must be considered. The technique must be standardised and all the potential sources of error and variability in the measurement of thermal thresholds must, therefore, be identified and their effects minimised or eliminated. The effective control of these variables will render the technique accurate, efficient, reliable and sensitive. The identification of these sources of variability and their elimination have been based on both an extensive review of the available anatomical, physiological and psychophysical body of knowledge about thermal sensation (see the first three chapters) and extensive studies in the laboratory of the Glasgow University Department of Neurology (Chapter 5). The sources of variability may be summarised as follows:

1. Variability due to stimulation procedures and conditions.
2. Variability due to transmission of thermal energy through the skin to the receptor zone.
3. Variability due to physiological properties of the thermal sensory system.
4. Variability due to experimental subject's response-bias and method of scoring.
5. Variability due to experimental subject's performance.

1. **Variables of stimulation procedures**

The particular aspects of the thermal stimulus (heat or cold) that give rise to thermal sensation are extremely important determinants of the measurement of thermal thresholds. The effects of the main stimulus variables on the operation and response of the temperature sensory system will be discussed in the following terms: (a) the temperature to which the skin is adapted and on the top of which thermal stimulus is applied; (b) the rate of change of temperature during stimulation; and (c) the pressure with which the contact thermode is applied on the skin to be tested. Other important factors are the thermal properties of the stimulating thermode. The latter factors are not discussed as one type of stimulator is used in all the investigations.

(a) **The basic skin temperature:** The initial temperature at which the skin is adapted before the application of thermal stimuli has been found to cause variability in the measurement of thermal thresholds (Hensel 1950b; Lele 1954; Kenshalo and Scott 1966; Kenshalo 1970,1978). Lele (1954) concluded from his studies that

"Clearly, therefore, skin temperature and threshold variability will have to be taken into account in future physiological and clinical studies concerned with thermal sensibility".

The relationship between the range of temperature at which complete adaptation can occur and concepts of physiological zero and temperature neutral zone require clarification. The "physiological zero" is the skin temperature which is thermally indifferent and to which the response is neither warm nor cool (Geldard 1953). On either side of this physiological zero there is a relatively narrow range of temperatures at which the skin does not evoke a thermal sensation, the "neutral zone". The range of this neutral zone is determined by several factors including the area, site and the rate at which the skin temperature is changed (Kenshalo and Scott 1966). If the change of

skin temperature is slow enough to allow time for adaptation (ie less than 0.007°C/s) then no thermal sensation occurs through this zone. At fast rates of temperature change the neutral zone virtually disappears. When the neutral zone is exceeded, a persisting thermal sensation is experienced. The neutral zone, therefore, is the range of skin temperature through which complete adaptation occurs and in which lies the physiological zero (Kenshalo and Scott 1966). Outside the neutral zone, small thermal stimuli are felt as changes of the existing thermal sensation rather than a warm or cold sensation. A temperature change and its direction is, therefore, associated with the sensation of heat and cold only if such change is applied on the top of basic skin temperature within the complete adaptation zone (Hensel 1950b; Kenshalo et al, 1961; Kenshalo 1970; Hensel 1981). It is important that the basic skin temperature prior to the application of thermal stimuli be within the range of complete adaptation where no existing thermal sensation is present. The range of complete adaptation was found to be between 30-36°C in most of the studies (Hensel 1950b; Kenshalo et al 1961; Kenshalo and Scott 1966; Kenshalo 1970; Lindblom 1981). Each subject, however, was found to have a unique temporal course and temperature range of complete adaptation (Kenshalo and Scott 1966). The effect of the temperature to which the skin has been adapted upon the measurement of thermal thresholds was found to be less pronounced at skin temperatures between 30-36°C, the range at which complete adaptation occurs (Ebaugh and Thauer 1950; Hensel 1950b; Lele 1954; Kenshalo et al, 1961). Hensel (1950b) found that the warm threshold at initial basic skin temperature of 25°C was four times and at initial basic skin temperature of 30°C twice the warm threshold at basic skin temperature of 35°C. He reported similar findings with cold threshold measurement. Lele (1954) reported similar changes in the heat and cold

thresholds as a function of the temperature of the skin. The least changes were found at temperatures of 34-35°C. At these temperatures the rate of adaptation is quicker, while at more extreme temperatures relatively longer periods of time are required to reach complete adaptation.

The dynamic overshoot in impulse frequency in response to the application of proper stimuli to the specific heat and cold peripheral units has been found to be closely related to the adapting temperature of the receptors prior to the application of equal thermal stimuli (Konietzny and Hensel 1977,1980; Konietzny 1981). The reason for the relation of thermal thresholds or the dynamic impulse frequency with the basic skin temperature is not known but it may be, at least in part, related to changes in thermal conductivity of the skin induced by changes of skin temperature and pronounced variation of the former was noted on changing the basic skin temperature (Chapter 2).

(b) **Rate of change of temperature:** Thermal thresholds vary considerably at different rates of temperature change (Hensel 1950b; Lele 1954; Hendler and Hardy 1960; Kenshalo et al, 1968; Molinari et al, 1977; Kenshalo 1978). The effect of this change of rate is variable in different people (Kenshalo et al, 1968; Kenshalo 1978). Hensel (1950b) found that thermal thresholds were considerably increased when the rate of temperature change of stimuli was less than 0.02°C/s. Kenshalo and his coworkers (1968) found that variations in thermal thresholds were smaller at rates higher than 0.1°C/s. Both inter-individual and intra-individual variabilities greatly increased at rates smaller than 0.1°C/s. The peak discharge frequency and the cumulative number of impulses in both specific heat and cold thermal receptors was intimately related to rate of change of temperature when the magnitude of the thermal stimuli and the adapting skin temperature were constant

(Konietzny and Hensel 1977,1980; Konietzny 1981). The variation in thermal thresholds and the average dynamic discharge frequency of peripheral thermosensitive units were found to be at their lowest at rates between 0.5-1.5°C/s (Kenshalo et al, 1968; Konietzny and Hensel 1980; Kenshalo 1976,1978; Molinari et al, 1977; Konietzny 1981; Hensel 1982). The rate of temperature change must, therefore, be kept strictly constant at a value between 0.5-1.5°C/s.

(c)**Pressure of application of the thermode:** In contact thermodes, complete and good contact with the underlying skin is important and variation in the application of the thermode is believed to be a significant source of variability of thermal threshold determination (Kenshalo 1970). Variation in the application of a thermode may possibly produce its effect on thermal thresholds through variation in the amount of heat conducted to the skin. Systematic investigation of this factor has not been done previously. Its role, therefore, in the reproducibility of thermal threshold measurements was studied in our laboratory (Chapter 5).

2. Variation of Transmission of Thermal Energy Through the Skin

The amount of thermal energy transferred to and the change of temperature which it produces at the receptor zone is the sole stimulus condition necessary to arouse thermal sensation (see Chapter 2). Thermal properties, and in particular the thermal conductivity of the skin, are important determinants of the conduction of thermal energy through the skin (Cohen 1977; Stoll 1977). The thermal conductivity of the skin varies with its physical architecture, chemical and fluid composition, homogeneity of various skin layers, the initial skin temperature and most important of all, the epidermal thickness (Buettner 1951; Weaver and Stoll 1969; Kraning 1973; Cohen 1977; Stoll 1977). The marked variation of the thermal

properties between the skin of various sites of the body probably leads to differences in thermal sensitivity of the skin of these sites (Aschoff and Weaver 1959; Poppendiek et al, 1966; Nadel et al, 1973; Stevens et al, 1974; Cohen 1977; Stoll 1977). These regional variations are greatest at threshold levels (Stevens et al, 1974; Cohen 1977; Stoll 1977).

Stoll (1977) showed that the thickness of the epidermis is the single most important determinant of the skin's thermal conductivity. The thicker the epidermis, which acts as an insulating layer, the less efficient is the thermal conduction in the skin and the greater is the resistance against heat transfer to the receptor zone (Cohen 1977; Stoll 1977). The thickness of epidermis varies considerably between skin of various sites of the body in the same individual and between identical sites from one individual to another (Stoll 1977). At the volar aspect of the wrist and forearm, however, the epidermis was found to be relatively thin with only negligible inter-individual variation (Stoll 1977).

Two points are, therefore, important to consider in the methodology of the new technique in this context to minimise the effect of this factor on the variability of thermal threshold measurement.

(a) The skin of the sites selected for testing should preferably have a thin epidermis and less variable epidermal thickness. This permits a more efficient transmission of heat and reduces the variability of its transmission to the receptor zone.

(b) The design of the system should also include a method that accounts for variations in the thermal properties of the skin and insures the transfer of equal amounts of energy to the intracutaneous receptor zone as far as possible. It is reasonable to assume that different amounts of energy are needed to produce equal changes of temperature at the receptor zone at different sites of the skin. A way to calculate this and calibrate the thermode accordingly is necessary.

3. **Variables due to physiological properties of the thermal system**

Spatial summation is an important factor in thermal sensation (Hardy and Oppel 1937,1938; Hensel 1950b; Kenshalo et al 1967; Stevens et al, 1974; Kenshalo 1978). The effect of spatial summation is both on the scaling of sensation and magnitude estimation and threshold determination by humans (Stevens et al, 1974; Kenshalo 1978). This effect is more pronounced at low intensity stimuli at or just above threshold levels (Stevens et al, 1974). The variability of thermal thresholds was found to increase with small thermodes (Lele 1954; Kenshalo et al, 1967).

The area of stimulation is an important factor in regards to thermal thresholds measurement from two aspects. Hensel (1950a,1952a) studied the effect of applying stimulators to the skin with various areas of contact but of the same temperature and he measured the thermal gradients established at the edge beneath these stimulators intracutaneously. Four stimulating surface areas of 0.25, 0.5, 1 and 2 cm^2 whose temperature differed from that of the skin stimulated by equal amounts were used (Hensel 1952a). It was observed that the smaller the area the less effective was the stimulator in conducting the temperature change to the intracutaneous depth of the receptor zone. Such an effect was especially pronounced at areas below $1cm^2$ and decreased dramatically with areas larger than $1cm^2$ (Hensel 1952a). Spatial summation of the thermosensitive neurones occurs at various levels (Hardy and Oppel 1938; Kenshalo et al, 1967). The first location is at the level of the peripheral unit. Single specific thermosensitive fibres in monkeys were found by Kenshalo et al (1967) to innervate up to 8 spots on the skin each about 1mm in diameter. Spots innervated by one axon were found to be separated by as much as 16mm. When any one of the spots was stimulated, an increase in the frequency of nerve impulses occurred. When several spots supplied by the same axon were stimulated, the increase in the impulse frequency of the axon was proportional to the number of spots stimulated. Summation, however, is

believed to occur at all levels of the neurones along the thermal pathway (Hensel 1981).

The size of the area stimulated was found to affect the limits of complete adaptation (Hensel 1950b; Kenshalo and Scott 1966; Kenshalo 1978). With larger area of stimulation the range of complete adaptation narrows and the speed of its occurrence slows down (Hensel 1950b; Kenshalo and Scott 1966). For areas of stimulation up to 14.5 cm^2, the zone of complete adaptation remained between 30-36^oC at a relatively fast rate (Kenshalo and Scott 1966).

It is, therefore, important to choose a thermode of a proper size which takes all these factors into account. The thermode size should be large enough to insure adequate stimulation of a reasonably wide sample of peripheral cutaneous thermal receptors and thereby have adequate summation but at the same time not large enough to limit the range and speed of complete adaptation.

4. Variables due to subject's response bias and scoring methods

Because threshold measurements are so affected by individual differences in subjective criteria and response bias (Chapter 3), it is extremely important to use a psychophysical method of threshold estimation which is objective and free from such variables. As discussed in the previous chapter, among all the available psychophysical methods the forced-choice method is ideal as it is free from response bias by the subject (Green and Swets 1966). The measure of the response derived from the forced-choice method is expressed in terms of the percentage of correct answers, when used in the measurement of sensory threshold (Green and Swets 1966). Of the various methods to estimate the percentage points of a quantal response (Wetherill 1963), the method proposed by Wetherill and coworkers (1966) of up-and-down transform rule (UDTR) is the most accurate,

suitable, easy to compute and extremely efficient and allows validation of the results. The method is outlined and discussed on page 87.

5. **Variables due to subject's performance**

The testing procedures should be easy to perform by the subject tested. These procedures should be carefully explained to him in simple terms to set him at ease, gain his cooperation and make sure that he understands what he is required to do. The test should be of short duration and not tiring to the subject, if it is to be practical to use.

The Technique used in this Study

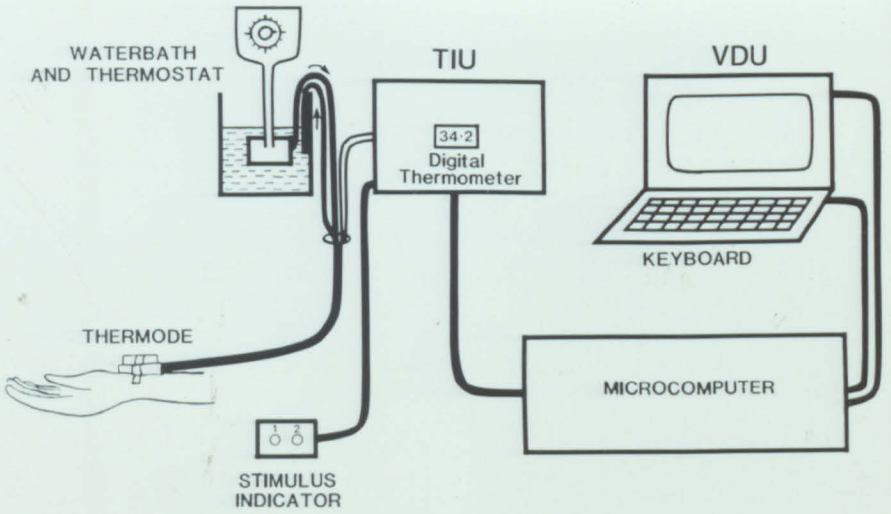
The system is made up of the following components: a thermode, a thermode interface unit (TIU) with a digital thermometer, a stimulus indicator, a microcomputer assembly, a waterbath with a thermostat, a visual display unit (VDU) with keyboard for communication with the computer (see simplified diagram, Figure 1).

The stimulating thermode, with a surface area of 12.5 cm^2, is constructed from arrays of semiconducting thermo-electric elements operating by the Peltier principle (Figure 2). An aluminium block is mounted on the top of the thermode and is continuously perfused with water at a constant temperature of 34 $\pm$ 0.1^{o}C from the waterbath. The circulation of water through the thermode has two main purposes: i) to maintain the background skin temperature within the desired range between the thermal stimuli, and ii) for the exclusive conservation of the heat pumping capacity of the thermode for stimulation, thereby increasing the thermode efficiency. The thermode surface, in contact with the skin, is heated or cooled according to the direction of the current passed through the thermode. A thermocouple, bonded to the centre of the thermode, measures the resultant temperature of the skin in contact with the thermode continuously. The temperature of the skin beneath the thermode is the

Figure 1 Components of the Glasgow Thermal System (Jamal et al, 1985a, reproduced with permission).

TIU = Thermal Interface Unit

VDU = Visual Display Unit


WATERBATH
AND THERMOSTAT
TIU
34·2
Digital
Thermometer
VDU
KEYBOARD
THERMODE
MICROCOMPUTER
1
2
STIMULUS
INDICATOR

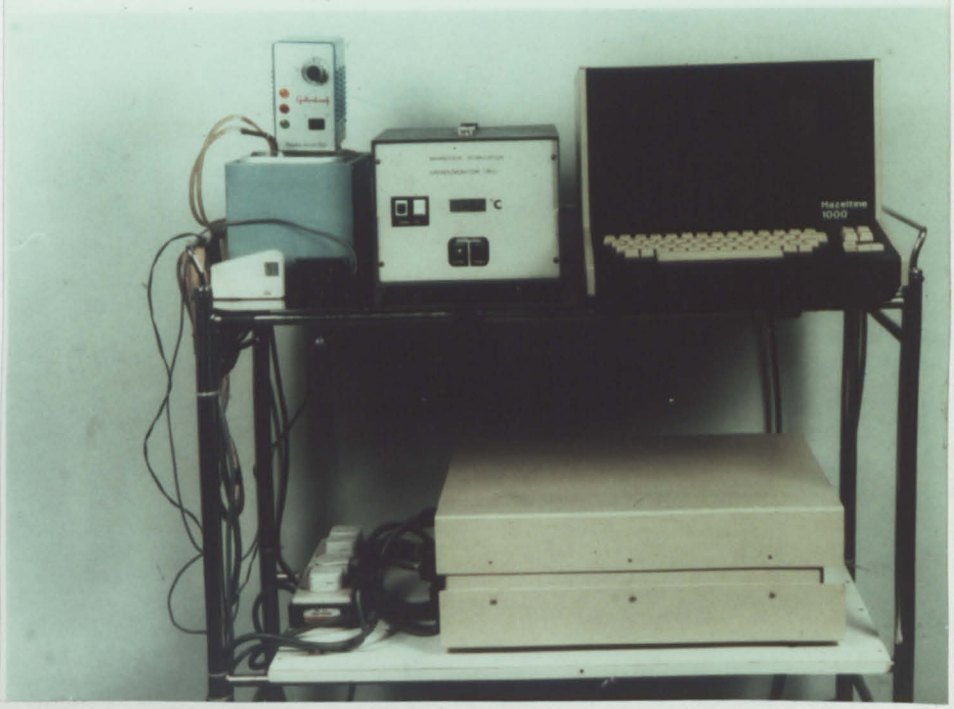
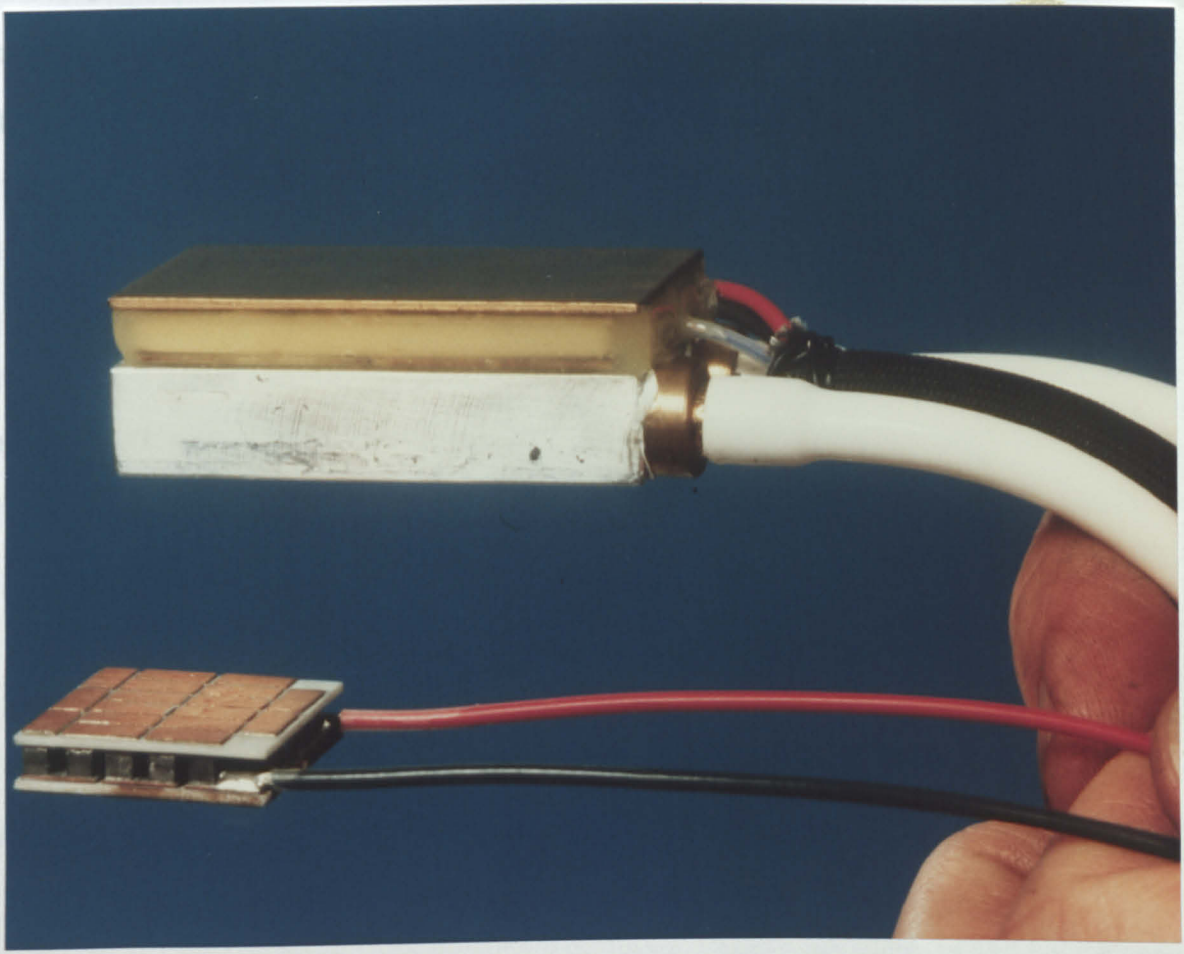

Hazeltine
1000

Figure 2 Above: The Peltier based thermode used in the Glasgow Thermal System

Below: A smaller sized block of Peltier elements.



balance between the skin temperature and the temperature of the thermode surface.

The TIU contains a thermocouple amplifier with analogue to digital converter and a digital to analogue converter. The former measures the skin temperature and displays it on the digital thermometer, while the latter provides input to a power amplifier which drives the thermode. The thermal stimulus output from the thermode is determined by the heat flow equation:

$$Q = S\ Tc\ I + \frac{1}{2} r\ I^2 - K\ T\Delta \qquad \text{where,}$$

Q: is the heat (or cold) output from the surface of the thermode (the output is heat when Q is positive and cold when Q is negative).

S: Soebeck coefficient

Tc: the absolute temperature* of the cold junction

I: the current passing through the thermode (the polarity of the current is either positive, when heat is produced, or engative, where cold output is produced)

r: the internal resistance of the thermode

K: the thermal conductivity of the thermode from one surface to another

T_Δ: the temperature difference between the two surfaces of the thermode.

The components of this equation could be summarised in three terms: (1) the pumped Peltier heat represented by (S Tc I) which is proportional to the current input I; (2) the joule heat generated by the flow of the current I through the thermode, represented by ($\frac{1}{2}r\ I^2$), is proportional to I^2. The joule heat helps the pumped Peltier heat when the thermode is used for heating while it opposes the Peltier heat when the thermode is used for

*The absolute temperature, measured in degrees Kelvin, is a different scale of temperature the zero of which is equivalent of -273°C and indicates the extreme of temperature with no possible colder temperature below it.

cooling; (3) the third term is the heat leak back represented by the formula ($K T_{\Delta}$). This occurs as a temperature difference develops between the two sides of the thermode and is always opposing the pumped Peltier heat.

The thermode current should, therefore, be accurately calculated continuously from the heat flow equation if maintaining a specified constant power ouput level is required as in this technique (see below). This task is performed by the microcomputer once every 100 ms. During the sampling interval the current is constant (equal to zero if no stimulus is applied). At the end of this interval the error in the power output due to change in temperature difference between junctions is less than 1%. The duration of the stimulus is in multiples of the sampling intervals. A stimulus, therefore, always starts and ends at the computer sampling times. In the standard method, the stimulus is graded by altering its duration while the power and thus the rate of change of temperature is constant (see below). The microcomputer system not only controls the thermode current but also runs the forced-choice trials and the modified up-and-down transform rule (UDTR).

The stimulus indicator is a small box with two light emitting diodes numbered 1 and 2 (Figure 1). It is placed in front of the subject to watch during testing. In the testing procedure each light is illuminated in sequence to indicate two separate time periods. During one of the periods there is a null stimulus while during the other a real stimulus is presented to the subject. The order of stimulus application is assigned to the time periods randomly by the computer and is unknown to both the subject and the operator (it may be made known to the operator if desired). At the end of the trial, the subject must choose the period during which he felt the stimulus (that is the forced-choice method). The answer is entered into the computer which then socres a success (S) or a failure (F).

This triggers the computer to give the next stimulus which is of the same, longer or shorter duration according to the algorithm chosen of up-and-down transform rule (UDTR) (Wetherill et al 1966).

In this mathematical rule, as the name implies, the level of the particular quantum (temperature stimulus) is changed to a higher (up) or a lower (down) value on a transformed response curve sequentially. In threshold measurement, the objective of the UDTR is to estimate the level at which the stimulus can truly be felt 50% of the time but to account for the element of guessing, threshold level is set at the 75% level (see Chapter 3). To accomplish this aim, UDTR has been shown to be the most accurate, simplest and easiest to compute (Wetherill et al, 1966). We have chosen the particular algorithm which estimates accurately the level corresponding to the 75% point (in this case L = 0.75) of the transformed response curve of the threshold measurement in the forced-choice testing. Programming is such that F, SF or SSFF causes a 100 ms change to a higher value while SSS or SSFS causes a 100 ms change to a lower value. After six changes in direction (three changes in direction up versus three changes down), the threshold is calculated as the mean of the points of change in direction. The threshold value is given as the change from the basic skin temperature and is displayed on the VDU.

The UDTR is modified in the Glasgow method so that initially, the stimulus duration, starting at any value between 1 to 9 seconds, is altered in steps of one second for each success (S) until the first failure (F) is encountered which causes a change in direction upwards. After this first change of direction the standard UDTR described begins and the steps of change in stimulus duration are then of 100 ms. This first change of direction following the initial large steps is of course excluded from the threshold level measurement. In all of the normal subjects whose thresholds were below $1^{o}C$, the algorithm was started from one second stimulus duration. The average number of trials needed to determine one threshold

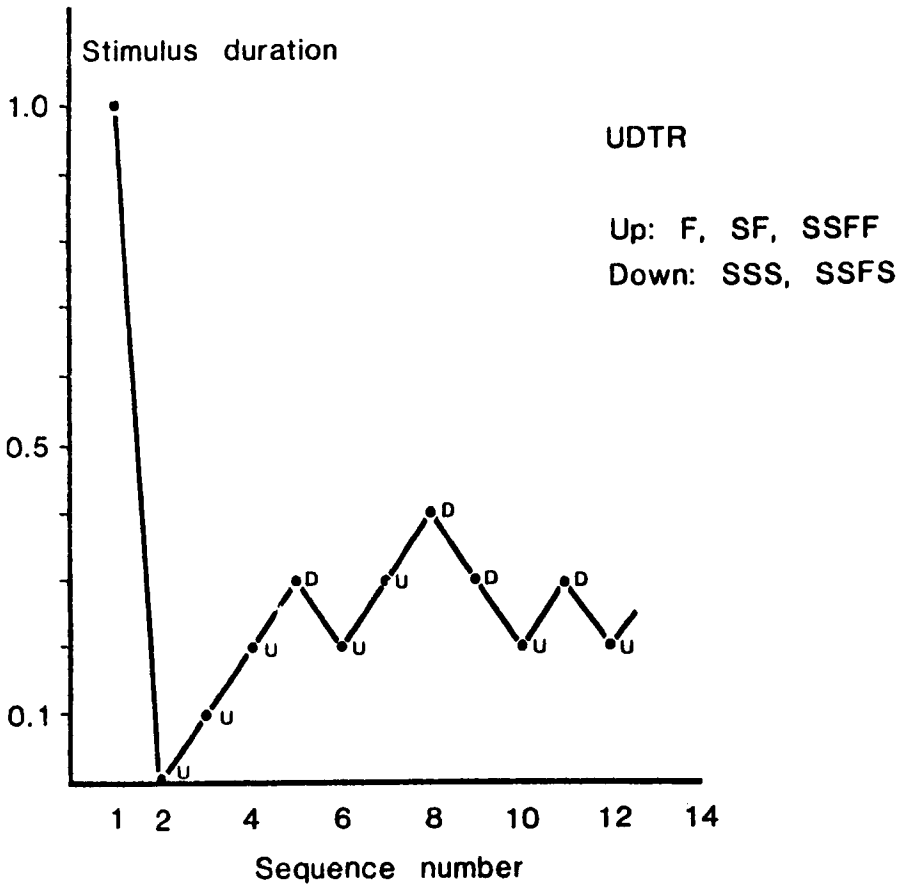
for one site is 15 (lasting about 9 minutes). Figure 3 shows a typical series of trials. These modifications of the standard UDTR have two important advantages. First they allow a fast approach to the threshold level and reduce the test time considerably, and secondly, they provide up to 90 levels of stimulus duration. This makes the technique very precise in determining the threshold value and increases the sensitivity of the technique in detecting mild changes in the threshold value on repeated testing.

There are certain critical aspects of the apparatus design that require further descriptions. These are as follows:

1. **Thermode size:** The Peltier thermode stimulating area of 12.5 cm^2 (25mm x 50mm) was selected for the following reasons. It was most suitable for the sites of the skin examined. It insured adequate spatial summation which is necessary to increase the sensitivity and decrease the variability of the threshold measurements (Kenshalo et al, 1967; Stevens et al, 1974). It guaranteed effective transfer of the applied stimuli to the receptor zone (Hensel 1952a), and with such area the range of complete adapttion of the skin temperature (30-36^{o}C) remains effective at a rapid rate (Kenshalo and Scott 1966). The variability of thermal thresholds increases with small sized probes (Lele 1954; Kenshalo et al 1967) and complete contact with the skin is difficult with larger probes.

2. **Thermode application:** The thermode pressure on underlying skin was standardised at all sites in all subjects by adding a fixed weight to the thermode. The total mass of the thermode and the additional weight was 350 g. The alteration of the cutaneous circulation caused by the application of the thermode was thought to be negligible. The effect

Figure 3 The graphical representation of tne up-and-down transform rule (UDTR) used in the determination of each thermal threshold in tne Glasgow Tnermal System. (Jamal et al, 1985a; Reproduced with permission).


Stimulus duration
1.0
0.5
0.1
UDTR
Up: F, SF, SSFF
Down: SSS, SSFS
U
D
1 2 4 6 8 10 12 14
Sequence number

of this standardisation on the reproducibility of thermal thresholds measurement was studied in our laboratory (see Chapter 5).

3. **Initial skin temperature:** The initial skin temperature under the probe was always kept between 34-35°C. In a few cases this was achieved by changing the temperature of the circulating water. At this chosen range of skin temperature, the influence of the initial skin temperature on thermal threshold variability is minimal (Ebaugh and Thauer 1950; Hensel 1950b; Lele 1954; Kenshalo et al, 1961). Complete and quick adaptation to this temperature occurs (Hensel 1950b; Kenshalo et al, 1961; Kenshalo and Scott 1966; Kenshalo 1978), and the thermal receptors are adequately sensitive to dynamic changes of temperature (Hensel and Boman 1960; Konietzny and Hensel 1980; Hensel 1981,1982). This factor was also investigated by our technique (Chapter 5).

4. **Rate of change of temperature of the stimuli:** The rate of change of temperature was kept constant throughout at 1°C/s. This rate of change of temperature is the middle of the preferred range of 0.5 - 1.5°C/s, at which the variation of thermal thresholds is at its lowest (Kenshalo et al, 1968; Molinari et al, 1977; Kenshalo 1978). This rate could be maintained constant over a wide range of temperature changes with the thermode used (Kenshalo 1963), it approaches conditions of daily experience with thermal sensation (Hilder et al 1974) and at this rate the numerical value of change of temperature in °C is equal to the duration of stimulus application in seconds. The effect of the rate of change of temperature on thermal thresholds was also investigated by the technique before choosing this rate (Chapter 5).

5. **Calibration of the thermode:** The thermode is calibrated on each application in all the subjects. The exact power (and hence the current) needed to obtain a rate of 1°C/s (or any other rate) is

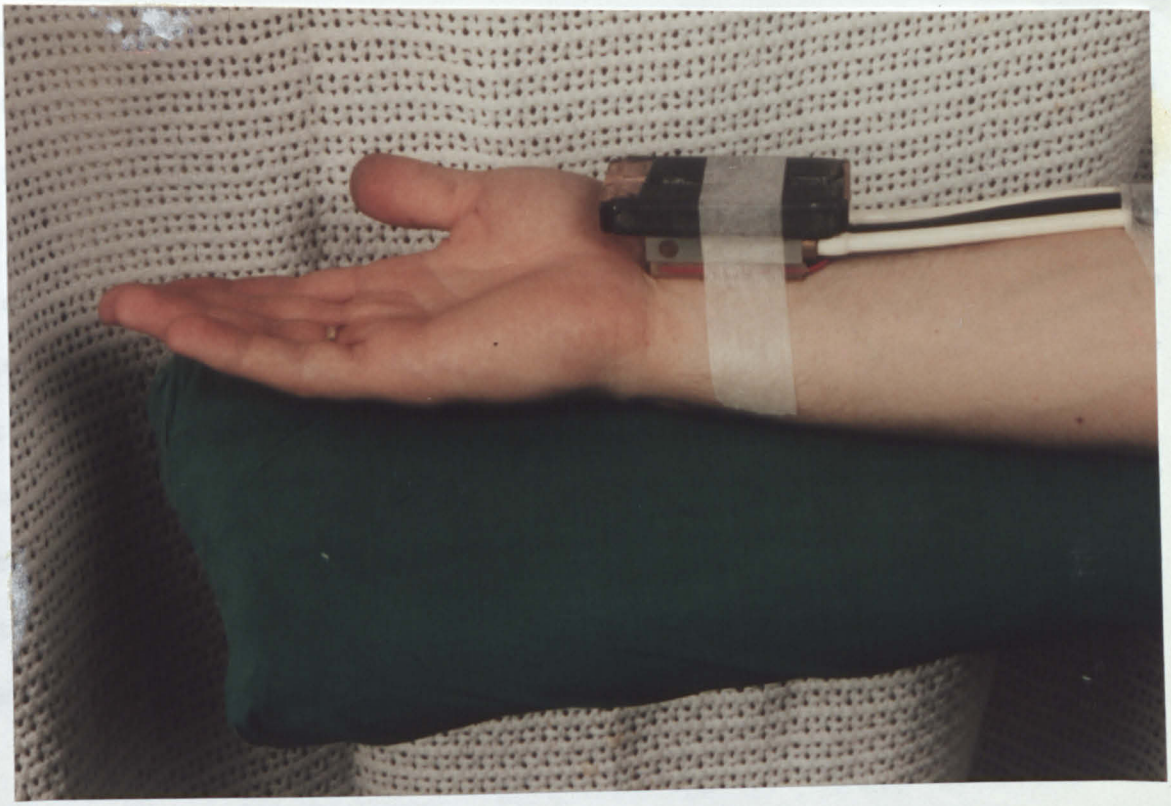
calculated prior to testing. Heat transfer and exchange in the skin depend not only on the power applied but also on the thermal properties of the skin (Chapter 2). This calibration of the thermode, therefore, at least minimises the effect of the variation of skin thermal properties on the measurement of thermal thresholds and helps to keep the rate of change of skin temperature at the set value. The power needed to give the same rate (1°C/s) of temperature change at the skin sites tested ranged between 2.8–4.2 W.

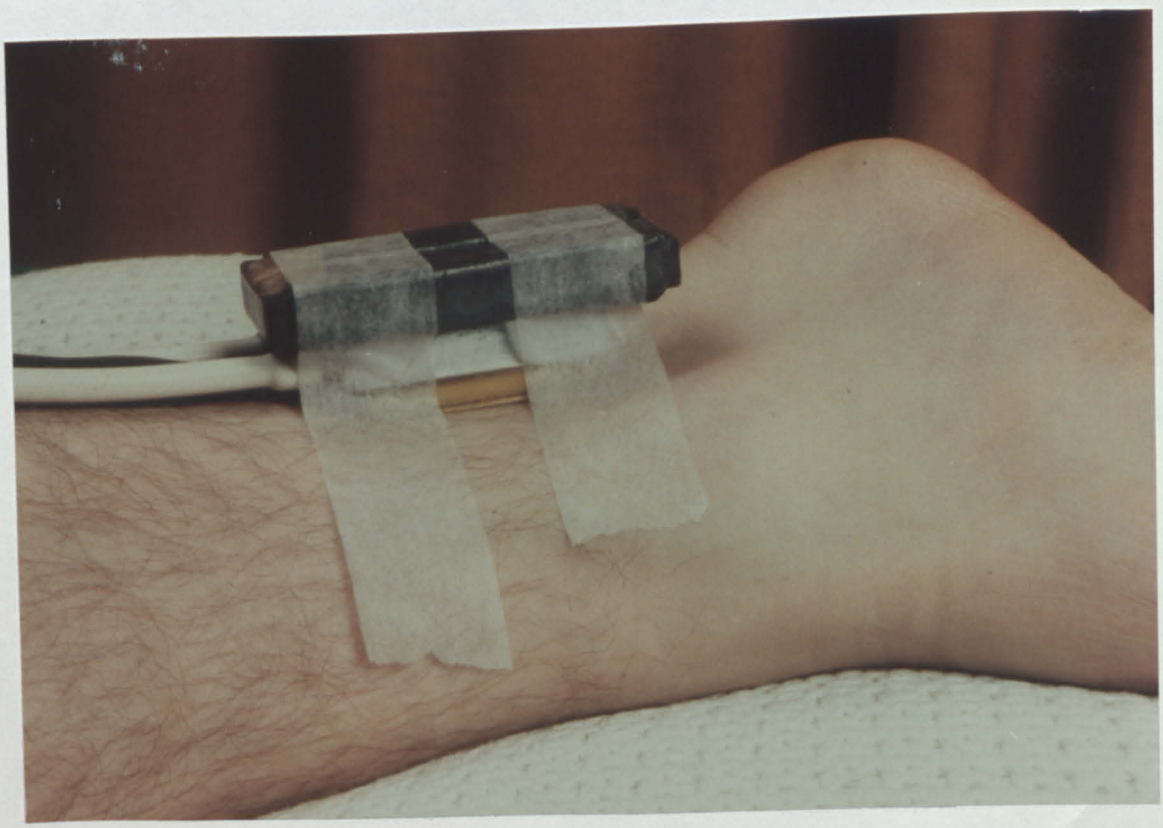
Methods

The tests were carried out in a quiet room at a constant temperature of 22 ± 2°C. Any site of the skin on which the thermode is applicable could be examined. Five sites were chosen for study in each subject. Four sites on the right side were used: (a) the volar aspect of the wrist just proximal to the distal wrist crease (Figure 4), (b) the volar aspect of the mid forearm, (c) the medial aspect of the ankle where the lower edge of the probe lies posterior to the medial malleolus (Figure 4), (d) the anterior aspect of the thigh midway between the anterior superior iliac spine and the tip of the patella. In order to study contralateral variations, the homologous site on the left forearm was also tested. These sites were chosen with the clinical applications of the technique in mind. At the volar aspect of the wrist and forearm (sites (a) and (b)) the epidermis is relatively thin with only negligible inter-individual variation (Stoll 1977). At the sites chosen the thermode had good contact with the underlying skin. The order of testing of these body sites was counterbalanced across subjects.

The subject was placed in a comfortable position so that the thermode and the weight, taped in place, acted perpendicularly on the site tested (Figure 4). Testing the wrist and forearm was done while the subject was

Figure 4 The application of the thermode to the volar aspect of the wrist (above) and to the ankle (below).





seated comfortably in a dental chair with especially designed arms; testing the thigh was done with the subject lying on his back and the ankle with the subject lying on his left side. Each subject was placed so that he/she could not see the VDU screen or the digital thermometer on the TIU. The subject was then handed the stimulus indicator and instructed that the two lights would illuminate in sequence at intervals of 30 seconds. With one of the lights a hot (or cold) stimulus would be applied, immediately following which the subject was forced to choose in which time period the stimulus occurred. A short demonstration of the test was carried out for most of the subjects. The sequence of determination of heat and cold thresholds was counterbalanced across the subjects.

CHAPTER 5

APPLICATION OF THE TECHNIQUE TO NORMAL SUBJECTS

Two main sets of studies were performed on normal subjects. In the first set, the aim was to investigate the effects of various factors which might affect the measurement of thermal thresholds and to identify the conditions in which such measurements show high reproducibility both among a group of normal individuals and in the same individual on repeated determinations. In the second set, the results of the application of the technique after its standardisation to a large number of normal subjects are presented.

The Effect of various Factors on the Variability of Thermal Thresholds

In each of these studies the methodology of the technique was as described in the previous chapter with the exception of the particular item under investigation. From the results of these studies and reviews of similar studies in the literature, the standardisation of the technique was achieved. The following factors were studied.

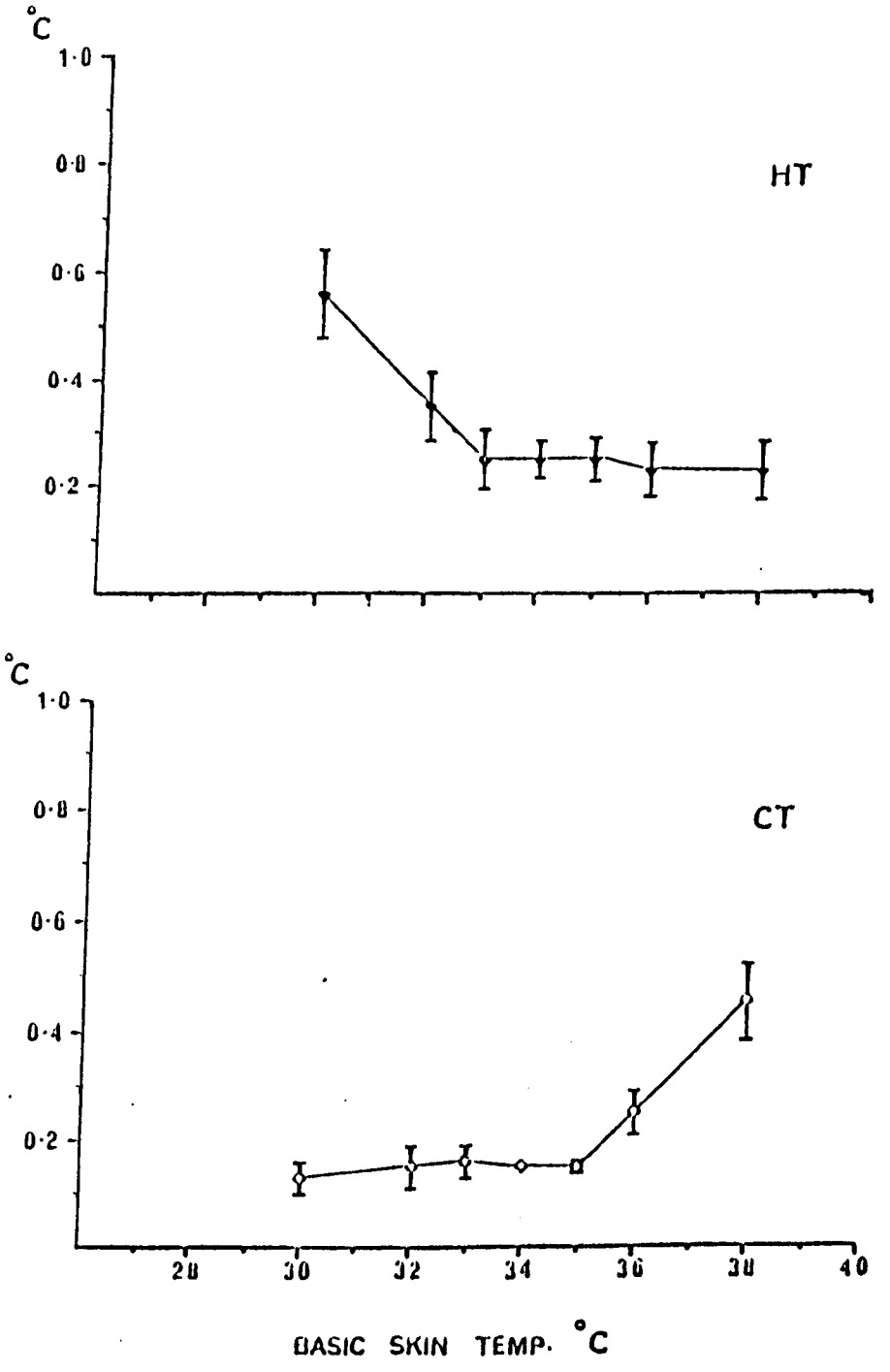
(a) The effect of the adapting basic skin temperature on thermal thresholds measurement.
(b) The effect of the rate of temperature change on thermal thresholds measurement.
(c) The effect of the standardisation of thermode application on thermal thresholds measurement.
(d) The effect of the response bias on thermal thresholds measurement.
(e) Determination of heat and cold pain thresholds.

(a) **The effect of basic skin temperature:** This study was performed to investigate the relationship between thermal threshold values and variability as a function of the basic skin temperature on the top of

which the stimuli are applied. The data obtained from this study are presented in Figure 5. Thermal thresholds for the volar aspect of the wrist just proximal to the distal wrist crease was estimated for a 28 year old female subject 10 times at each adapting skin temperature ranging from 28-40°C at 1°C intervals. All temperature changes were presented at a rate of 1°C/s. At the start of a measurement session, the subject was seated comfortably in a dental chair. The measurements were made in a room at a constant temperature of 22 ± 2°C. The subject was allowed 20 minutes to accommodate to the room temperature. Any single session lasted for not more than 30 minutes. The thermode was put in place as described before (Chapter 4) and the temperature of the waterbath was changed until the desired basic skin temperature was obtained with an accuracy of ± 0.1°C.

It is clear from Figure 5 that both HT and CT are dependent on the basic skin temperature. HT is large at low adapting skin temperature and small at higher adapting temperature. The opposite changes are noted for CT. The intra-individual variability of HT and CT also changed with the change of adapting basic skin temperature. The intra-individual variability and the actual values of HT and CT, within the complete adaptation zone, were least between basic skin temperatures 34-35°C. These findings are in agreement with those of Hensel (1950b) and Lele (1954). The divergence of the thermal threshold values at the extreme temperatures appears to be, at least in part, related to the temperature limits to which complete adaptation occurs and the change in TC of the skin. The findings of microneurographic studies on peripheral thermosensitive units show that their dynamic impulse frequency is dependent on the basic skin temperatures within the range (Konietzny and Hensel 1977,1980; Hensel 1981). The subject in this study consistently reported sustained warm and cold sensations at

Figure 5 Changes in the mean value and the intra-individual variability of thermal thresholds as a function of the basic skin temperature in a 28 year old female subject. The diamond shaped points are the mean of 10 repeated measurements at daily intervals while the perpendicular lines between the two bars represent one SD above and below the mean being a measure of the intra-subject variability. It is clear that the best reproducibility of HT and CT measurements was encountered at basic skin temperatures of 34 and 35°C.


°C
1·0
0·8
0·6
0·4
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HT
°C
1·0
0·8
0·6
0·4
0·2
CT
28
30
32
34
36
38
40
BASIC SKIN TEMP. °C

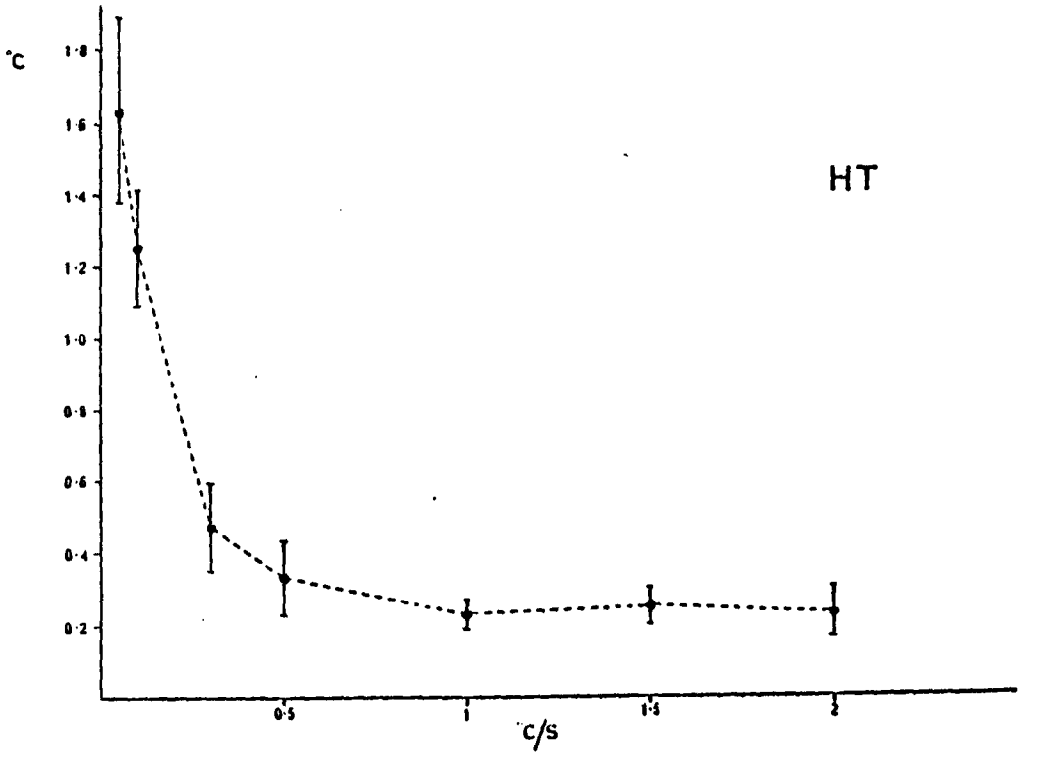
temperatures above 36°C and below 29°C respectively. Careful description of sensations to changes of skin temperature above and below the zone of complete adaptation is presented in Hensel's report of 1950b.

(b) **The effect of rate of change of temperature:** This study was performed on the same subject as in the previous study, that is, a 28 year old female subject. The volar aspect of the R wrist (site a) was chosen for testing. Each of HT and CT measurements were repeated 10 times at each of the rates studied at intervals of at least one hour. The basic skin temperature was always kept between 34-35°C and the rest of the methodology was as described before in Chapter 4. The measurements were made while the subject was seated comfortably in a dental chair with the arm supported. Each session did not last for more than 30 minutes.

The data concerning the relation between the rate of change of temperature and thermal thresholds are summarised in Figure 6. It is clear that the value of the thresholds and their intra-individual variability are high at slow rates of temperature changes, especially at rates below 0.1°C/s. The least intra-individual variability is encountered at rates of change of stimulating temperature between 0.5-1.5°C/s. This finding is in agreement with other studies (Kenshalo et al, 1968; Molinari et al, 1977). The increase of intra-individual variability at rates of 2°C/s or above is believed to be due to the difficulty of maintaining the rate of change of temperature at the specific value (Kenshalo 1963).

(c) **The effect of standardisation of thermode application:** This study was performed on a 26 year old male subject on the R wrist (site a, Chapter 4) to test the effect of a fixed pressure of application of the thermode on the intra-individual variability of thermal thresholds

Figure 6 The effect of the rate of change of the stimulus temperature on thermal threshold measurements in the same subject as in Figure 5 (28 year old female). Each solid dot or open circle represents the mean of 10 repeated measurements at daily intervals while the perpendicular lines with bars at the ends represent one SD above and below the mean. Both HT and CT values and their intra-individual variability increase with a decrease in the rate of change of the stimulus temperature, especially at rates below 0.5°C/s. The variability of both HT and CT is small at a rate of 1°C/s.


°C
1·8
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HT
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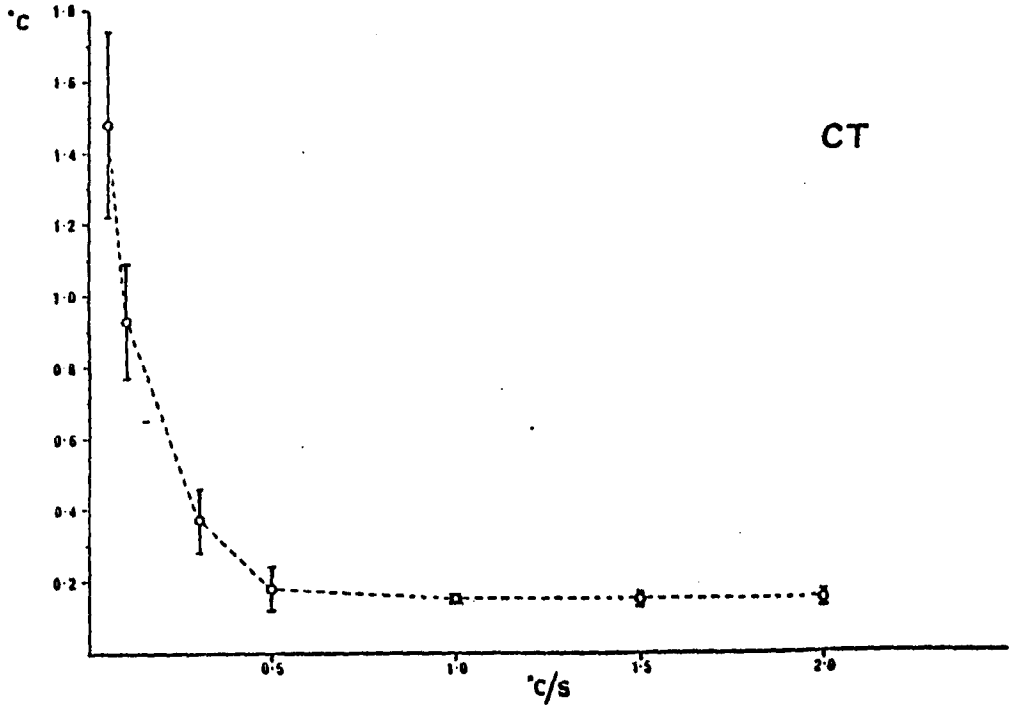
2
°C/s


°C
1·8
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0·4
0·2
CT
0·5
1·0
1·5
2·0
°C/s

measurement. Two sets of investigations were carried out. In the first, the thermode was applied to the wrist with the fixed weight on the top (both equal to 350 g) in a perpendicular direction as described previously (Chapter 4). The thermode and the weight were taped in place without adding any extra pressure. In the second set of investigations, the thermode (without additional weight) was strapped to the site by a different operator who was instructed to try to strap it with equal force each time. The test was repeated 10 times for each of the applications for each CT and HT measurement. The results are summarised in Table 1. The standard deviation for the repeated studies in the same individual is the measure of intra-individual variability and it is high in the second set of studies, where the thermode was applied without standardisation,both for HT and CT (Table 1). Failure to standardise the appliction of thermode has been suggested as a possible cause of variability of thermal threshold measurements (Kenshalo 1970). Its effect, however, has not been tested previously.

(d) **The effect of response bias:** The effect of using various psychophysical methods for the determination of sensory thresholds on thermal threshold measurements and their reproducibility was studied. The subject, a 23 year old male undergraduate medical student, underwent three sets of studies each consisting of 10 repeated measurements of wrist HT. In the first set, the switch pressing method was used where he was asked to press a switch immediately with the first feeling of the warm sensation. In the switch method, the average of 5 readings was taken for each HT measurement. In the second set of studies, the classical method of threshold determination with preset heat intensity levels was used (Guilford 1954). The subject was warned shortly before the application of a stimulus and he was asked to report

TABLE 1: Comparison of means, SDs and largest deviations from the initial values of the right wrist HT and CT on 10 repeated measurements for each with and without the standardisation of the pressure of application of the thermode in a 26 year old male subject

	Thermal Thresholds(°C)	
	Controlled thermode application	Uncontrolled thermode application
HT mean	0.248	0.274
SD	0.006	0.120
largest deviation from the initial value	0.02	0.18
CT mean	0.15	0.17
SD	0	0.08
largest deviation from the initial value	0	0.13

HT : heat threshold

CT : cold threshold

honestly whether or not he felt the stimulus. If the subject gave a positive response the next stimulus intensity was reduced by $0.1^{o}C$ and if he gave a negative response the following stimulus intensity was increased. In order to make comparison easy, the UDTR method of sequential analysis was used where the average of six changes of direction was taken as the HT in a manner identical with that described in Chapter 4. In the third set of studies the forced-choice method and the UDTR as described in the standard method (Chapter 4) was used. The rest of the methodology for the three sets of studies was identical and as described before (Chapter 4).

Table 2 summarises the results of the three sets of studies in terms of the means and standard deviations of the 10 HT measurements by each method. The mean values represent the value of the threshold while the values of SD represent the variability of HT measurement in that subject. The lowest value of HT and the least intra-individual variability are clearly obtained with the forced-choice method.

In the switch method, the subject is required to switch off the heating once the sensation was appreciated. This introduces a considerable error as once the perception threshold is reached, the thermal stimulus continued to change for a period of time equal to the delay in the afferent pathway (delay of perception) and the subject's reaction time. The measured threshold was, therefore, greater than the real threshold by the heat produced over that time interval. This reaction time and the subject's response bias were most probably the main reasons behind the pronounced intra-individual variation noted in this method (Table 2). In the second method, the subject judges the presence or absence of the presented stimulus using an internal standard or criterion which may vary considerably from time to time (Green and Swets 1966). This is probably the reason for the increase

TABLE 2: The value and the reproducibility of HT measurement on a 23 year old male subject using three different psychophysical methods of threshold determination. For each method, 10 repeated measurements were performed at intervals of at least 24 hours.

R Wrist HT(^{o}C)	Switch method	Classical method	The Forced-Choice method and UDTR
mean	0.88	0.56	0.246
SD	0.39	0.12	0.008
largest deviation from the initial value	0.45	0.30	0.02

UDTR : up-and-down transform rule

of mean HT value and the intra-individual variability. In the third method, where the intensity of the heat stimulus is predetermined the effect of reaction time is eliminated and the use of the forced-choice eliminates the subject's response bias (Green and Swets 1966). The HT value and the intra-individual variability are smallest in the third method (Table 2). The forced-choice method, therefore, gives a more accurate and less variable measure of thermal threshold.

(e) **Measurement of heat and cold pain thresholds:** This study was performed to determine the average limits of heat and cold stimuli at which heat pain and cold pain sensations start using the same thermode, with identical application, the same rate of temperature change ($1^{o}C/s$) and basic skin temperature ($34-35^{o}C$) as in the standard methodology for measurement of thermal thresholds (Chapter 4). A different psychophysical criterion, however, was used as it is impossible to apply the forced-choice method for thermal pain thresholds measurement. The subject was instructed that, following an indication of the start of a test, an increasing intensity of heat (or cold) stimulus would be applied and he was asked to press a switch with the first feeling of pain. Pressing this switch stopped the stimulus increment and the stimulus intensity at that point was displayed as the pain threshold measured in ^{o}C. For each heat (or cold) pain threshold, the average of five consecutive readings differing by less than $0.5^{o}C$ was taken to represent its value. Measurement of thermal pain thresholds was carried out in 63 of the normal subjects who participated in the thermal thresholds' studies. They consisted of 29 male and 34 female subjects whose ages ranged between 17-63 (mean = 34, SD = 14.7) years. Thermal pain threshold measurements were performed on sites a (the R wrist) and c (the R ankle) in a room with controlled ambient temperature of $22 \pm 2^{o}C$.

The results are summarised in Table 3 in terms of means and SDs. These values of thermal pain thresholds are in close agreement with other studies with a similar set up and an identical thermode (Fruhstorfer et al, 1976a; Lindblom and Verillo 1979). Pain threshold is variable and depends mainly on subjective criteria (Fruhstorfer et al, 1976a). The higher SDs for cold pain are explained by the fact that the criterion for cold pain is more difficult to establish by the subject (Lindblom and Verillo 1979). The mean heat and cold pain thresholds are all well outside the range of temperatures in which the standard thermal technique operates, that is 9°C on either side of a basic skin temperature of 34-35°C (Chapter 4). It is concluded, therefore, that at least in normal subjects the range of thermal stimulus intensities of the technique investigates the thermal system primarily.

STUDIES AFTER STANDARDISATION OF THE THERMAL TECHNIQUE

Quantitative tests of sensation are used at the bedside to answer two main questions: (1) Does the patient have an abnormality of sensation? The essential data needed to answer this question are a large bank of control measurements from subjects of a wide age range from both sexes. From this a range of normal values according to a particular criterion (eg 99% CL) is established. Loss of peripheral nerve fibres is a normal phenomenon of aging (Jacobs and Love 1985). Age dependent confidence limits therefore should also be obtained. (2) The second important question to answer is: Do the results indicate a significant change of function of the sensory system since the last test? To answer this question, control intra-individual variability studies over short and long time are needed. Paired observations must be made in a large group of subjects and the data of differences between paired values of individuals must be analysed. A significant change can then be recognised if two

TABLE 3: Mean and SDs of heat pain and cold pain thresholds in 63 normal subjects

Site	Pain threshold	mean (^{o}C)	SD
Wrist	heat pain	46.2	3.2
	cold pain	18.3	7.1
Ankle	heat pain	46.4	2.3
	cold pain	14.0	6.9
Thigh	heat pain	46.8	2.5
	cold pain	15.8	8.1
Forearm	heat pain	45.9	2.7
	cold pain	16.2	10.8

sequential measurements differ by more than a certain probability value (eg 99% CL) of all paired differences.

To answer these and other questions, the standard technique, as described in Chapter 4 was applied to 106 control subjects, aged between 6-73 (mean = 33, SD = 17) years, all free of neurological illnesses and none taking drugs or excessive quantities of alcohol. These subjects were drawn from among the staff and their relatives of the Institute of Neurological Sciences, Southern General Hospital, Glasgow. Of these, 45 were male and 61 female. None had previous experience of sensory testing. In each subject all the sites described were studied.

The results of thermal threshold values are given as the deviation from basic skin temperature with mean SD and the 99% upper confidence limit for various sites tested. The normal mean HT for the wrist was 0.23°C (SD = 0.06°C). The SDs of HT and CT for wrist, forearm and thigh and CT for ankle were almost half the smallest step in the stimulus intensity. Thermal thresholds varied only slightly between wrist, forearm and thigh (Table 4). HT and to a lesser extent cold thresholds were higher at the ankle than elsewhere. The reasons for this increase are not known. In 80 subjects above the age of 20 years the leg length measured from the anterior superior iliac spine to the tip of the medial malleolus did not correlate with HT ($r = 0.0225$) or CT ($r = 0.0195$). As expected, there was also no correlation between age and leg length ($r = 0.0249$). Subjects older than 20 years of age were selected for this correlation because of the epiphyseal closure after which minimal growth of the leg length occurs. Leg length, therefore, does not contribute to the findings of higher thermal thresholds at ankle.

Thermal thresholds are known to vary at different sites of the human body (Lele 1954; Kenshalo 1960,1970,1978; Poppendiek et al, 1966; Nadel et al 1973; Stevens et al, 1974; Stoll 1977; Dyck et al, 1984). The skin of

TABLE 4: Thermal threshold values for 106 normal subjects

Site	Type of threshold	Mean	Standard deviation	Upper limit of normal (99% CL)
		°C	°C	°C
Wrist	HT	0.23	0.06	0.40
	CT	0.15	0.05	0.27
Forearm	HT	0.24	0.06	0.41
	CT	0.15	0.05	0.29
Thigh	HT	0.23	0.06	0.40
	CT	0.15	0.05	0.27
Ankle	HT	1.35	0.73	3.28
	CT	0.17	0.06	0.32

Threshold values represent the change from the basic skin temperature.

(Jamal et al 1985a, reproduced with permission)

the calf, for example, among other sites examined, has been found to be the least sensitive especially at threshold levels (Stevens et al 1974; Cohen 1977; Stoll 1977). This may be due to differences in the thermal properties of the skin (Cohen 1977; Stoll 1977). A considerable variation in the density of thermal receptors and warm and cold spots from one region of the skin to another has been reported (Strughold and Porz 1931; Wall 1971; Stevens et al, 1974). The density of heat receptors is absolutely less but their variability is greater than that of cold receptors (Strughold and Porz 1931; Light and Perl 1984). If these thermal receptors are present in a lower density distally this might explain the higher thresholds at ankle. If the heat receptors are disproportionately fewer at the ankle, this will account for the greater increase of ankle HT. The influence of central processing on variation in temperature appreciation at various sites is also a possible factor in this context.

Comparison between two sides (Table 6) showed that there was no significant difference between the right and left forearm measurements of HT and CT. Measurements of thermal thresholds for both sides were performed with less than 24 hours interval between the two tests for each of the 106 normal subjects.

Thermal thresholds in both sexes

Among the 106 normal subjects examined there were 45 male and 61 female subjects. There was no significant difference between ages of males (mean = 32.5, SD = 17.8 years) and females (mean = 34.7, SD = 17.1 years) using student's t test. Table 5 summarises the means, SDs and their comparisons for male and female subjects and shows the absence of any significant difference in thermal thresholds between the two sexes. Kenshalo and his co-workers (1961) have found no difference between two male and two female subjects in their thermal thresholds when warm and cooling stimuli were applied to their skin within the complete adaptation range of skin

TABLE 5: Comparison of thermal thresholds in both sexes

Item			Male (n = 45)	Female (n = 61)	P
Age		mean	32.5	34.7	NS
		SD	17.8	17.1	
Wrist	HT	mean	0.24	0.24	NS
		SD	0.06	0.07	
	CT	mean	0.15	0.14	NS
		SD	0.05	0.05	
Ankle	HT	mean	1.46	1.38	NS
		SD	0.86	0.84	
	CT	mean	0.18	0.17	NS
		SD	0.07	0.06	
Forearm	HT	mean	0.24	0.24	NS
		SD	0.05	0.05	
	CT	mean	0.15	0.15	NS
		SD	0.05	0.05	
Thigh	HT	mean	0.24	0.24	NS
		SD	0.06	0.05	
	CT	mean	0.15	0.15	NS
		SD	0.05	0.04	

temperature (30-36°C). Other workers have also found no significant sex difference (Dyck et al, 1978,1984). This finding is in line with the consensus that most sensory processes are remarkably without sexual differentiation, except perhaps for olfaction (Beidler 1961).

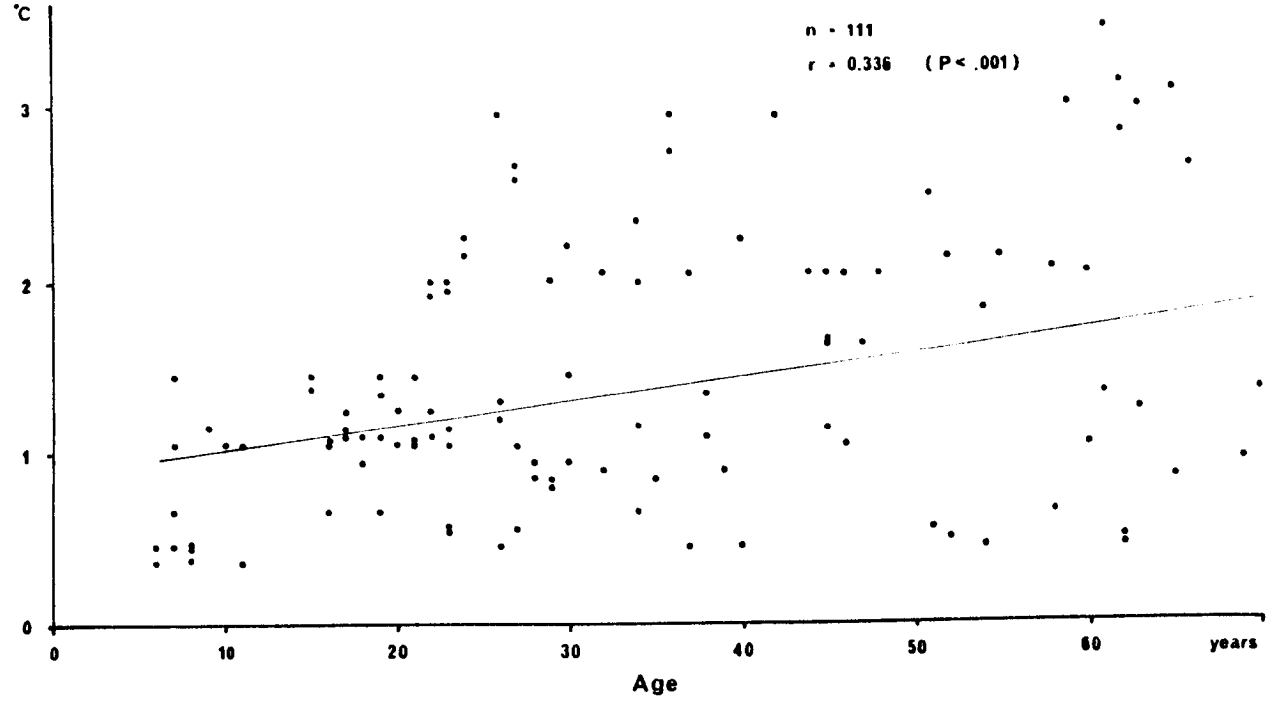
Kenshalo and his co-workers in 1961 demonstrated that at basic skin temperatures higher than 36°C, female CT was consistently smaller than male CT. In a further study, Kenshalo (1966) demonstrated that there is an effect of the menstrual cycle on CT values in females but only when the CT is measured from basic skin temperatures higher than 36°C - 40°C. The CT values were found to be smaller at the time of ovulation and throughout the post-ovulatory period to the onset of the next menses at which time the CT was larger. These changes were attributed to the hormonal changes accompanying the menstrual cycle (Kenshalo 1966). They disappeared at basic skin temperatures between 30-36°C (Kenshalo et al 1961; Kenshalo 1966). All of our subjects were examined at basic skin temperature of 34-35°C.

Age and thermal thresholds

To investigate the relation of thermal thresholds with age, wrist and ankle HT and CT values were correlated with ages of 111 normal subjects whose ages ranged between 6 and 73 (mean = 33.6; SD = 17) years. The distribution of ankle HT and CT values as a function of age is shown in Figure 7. There was a significant linear increase of these values with age for ankle HT ($P < 0.001$) and CT ($P < 0.005$). Figure 8 shows the means and SDs of ankle HT and CT values for the various age decades. It clearly shows that there is a trend for both their mean threshold values and SDs to increase with age. Many older subjects, however, were as sensitive as younger subjects (Figure 7). There was also a significant linear increase of wrist CT with age ($P < 0.001$) but not in the case of wrist HT and age (r

Figure 7 Ankle HT and CT changes with age.

Ankle HT



Ankle CT

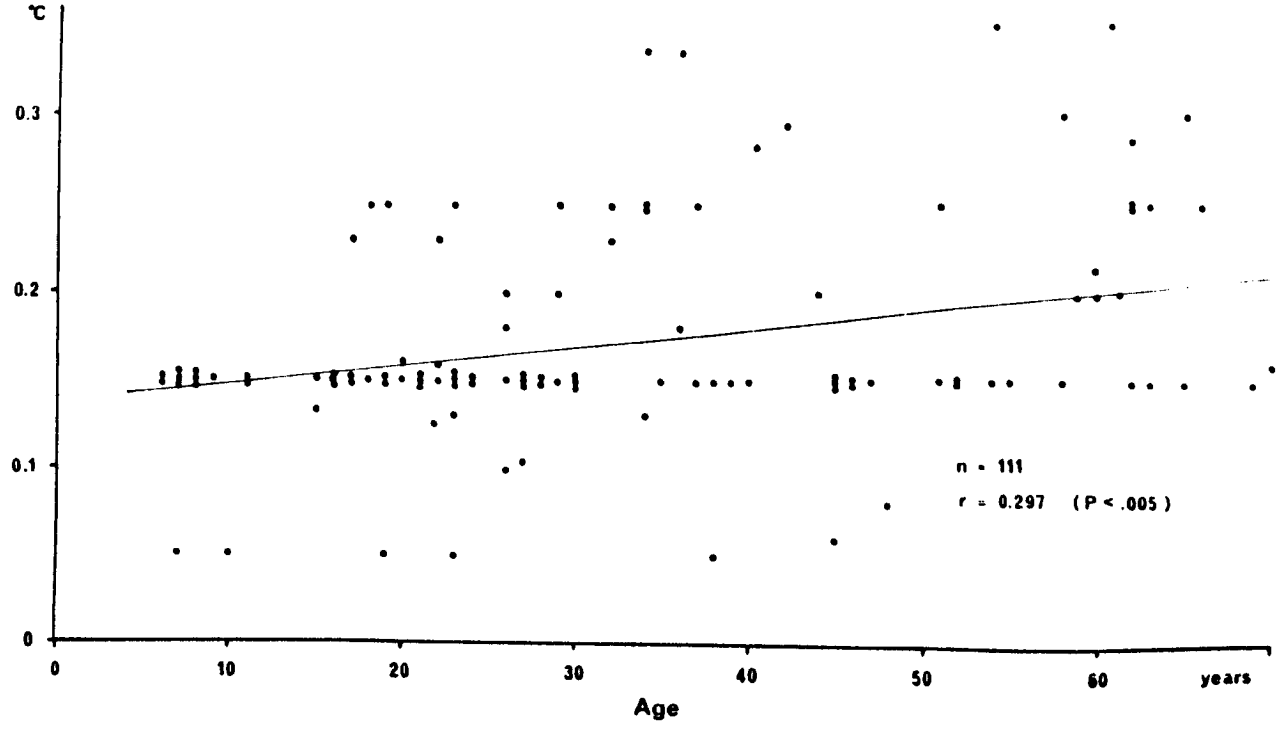
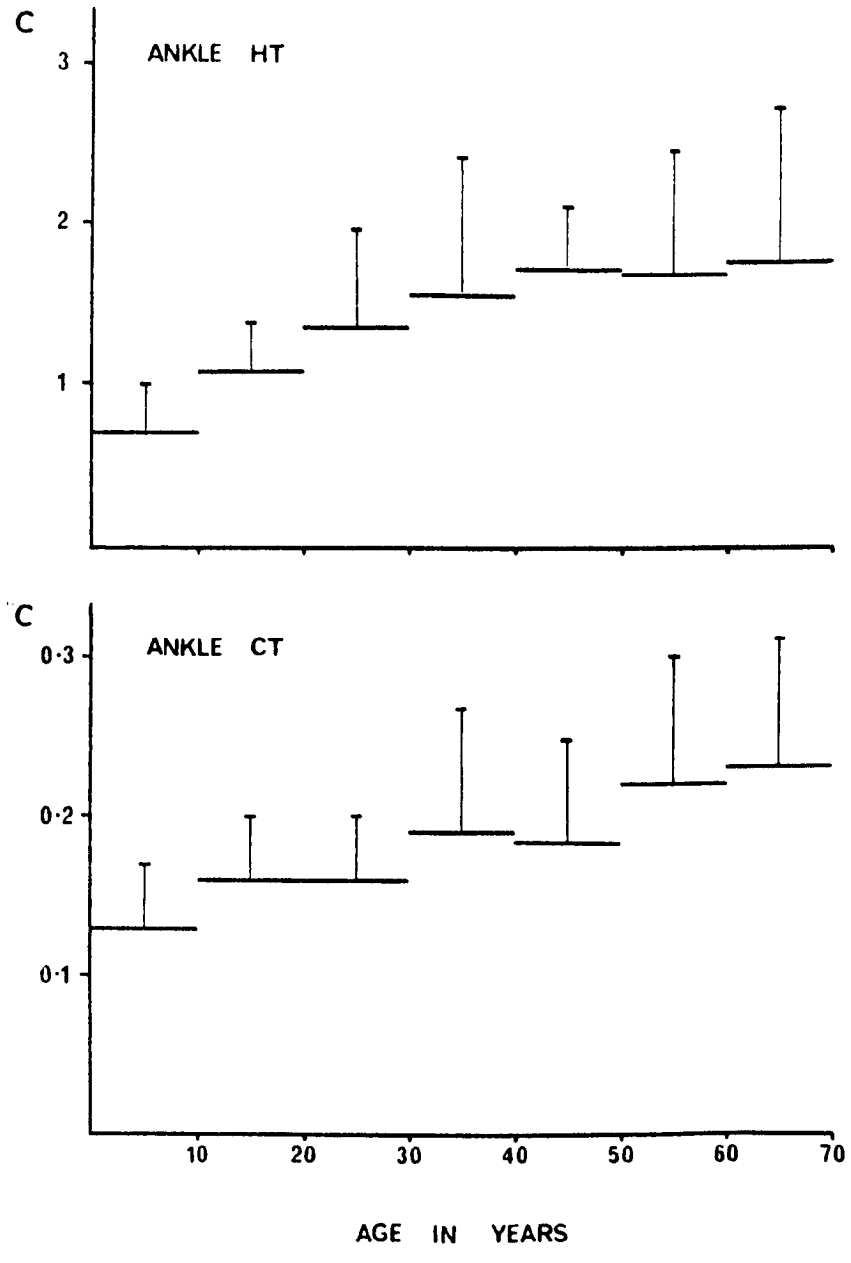


Figure 8 Means (thick horizontal lines) and SDs (thin vertical lines) of ankle HT and CT in various age decades. With increasing age there is a trend for both the mean and SD of thermal thresholds to increase.


C
ANKLE HT
3
2
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50
60
70
AGE IN YEARS

= 0.17; NS).

The increase of thermal thresholds with age, as with most other sensory systems, is expected and has been reported in other studies (Kenshalo 1970; Fruhstorfer et al, 1976a; Dyck et al, 1978,1984). This may be due to a progressive reduction in the number of nerve fibres with age (Jacobs and Love 1985) and/or a decrease in the number of receptors per nerve fibre (Wall 1971). Alternatively, changes in the functional properties of these fibres and/or receptors in the absence of structural changes may be important (Dyck et al 1984). The greatest increase of thermal thresholds at the ankle is consistent with the fact that age related changes are likely to be more pronounced in longer nerve fibres and their end organs. If fewer thermal fibres and their end organs are present at the ankle, then mild fibre loss due to aging is probably more evidently reflected in thermal thresholds as the latter are dependent on spatial summation.

Diurnal variation in thermal thresholds

To test for variation of thermal thresholds determined at different times of the day, some subjects were tested at site (a) in the morning (n = 39), others in the afternoon (n = 35) while a third group was tested during both periods (n = 32). Comparison of the wrist HT in the morning (mean = 0.244; SD = 0.05^{o}C) with wrist HT in the afternoon (mean = 0.246; SD = 0.05^{o}C) showed no significant difference (t = 0.0524). Similarly, comparison of the wrist CT for subjects tested in the morning (mean = 0.17; SD = 0.05^{o}C) with those tested in the afternoon (mean = 0.16; SD = 0.05^{o}C) showed no significant difference (t = 0.014). Paired 't' test was performed on the paired values for wrist HT and CT for 32 subjects each of whom had both measurements made in the morning and in the afternoon. This also showed no significant difference both in the case of wrist HT (r = 0.0682, NS) and wrist CT (r = 0.0126, NS). Kenshalo and his co-workers (Kenshalo et al 1961; Kenshalo 1966,1970) found no diurnal variation in the

measurement of HT at all adapting basic skin temperatures and of CT at adapting basic skin temperature below 36°C. These workers, however, did find that the afternoon values for CT were lower than the morning values if basic skin temperatures between 36 and 40°C were used. This change was particularly pronounced at basic skin temperature of 40°C ($P < 0.05$). Kenshalo (1970) postulated that this was due to variation of the body core temperature. As all the measurements in the present study were made at basic skin temperature of of 34-35°C, such variation is not expected to occur and this was confirmed.

Reproducibility of thermal thresholds measurement

To test the technique for its reproducibility in the measurement of thermal thresholds, both HT and CT determinations were repeated in the 106 subjects in the R forearm three times at intervals of 24-48 hours (between the first and the second) and more than two weeks (between the first and the third). In some cases the second interval was up to two months. These intervals were chosen to assess the short and long term reproducibility of the threshold measurement by the technique. The means, SDs, and the differences between means of the first, second and third determinations are presented in Table 6. The largest mean deviation from the initial determinations was 5%. The method of analysis of variance (ANOVAR) was applied to assess the significance of these changes. ANOVAR of HT values showed significant difference only between the first and the third test (two or more weeks later) ($P < 0.01$). The difference between the first and the third test for mean HT was only 1/10 of the smallest available step in the stimulus intensity. No significant difference was noticed between the first and second testings for HT and between first, second and third tests for cold thresholds. In the repeated measurements of R forearm in the 106 subjects, there was, however, a weak trend towards lower values with

TABLE 6: Consecutive thermal thresholds comparing repeated ipsilateral and contralateral investigations in 106 normal subjects

Site and type of the thermal threshold		Mean °C	Standard deviation °C	Change in Mean	
HT - R Forearm	1st	0.243	0.063		
	2nd (24-48 h)	0.236	0.061	- 2.9%	from 1st investigation
	3rd (> 2 wk)	0.230	0.059	- 5.3%	from 1st investigation
L Forearm		0.229	0.059	- 0.4%	from R side
CT - R Forearm	1st	0.152	0.052		
	2nd (24-48 h)	0.151	0.050	- 0.6%	from 1st investigation
	3rd (> 2 wk)	0.148	0.051	- 2.6%	from 1st investigation
L Forearm		0.142	0.046	- 4%	from R side

consecutive determinations of both HT and CT measurements, perhaps suggesting that a learning process is operative.

Long term intra-individual variation (at two or more weeks interval) was also assessed in 27 subjects for each of HT and CT at right wrist (site a) and right ankle (site c). The age of the subjects ranged between 17-60 (mean = 36; SD = 16.8) years. These subjects were among the 106 normal subjects referred to earlier. ANOVAR on this smaller group did not show significant difference between the initial and the subsequent test (at $>$ 2 weeks) for both HT and CT at the wrist and the ankle.

In the two groups (the 106 and the 27 subjects), paired 't' test was performed on the initial threshold values and the values obtained two or more weeks later to assess both the significance and the extent of long term intra-individual variation at the various sites tested. These results are summarised in Table 7. For each threshold at each site, the minimal change required to occur on consecutive tests to be significant at 99% CL in terms of absolute values and number of steps of stimulus intensity is shown in the last two columns of Table 7. Since the stimulus intensity steps in the Glasgow method is 0.1^{o}C and there are at least 90 available steps on the scale of testing, the measurements made by the technique are highly reproducible and the small changes noted, whether or not statistically significant, are of no practical significance in the implementation of the technique.

In addition to the above mentioned studies of repeated determinations of thermal thresholds, the reproducibility of the technique is also evaluated from the following studies:

1. On two subjects, a 29 year old female and a 26 year old male, 20 repeated measurements of the R forearm HT and CT were performed. The time intervals between the initial three tests were identical to those described above (24-48 hours for the first and more than two weeks for

TABLE 7: Comparison of longitudinal studies of thermal thresholds

Item			1st Test	2nd Test (> 2 weeks)	Difference*	P+	°C	Significant change at 99%CL smallest number of stimulus intensity steps
Wrist	HT	mean	0.234	0.229	-0.004	NS	0.1	1
		SD	0.06	0.07	0.036			
Wrist	CT	mean	0.145	0.144	0.006	NS	0.094	1
		SD	0.05	0.06	0.032			
Ankle	HT	mean	1.36	1.38	0.001	NS	0.134	2
		SD	0.73	0.75	0.048			
Ankle	CT	mean	0.170	0.177	0.004	NS	0.115	2
		SD	0.08	0.09	0.04			
Forearm	HT	mean	0.243	0.23	0.014	0.01	0.10	1
		SD	0.06	0.06	0.043			
Forearm	CT	mean	0.152	0.148	0.005	NS	0.09	1
		SD	0.052	0.051	0.037			

Wrist and ankle studies were performed on 27 subjects while forearm studies were done on 106 subjects

* For each subject, a value was obtained from 2nd test - 1st test, which would be either zero (if no change between 2nd and 1st measurements), negative (if 2nd test was smaller) or positive (if 2nd test was larger) value. Means and SDs of these 27 values were calculated and are shown in this column.

\+ paired 't' test.

the second interval). The subsequent 17 tests were done at daily intervals. For HT, the largest deviation from the initial determinations (0.25°C for both subjects) was equal to 0.03°C. For the first subject, the mean HT was a 0.246°C (SD = 0.01); for the second subject the mean HT was 0.248°C (SD = 0.006). The values of CT for the first subject were identical to their initial values. For the second subject, CT values on subsequent tests varied to a maximum of 0.02°C from the initial measurement of 0.15°C (the mean CT = 0.149; SD = 0.009°C).

2. Evaluation of the results of repeated measurements performed on normal subjects comparing the intra-individual variability of the standard technique with that of alternative methodologies (see first section of this chapter) provides similar results on the reproducibility of the standard technique. These studies include the following:

Subject (a) In a 27 year old female nurse, wrist HT and CT measurements were repeated 20 times at daily intervals (Table 8 in Chapter 6). The largest deviation from the first HT value was 0.02°C (mean of 20 HT values = 0.025; SD = 0.01°C). The largest deviation from the first CT value was 0.03°C (mean CT = 0.15; SD = 0.01°C).

Subject (b) In a 23 year old male medical student, 10 repeated measurements of wrist HT showed that the largest deviation from the initial measurement of 0.25°C was 0.02°C (mean wrist HT = 0.24; SD = 0.01°C) (Table 2).

Subject (c) In a 26 year old male nurse 10 repeated measurements at daily intervals of wrist HT and CT were performed. The largest deviation from the initial value of HT (0.23°C) was 0.02°C (mean HT value = 0.248; SD = 0.006°C). All

subsequent values for the wrist CT were identical to the initial one of 0.15°C (Table 1).

Subject (d) 10 repeated measurements of wrist HT and CT in a 28 year old female subject showed similar reproducibility (Figure 5). The largest deviation from the initial value of wrist HT (0.23°C) was equal to 0.04°C (mean of HT values = 0.23; SD = 0.03°C). In the case of wrist CT, the largest deviation from the initial value of 0.15°C was equal to 0.03°C (mean CT value = 0.17; SD = 0.008°C).

In these four subjects, therefore, the largest difference between the initial threshold measurement and the subsequent 10 or 20 values was less than half the smallest step in the stimulus intensity (range from 0-0.04°C). The coefficient of variation ranged from zero to 13%.

CHAPTER 6

COMPARISON OF THE GLASGOW THERMAL SYSTEM WITH CURRENT TECHNIQUES

Values for thermal threshold measurement in the contemporary literature provide little consistency due to variations in the methodology of measurement including the stimulating apparatus, control of thermal stimuli and other variable factors (Chapters 3 and 4). It was clearly shown in Chapter 5 that using the same apparatus, type and size of thermode, pronounced variation in the values of thermal thresholds are obtained by changing the methodology.

Thermal threshold values obtained with the Glasgow method are in close agreement with measurements done on individual subjects in the psychophysical studies of thermal sensation performed by Kenshalo and others using Peltier based thermodes of more or less similar sizes to that used in the Glasgow technique (Kenshalo et al 1961,1967,1968; Kenshalo 1970; Molinari et al 1977). Using a thermode of 14.4 cm^2 stimulating surface area, a basic skin temperature of 32°C and a rate of change of stimulating temperature of 0.3°C/s, Kenshalo and his co-workers measured the HT value for the dorsal aspect of the R forearm in a normal subject at approximately 0.2°C (Kenshalo et al 1967) and for the same site in three other subjects at values ranging between 0.1 to 0.5°C (Kenshalo et al 1968). CT values for these subjects ranged from 0.1 to 0.3°C (Kenshalo et al 1968). At basic skin temperatures of 34-35°C, Kenshalo (1970) reported HT values for the same site ranging from 0.25 to 0.3°C for HT and from 0.2 to 0.25°C for CT in another seven normal subjects. Using a radiant heat method, a rate of 0.3°C/s and a stimulating surface area of 12 cm^2, the HT at the dorsal aspect of the R forearm was at values of 0.25 and 0.3°C for two normal subjects (Kenshalo et al 1967). In these experiments, the authors used the method of limits and not the forced-choice method. These

values clearly coincide with our reported values (Chapter 5).

Culler (1926) reported that the neutral zone in human finger, that is, the zone at which no thermal sensation occurs, is as low as 0.3°C (this results in HT and CT values of about 0.15°C, if we assume that the physiological zero lies in the middle of this zone). For this purpose he used waterbaths set at different temperatures with the subject moving the hand from the reference bath, after 5 minutes adaptation to the stimulating bath. Hardy and Oppel (1937,1938) and Oppel and Hardy (1937a,b) using the radiant energy method, demonstrated that the thermal system in man is extremely sensitive for detecting very small changes in the temperature of the skin. Values as low as 0.009°C (at a rate of 0.003°C/s for 3 seconds) for warm threshold were reported when stimulating a large surface area of more than 1500 cm^2 (Hardy and Oppel 1937). Low values for HT and CT were also reported by other workers using similar methods of stimulation (Ebaugh and Thauer 1950); they reported HT values of 0.03°C and CT values of 0.02°C. Hunt and McIntyre (1960) demonstrated in the cat that certain thermosensitive C fibres showed selective activity at changes of temperature of 0.2°C in their receptive fields.

The consistently lower values for thermal thresholds obtained by the Glasgow system contrasts with higher values obtained by some of the other methods employing Peltier based thermodes (Fruhstorfer et al, 1976a; Dyck et al, 1978,1984). In the Marstock method (Fruhstorfer et al, 1976a,b) the subject was required to switch off the heating (or cooling) once the sensation was appreciated. A similar switch method to that employed in the Marstock system was directly compared to the standard Glasgow system method and this produced higher thermal threshold values (Chapter 5; Table 2). In these two methods identical probes, rate of temperature change, basic skin temperature and thermode application were used. In the switch and the Marstock methods both the delay of perception and the subjects' reaction time are included in the time from the onset of the stimulus till the

subject presses the switch (see Chapter 5). The measured threshold is, therefore, greater than the real threshold by the heat (or cold) produced over the additional time interval. In the Glasgow system, where the time of application of thermal stimuli is predetermined by the computer, this problem does not arise leading to lower threshold values.

In the method of Dyck et al (1978,1984) a smaller thermode was used of 3.5 cm^2 stimulating surface area (versus 12.5 cm^2 in the Glasgow method). In their method the rate of change of stimulating temperature was variable and ranged from zero to 1.6°C/s. Kenshalo and others (Kenshalo et al 1967; Kenshalo 1970) have clearly demonstrated that thermal threshold values increase with decreasing area of stimulation especially with areas smaller than 4 cm^2. It was also demonstrated both in this laboratory (Chapter 5) and by other authors (Kenshalo et al 1968; Molinari et al, 1977) that at very low rates of change of stimulating temperature, thermal threshold values increase considerably. The higher values obtained in the method of Dyck et al (1978,1984), therefore are probably due to the smaller size of the thermode (3.5 cm^2) and the variation of the rate of change of stimulating temperature.

It should be stated that the Glasgow method was not designed to provide information concerning the absolute values of HT and CT, but rather to produce a reproducible and sensitive technique to investigate the thermal system and to apply the technique to clinical situations for detection of subtle abnormalities in this system. More detailed discussion, therefore, will be directed at comparing the reproducibility of the method (intra-individual and inter-individual) with the contemporary methods. Two such methods have been described prior to the introduction of the Glasgow method. These include the Marstock method (Fruhstorfer et al 1976a,b; Fagius and Wahren 1981; Lindblom 1981) and the automated method of the Mayo Clinic (Dyck et al 1978,1984). Since the introduction of the Glasgow

method (Jamal et al 1985a,b), two other methods have been described, one six months later from Amsterdam (Bertelsmann et al 1985) and 13 months later (Fowler et al 1986) from the Middlesex Hospital, London.

The Marstock Method

The name 'Marstock' came from the fact that this system was introduced as a result of collaboration between the Departments of Neurological Sciences in Stockholm (Sweden) and Marburg (W Germany). The method was described in 1976 by Fruhstorfer and his co-workers (Fruhstorfer et al, 1976a,b) and was the first to use a Peltier based thermode for clinical use. In this method, a thermode of 12.5 cm^2 stimulating surface area, a thermocouple to measure the changes of temperature are used with the switch method, where the subject is asked to press a switch once the sensation is felt. The warm-cold difference limen,that is, the indifferent temperature range in which no thermal sensation occurs is measured in the Marstock method and the value of this was found to range between 0.9 - 4^{o}C in normal subjects (Fruhstorfr et al 1976a,b; Fagius and Wahren 1981; Lindblom 1981). The results are recorded as pen deflections on a running graph paper. This method is very quick to perform

In their report of the Marstock method, Fruhstorfer et al (1976a) have conceded that there was a large inter-individual variability obtained in the measurement of thermal thresholds in 26 normal subjects, but claimed that the intra-individual variability "was much smaller", without supporting this claim with any data for repeated measurements. However, Fagius and Wahren (1981) have looked closely at the intra-individual variability in 13 normal subjects using the same method and concluded that "the intra-individual variability is indeed pronounced" and that this significantly restricts the usefulness of the method in longitudinal studies of individual patients. The change in the mean of repeated studies quoted by Fagius and Wahren (1981) was 39% (ranged from -24% to +15% from

the initial determination) versus 4.7% in the Glasgow system (ranging from -5.3% - 0.6% from the initial determination; Table 6). Their quotation, however, was for mixed data for repeated studies of vibration and touch in addition to the temperature sensation, but they stated that "the pattern was similar for all sensorymodalities and sites of measurements". Fagius and Wahren (1981) also indicated that confidence limits derived from analysis of variance of the temperature data showed that a change of less than -60% or more than 160% from the original threshold value was needed to ascertain with 95% probability that a subsequent value represents a true change of sensory threshold in the Marstock method. These authors also reported that they encountered some normal subjects with a normal threshold initially who had an abnormal threshold on a subsequent examination. They also indicated that in the Marstock method, older subjects or those under influence of drugs, fatigue, mental irritation and presence of noise showed a tendency for higher threshold values probably due to slowing of processing of sensory information and/or increased reaction time of the subject in these circumstances and, therefore, these higher values did not represent true abnormality in the thermal pathways but were attributable to the method.

A direct comparison of the Marstock system and the Glasgow method is exemplified in the study reported in Chapter 5 (Table 2) on a 23 year old male subject. The switch method, which is very similar to that used in the Marstock technique was compared with the standard method adopted for the Glasgow system. HT measurement at the R wrist (site a) was performed using the two methods instead of the measurement of the warm-cold difference limen. Table 2 shows that both the HT value and the intra-individual variability are significantly increased in the switch method.

The main reasons for the larger inter- and intra-individual variability in the Marstock method could be summarised as follows:

1. Variability arising from subject's response bias (Chapter 3).

2. The reaction time of the subject is included in the measurement and this contributes to the variability (Fagius and Wahren 1981).
3. No standardisation of thermode application is performed (Chapter 3).
4. Variability in the thermal properties of the skin is not accounted for (Chapter 3).

The Mayo Clinic method

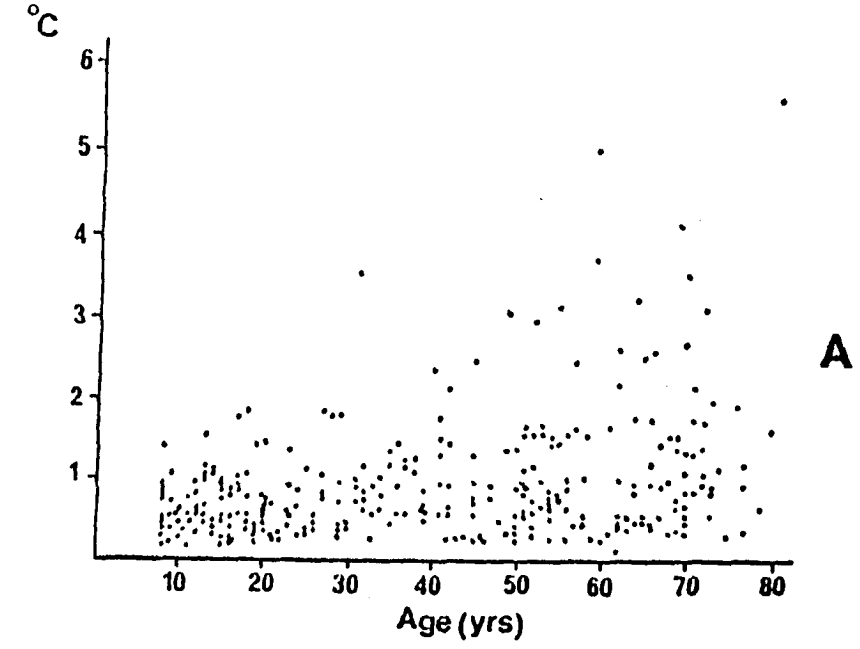
This method was described by Dyck et al (1978) and was part of an automated system for sensory system examinations including, as well as the thermal sensation, other modalities of touch and vibration sense. They used the forced-choice method and the UDTR and had 21 predetermined thermal stimulus levels intervalled logarithmatically. The thermode was a Peltier based one of 3.5 cm^2 stimulating surface area. The levels of stimuli were altered by changing the power input into the thermode while fixing the time of the application of the stimulus at 5 seconds. This resulted in a pronounced variation of the rate of the change of stimulating temperature between values of almost zero and 1.6°C/s in their scale of stimulus intensity levels.

In their papers, they reported the technique to be reproducible, but after being in clinical use in their laboratory for almost 8 years since their first report in 1978, no data are given about the reproducibility of the thermal threshold measurements in single individuals on repeated measurements (Dyck et al 1978,1983,1984,1985). The authors have also not produced figures for inter-individual variability, but examination of their results suggests that this variability is indeed large (Dyck et al 1984). Data have been extracted from their graph of normal 'thermal-cooling thresholds' at the foot where the range of values at the ages 10-20 years are from 0.4-4.0°C and at ages 60-70 years from 0.3-8°C, that is,

from almost the bottom to the top of their preset stimulus intensity levels (Dyck et al 1984). The ankle CT values for the corresponding age groups with the Glasgow method are 0.05 to 0.25°C and 0.15 to 0.37°C respectively (Figures 7 and 8). These values for the normal subjects in the Glasgow method fall within the bottom four steps of 90 available steps of preset stimulus intensity levels. Figures 9 and 10 show a direct comparison of the inter-individual variability between the Mayo Clinic method and the Glasgow method. The CT values at both ankles and wrists of the 110 normal subjects examined by the Glasgow method (Chapter 5; Figure 7) were replotted using exactly the same scales as Figures 49-17 and 49-18 of Dyck et al (1984) for 'thermal-cooling' thresholds for the hand and the foot. Figures 9 and 10 clearly show that the inter-individual reproducibility of the Mayo Clinic method is indeed poor. Dyck et al (1984) reported that many normal people have thresholds outwith the highest level of stimulus intensity of the technique and these were called 'insensitive' subjects. Moreover, although they indicated that their method was designed to test 'warm' as well as cold sensation, no data have as yet been presented in all their publications concerning the 'warm' threshold measurements (Dyck et al 1978,1983,1984,1985). The only mention of warm threshold measurement is in a single subject in their 1978 paper where a value of 0.69°C at the dorsum of the hand was reported (Dyck et al 1978).

To compare the intra-individual variability in the Mayo Clinic and the Glasgow method, an additional programming of the Glasgow thermal system was achieved whereby heat and cold stimuli were applied for a fixed duration of time (5 seconds) and the intensity of the thermal stimuli was altered by changing the power input into the thermode, that is, the varied power and fixed time method. The rate of change of the stimulating temperature varied between zero and 1.8°C/s along the scale of the stimulus intensity (from zero to 9°C). This method is similar to that adopted in the Mayo Clinic

Figure 9 Comparison of the inter-individual reproducibility between the Mayo Clinic method (A) and the Glasgow method (B). The diagram for the Mayo Clinic method (A) is identical to figure (49-17) in the report of Dyck et al (1984) plotting 'thermal-cooling threshold' values for the dorsal aspect of the hand of 331 healthy subjects. In B, wrist CT values obtained by the Glasgow method for 110 normal subjects were replotted using the same scales as A.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Age (yrs)
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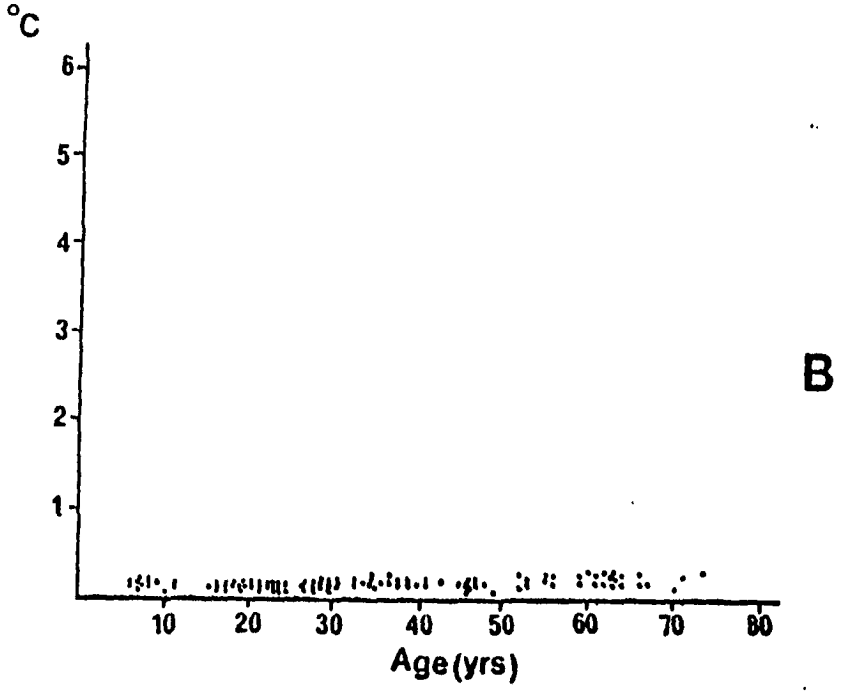
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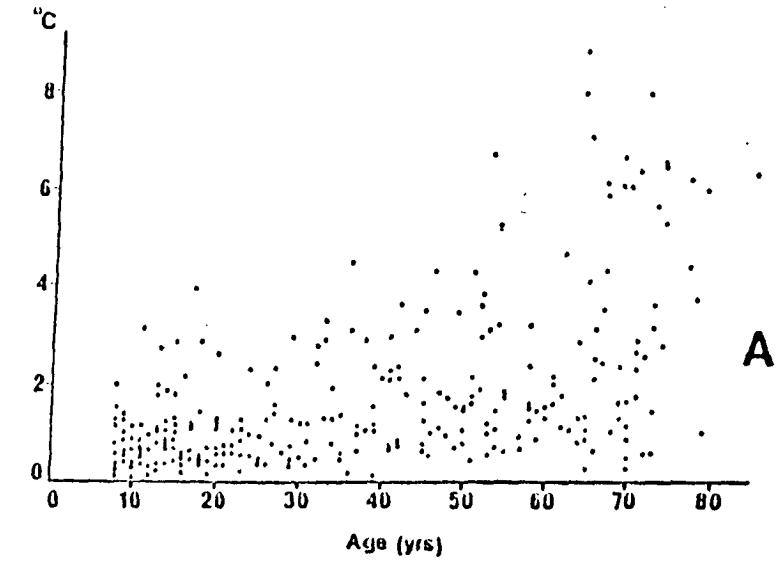
80
Age (yrs)
B

Figure 10 Comparison of the inter-individual reproducibility between the Mayo Clinic method (A) and the Glasgow method (B) for cold threshold measurement at the dorsum of the foot in the former and the ankle in the latter. The upper diagram (A) is identical to Figure (49-18) in the report of Dyck et al (1984a) and represents values for 303 healthy subjects and the lower diagram (B) was obtained by replotting ankle CT values for 110 normal subjects using the same scales.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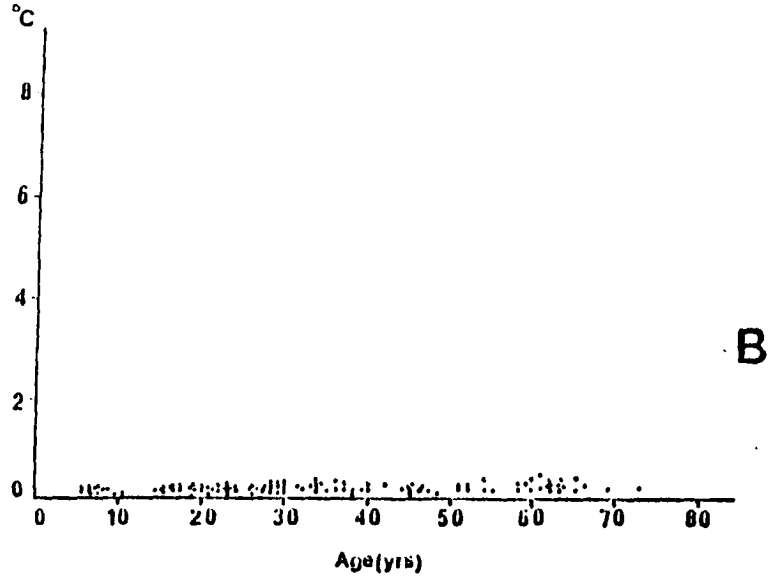
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technique. Unlike the latter, other variables of thermal threshold measurements were standardised as in the standard Glasgow system; the thermode application, the basic skin temperature and the same sized thermode (which is larger than the Mayo Clinic method) were used. The study was performed on a 27 year old female subject and the two methods were applied to measure HT and CT values for the R wrist (site a) 20 times at one day intervals by each method. Means and SDs were calculated for HT and CT to represent the threshold values and their intra-individual variability, respectively, for both methods (Table 8). Table 8 clearly shows that both the values and their intra-individual variability are much smaller in the standard Glasgow method compared to the Mayo Clinic method indicating that thermal threshold measurements are both more accurate and more reproducible using the former.

As outlined previously, in both the Mayo Clinic and the varied power, fixed time methods, the rate of change of the stimulating temperature applied is pronouncedly varied (between zero - 1.8°C/s). Kenshalo and others (Kenshalo et al 1968; Molinari et al 1977) using Peltier based thermodes, have all clearly shown that both the value of thermal thresholds and their reproducibility in the same individual on repeated measurements are greatly influenced by the rate of change of stimulating temperature. The increase in thermal threshold values and their variability in the Mayo Clinic method, therefore, is accounted for at least in part by the variability of the rate of change of stimulating temperature. The main reasons for the poor inter- and intra-individual reproducibility of the Mayo Clinic method could be summed up as follows:

1. Variability arising from variation of the rate of change of stimulating temperature.
2. The method does not standardise thermode application and the thermode was "strapped to the part being tested" (Dyck et al 1984). This is a

TABLE 8: Results of repeated determinations of thermal thresnolds of the R wrist using two different methods of stimulus application as discussed in the text in a 27 year old woman. The means, SDs and the largest deviations from initial values for 20 repeated measurements for each of HT and CT using each of the two methods are shown.

		Thermal Thresnolds (°C)	
		The varied-power and fixed-time method	The Glasgow method
HT	mean	0.68	0.25
	SD	0.24	0.01
	largest deviation from the initial value	0.70	0.02
CT	mean	0.54	0.15
	SD	0.22	0.01
	largest deviation from the initial value	0.70	0.03

source of variabiltiy (Kenshalo 1970; Chapter 5 and Table 1).

3. Variability of the thermal conductivity of the skin is not accounted for (Chapters 2 and 4).

4. An important disadvantage of the Mayo Clinic method is the long testing time; measuring one temperature threshold at one site requires 40 minutes (Dyck et al 1978) which means a testing time of at least 80 minutes if both HT and CT values are measured for one site. The testing time in the Glasgow method for HT and CT measurements at one site is 15-20 minutes. Fatigue and lack of concentration, likely to arise as a result of long testing time, are important factors in these methods and affect patient's performance in the test which in turn is reflected on the measurements.

5. The Mayo Clinic method does not control the basic skin temperature, an important source of variability of thermal threshold determination (Chapters 4 and 5).

6. It is also possible that some of the pronounced variability encountered in the Mayo Clinic method is due to the use of a small probe of 3.5 cm^2 stimulating surface area (Dyck et al 1978,1984). Spatial summation is an important factor in thermal sensation (Stevens et al, 1974; Kenshalo 1976) and in testing the thermal system activation of an optimum number of thermal receptors is required. Kenshalo et al (1967) investigated the effect of the area of stimulation on the reproducibility of thermal threshold measurements in the same subject and found that the intra-individual variability increases with smaller areas of stimulation, that such variability decreases when areas above 6 cm^2 are stimulated and that this variability is pronounced especially when using areas less than 4 cm^2 of stimulation. Their findings were the same whether radiant or conducted energy through Peltier thermodes were used.

The Amsterdam Method

This method was reported by Bertelsmann et al (1985) six months after our initial report of the Glasgow method (Jamal et al 1985a,b). In summary, this technique uses two plates numbered 1 and 2 both of which are constructed on the basis of the Peltier principle each with a 3 x 4 cm^2 stimulating surface area. For each test these plates are manually applied in sequence by the operator and the subject is asked to indicate which plate is "active", that is, warmer or cooler. One plate, the "passive", is kept at a value of skin temperature measured at the start of the test and the other, termed "active" plate, is warmed or cooled randomly in subsequent trials during the same test at values according to a predetermined scale. In a test of 'Thermal Discrimination Threshold' with this method, therefore, two aspects of the thermal stimuli are randomised, the assignment of "active" and "passive" states to the plates 1 and 2 and the polarity of the temperature stimulus in the "active" plate. The plates are manually applied to the test site by the operator and the authors claimed that standardisation of the pressure of application of the thermodes in the trials was accomplished by using a spring mechanism attached to each plate. It seems from their description of the method that timing of the duration of the application of the plates to the test site by the operator (3 seconds) and of the intervals between the trials were approximate with no objective checking. The data were manually recorded on a special sheet which contained the order of randomisation of the assignment of thermal stimuli to the plates and of the polarity of the stimulating temperature and this was of course known to the operator. The forced-choice method and the UDTR were used. Eight levels of stimuli were available at values between 0.1°C and 10°C. The control panel of the apparatus consisted of switches to set the temperatures of plates 1 and 2, to alternate the assignment of "active" and "passive" plates to 1 and 2 and

to change the polarity of thermal stimuli. There is no mention in the report whether and how the initial measurement of skin temperature in their method is used to modify the value of the "Thermal Discrimination Thresholds".

The normal values reported by these authors ranged from 0.15°C to 1.3°C (dorsum of the hand) and between 0.15°C, at the bottom of their intensity scale, to 10°C, at the top of their intensity scale, for the dorsum of the foot (Bertelsmann et al 1985, Figures 2 and 3). In the Glasgow method normal values for wrist CT ranged from 0.05°C to 0.35°C, for wrist HT from 0.05°C to 0.37°C, for ankle CT from 0.05°C to 0.37°C and for ankle HT from 0.4°C to 3.5°C. The inadequate sensitivity of the Amsterdam technique is exemplified by its application to 20 diabetic patients with clinically severe neuropathy all of whom had abnormalities on conventional nerve conduction studies where 14 (70%) of these patients had their 'Thermal Discrimination Threshold' within the 95 percentile (Bertelsmann et al, 1985). Application of the Glasgow method to 30 patients with diabetic neuropathy showed abnormality in all patients (Chapter 7).

The intra-individual variability in the Amsterdam technique was also pronounced (see Figure 4 of Bertelsmann et al, 1985) and variations up to 0.5°C on repeated measurements were reported. Data extracted from their Figure 4 showed that subsequent values could vary from -51% to +210% of the original measurement of "Thermal Discrimination Threshold".

Having the Amsterdam technique available at the Institute of Neurological Sciences laboratory, a direct comparison of reproducibility of the Glasgow versus the Amsterdam method was performed. Ten normal subjects aged between 19 to 64 (mean = 40.4; SD = 16) years, 7 male and 3 female, were examined by both methods. 'Thermal Discrimination Threshold' as described by Bertelsmann et al (1985) and HT values were measured for the R wrist (site a) twice for each subject at two weeks' interval. HT measurement, which showed slightly more variation than CT measurement in

the Glasgow system, was chosen in order not to bias in favour of the Glasgow method (Chapter 5). 'Thermal Discrimination Threshold' measurement for one site took between 26 and 43 (mean = 33) minutes unlike the '15 minutes' reported by Bertelsmann et al (1985) while HT measurement in these subjects took 5 to 8 (mean = 6.5) minutes using the Glasgow method. The normal skin temperature in these subjects varied between 24°C and 34.5°C. Lele (1954) reported normal human skin temperature to range between 18°C and 35°C. Table 9 shows means, SDs and range of values for the initial measurements obtained using the two methods in these 10 subjects. The values of 'Thermal Discrimination Threshold' in Table 9 are in close agreement with those reported by Bertelsmann et al (1985). The superiority of the Glasgow method in terms of inter-individual reproducibility is evident from the Table.

The intra-individual reproducibility of both methods in the 10 subjects is presented in Figure 11. The range of variability in the same individual on repeated measurements of 'Thermal Discrimination Threshold' in the Figure is actually smaller than that reported by Bertelsmann et al (1985). Despite this, however, the Figure clearly shows the much improved intra-individual reproducibility in the Glasgow method.

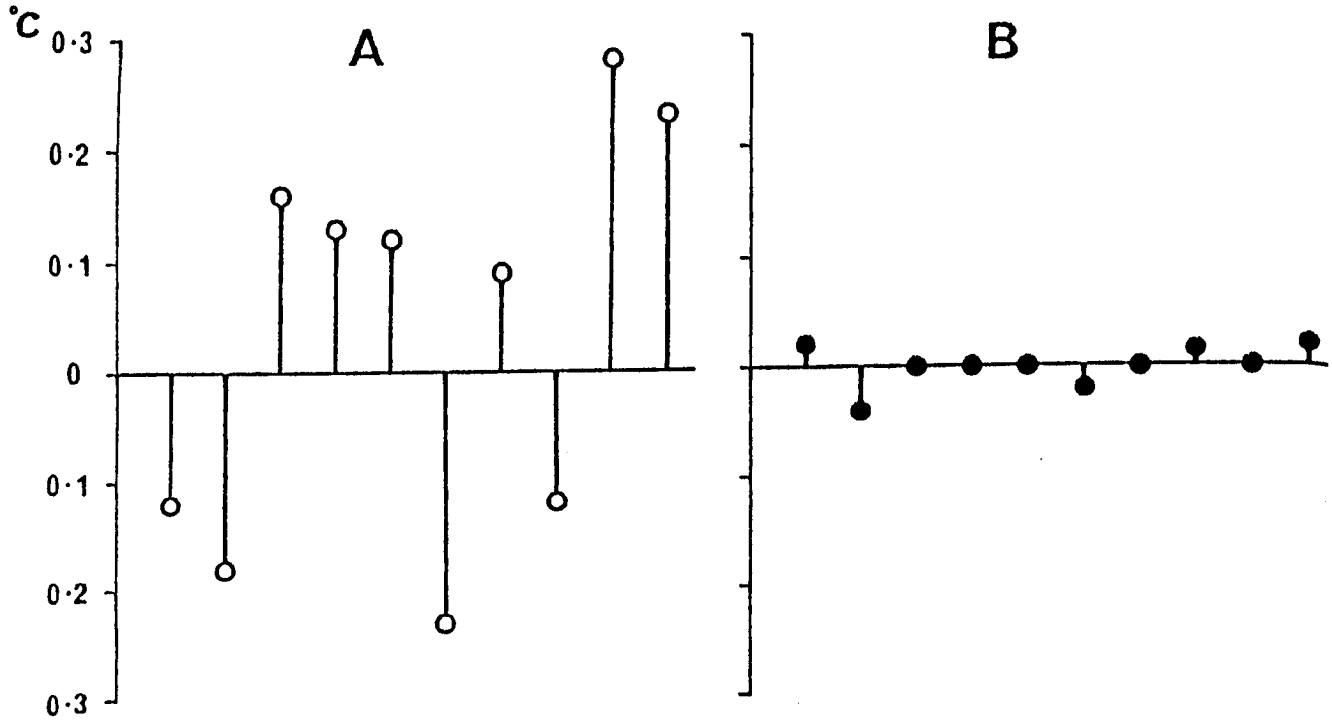
To sum up, a number of points of principle and methodology in the Amsterdam method might be responsible for its poor reproducibility (Jamal et al, 1986b):

1. The 'Thermal Discrimination Threshold', as described by Bertelsmann et al (1985), is compounded of both heat and cold thresholds. Reports in the literature, however, indicate the individuality of these sensations, their receptors and fibre pathways (Chapters 1 and 2). In the studies with the Glasgow method it was found that heat and cold thresholds frequently vary independently and unpredictably. The combination of these sensations in a single measurement is, therefore,

TABLE 9: Means, standard deviations and range of values of the first of two measurements of the heat threshold (HT) and the 'Thermal Discrimination Thresnold' (TDT) as described by Bertelsmann et al (1985) for the R wrist in 10 nomral subjects.

	The Glasgow Method	The Amsterdam Method
	(HT)^{o}C	(TDT)^{o}C
Mean	0.25	0.48
SD	0.06	0.42
Range	0.15-0.35	0.15-0.88

Figure 11 Shows individual ranges of variation of the second measurements of 'Thermal Discrimination Thresholds' (TDT) using the Amsterdam method (A) and of HTs using the Glasgow method (B) two weeks after the first measurements in 10 normal subjects. Each subject is represented by a line, open circles represent differences from the first TDTs and solid circles represent differences from the first HT values. For each subject, values of the first measurements are represented by zero. Values above the line mean higher and values below the line mean lower values of the second measurement from the first determination.


°C
0·3
0·2
0·1
0
0·1
0·2
0·3
A
B

unlikely to produce an accurately quantified index of thermal sensation.

2. There is no mention in the Amsterdam method of standardisation of basic skin temperature. Pronounced variation of the skin temperature of normal subjects occurs (Lele 1954; and our study) and this is an important source of both inter- and intra-individual variation (Chapter 4).
3. The method of standardisation of the "pressure"of the thermode adopted by Bertelsmann et al (1985) was previously investigated in this laboratory and was found unsatisfactory. This was reinvestigated using the available Amsterdam apparatus and it was found that the force of application, within the range of the spring mechanism, ranged from below 200 to above 1000 g. This manual spring-assisted application of the thermode is not reproducibly quantifiable. This is, therefore, a possible source of variation (Chapters 4 and 5).
4. In the Amsterdam method, two stimuli are applied to the skin tested more or less simultaneously. There is the tactile stimulus when the thermode is applied to the skin and the specific thermal stimulus. It is particularly important, however, for the accurate assessment of thermal sensibility to use as pure a stimulus as possible and for the specific stimulus to be applied without tactile cues (Kenshalo 1970; Hensel 1973,1981; Lindblom 1981).
5. The rate of change of thermal stimuli is not fixed and this is an important source of variation (Chapters 4 and 5).
6. A variation is likely to be encountered from variation of the duration of the application of the thermodes and the amount of heat conducted to the skin.
7. The Amsterdam method does not account for variation in the thermal properties of the skin (Chapter 4).

The Middlesex Method

This technique was reported about 13 months following reporting of the Glasgow method by Fowler et al (1986) from the Department of Neurological Sciences, Middlesex Hospital, London. Their method uses a Peltier based thermode of 7.5 cm^2 stimulating surface area, a fixed rate of temperature change of $1^oC/s$, preset steps and the 'yes/no' procedure of psychophysical method. The only data published in their report were mean values for the dorsum of the hand and the foot which were higher than the values reported by the Glasgow method and no data are as yet available for inter- and intra-individual variability of thermal threshold measurements by this method.

There are, however, several points in this method likely to lead to marked variability and these include the following:

1. The 'yes/no' procedure adopted by this technique does not exclude subject's response bias and this is likely to produce significant variability both in the same individual on repeated measurements and between individuals (Chapters 4 and 5; Table 1).
2. The time intervals between the trials increases proportionately to the increase of thermal stimuli and this clearly provides the subject with a clue as to the value of the thermal stimulus.
3. The application of the thermode is not standardised (Chapters 4 and 5).
4. The basic skin temperature is not adequately standardised. It is mentioned in the methodology that skin temperatures were kept 'above 30^oC' for the hand and 'above 29^oC' for the foot (Fowler et al 1986). More adequate control of this factor is necessary to minimise variability of thermal threshold measurements (Chapters 4 and 5).

In conclusion, the main advantages of the Glasgow method over others in the literature are as follows:

1. The intensity of the thermal stimulus is varied by altering the stimulus duration. The rate of change of temperature is constant throughout at $1^{o}C/s$.
2. The forced-choice method excludes response bias.
3. The thermode is calibrated at each site in each subject to measure the exact amount of power required to obtain a rate of temperature change of $1^{o}C/s$. This reduces errors due to differences in the thermal properties of the skin at different sites.
4. The thermode pressure on the underlying skin is standardised at all sites.
5. The larger probe reduces variability of the response.
6. The initial skin temperature under the probe is always in the range of $34-35^{o}C$. This significantly reduces variability in thermal thresholds.
7. Threshold determinations take a short time (15-20 minutes for both HT and CT determinations at one site).

CHAPTER 7

RESULTS OF THE APPLICATION OF THE TECHNIQUE IN DISORDERS OF THERMAL SENSATION

The inadequacy and inaccuracy of the bedside clinical assessment of thermal sensation in neurological patients and the need for a quantitative and reproducible technique for this purpose were outlined in Chapter 3. By the application of such a technique, therefore, reliable, quantitative and reproducible indices of the functional integrity of the specific thermal endorgans and their peripheral nerve fibres and the central thermal pathways could be obtained. In this Chapter, the results of the application of the Glasgow Thermal System to a number of neurological diseases affecting either peripheral or central nervous system, in which involvement of thermal sensation is expected, are presented and the implications of these findings are discussed.

GENERALISED PERIPHERAL NEUROPATHY

Activity in the non-myelinated (C) and thinly myelinated (Aδ) peripheral nerve fibres, among which the peripheral thermal fibres are contained, is not tested by conventional electrophysiological methods (Buchthal et al, 1984). Evaluation of the integrity of the peripheral thermal fibres and their endorgans is likely to be extremely useful for the detection of dysfunction in the small fibre population of peripheral nerves as an early manifestation of peripheral neuropathy and to detect small fibre damage in ongoing generalised neuropathy, both regarded as important points in the context of clinical and pathophysiological evaluation of patients with this disease. The technique has, therefore, been applied to a large group of patients with peripheral neuropathy from different causes. The primary aim was threefold: (1) to illustrate the clinical usefulness of

the technique, (2) to evaluate the frequency of involvement of the small unmyelinated and thinly myelinated fibres in neuropathy in general through the evaluation of peripheral thermal fibres, and (3) to compare the sensitivity of this technique with electromyography and nerve conduction studies in the early diagnosis and the ongoing assessment of peripheral neuropathy.

Methods

(a) Electromyography and nerve conduction (EMG and NC) studies were undertaken on a Medelec MS6 electromyograph. The fastest motor nerve conduction velocity (FMNCV) and the shortest distal motor latency (SDML) for the R common peroneal and median nerves were obtained recording from surface electrodes over the target muscle by conventional techniques initiated by Simpson (1956). The amplitude and duration of the evoked compound muscle action potential were also measured. Sensory nerve action potentials (SNAPs) were elicited orthodromically in the R median, ulnar and sural nerves. For each SNAP measurement, 64 evoked potentials were averaged. Sensory latencies were measured from the onset of the stimulus artefact to the peak of negative deflection. Amplitudes were measured from peak to peak. For median and ulnar nerve sensory potentials, the method used by Gilliatt and Sears (1958) was followed. The sural nerve was stimulated at the lateral aspect of the foot immediately inferior and anterior to the lateral malleolus and the potential recorded by surface electrodes 14 cm proximal to the malleolus lateral to the tendo Achillis. The distance between the pair of recording electrodes was 4 cm. EMG studies were performed with concentric needle electrodes in one or more of the following muscles: the R extensor digitorum brevis, the R tibialis anterior and the R first dorsal interosseous muscles. The ambient room temperature was kept at 22 ± 2°C. Skin temperature of the

limb was maintained at 34 ± 0.1°C using a thermostatically controlled heating lamp.

(b) HT and CT measurements were determined by the Glasgow method in the two distal sites (site a, the R wrist and site c, the R ankle) relevant for examination of polyneuropathy. The standard methodology described in Chapter 4 was used.

Patients and Control Subjects

The control subjects for the thermal thresholds consisted of the 106 healthy volunteers described in detail in Chapter 5. The control group for the EMG and NC studies were 42 healthy subjects aged between 18-59 (mean = 35; SD = 10) years. There were 143 patients with generalised polyneuropathy of varied severity and aetiology. Most were ambulant and in good general health. All were cooperative and informed. Their age ranged between 9-77 (mean = 49; SD = 16) years. The mean duration of neuropathy was 48 months with a range of 2 days - 40 years. The causes of the neuropathy in the 143 patients are summarised in Table 10. Full general and neurological examination was performed on all the patients and any abnormalities of touch, pinprick, temperature and vibration sensations were noted. Full laboratory examination was undertaken to determine the aetiology of the neuropathy (Dyck et al 1981; McLeod and Polard 1984). The diagnosis in the suspected cases of hereditary aetiology was established by the clinical examination and laboratory investigation of the patients and relatives.

The aetiology of the polyneuropathy was determined in 70% of the patients. In 47% an acquired cause (toxic, metabolic-endocrine, autoimmune, paramalignant or allergic) was responsible while hereditary factors were operative in 23%. In the remaining 30% no cause was discovered (Table 10).

TABLE 10: Classification of the 143 neuropathy cases by aetiology

Aetiology	Number and percentage
ACQUIRED KNOWN CAUSE (TOTAL)	67 (46.8%)
Diabetes mellitus	30
Hypothyroidism	3
Alcoholic neuropathy	10
Blood disorders (folate, Vit B12 deficiency)	3
Rheumatoid arthritis	2
Porphyric neuropathy	1
Carcinoma associated	2
Guillain Barré Syndrome	4
Heavy metals (eg mercury, lead)	5
Drugs (eg phenytoin, aminodarone, thalidomide, isoniazid)	7
HEREDITARY NEUROPATHIES (TOTAL)	33 (23.1%)
HMSN type I	13
HMSN type II	9
HMSN type IV (Refsum's syndrome)	1
HSN type II	1
Friedreich's ataxia	5
Hereditary spastic paraplegia and neuropathy	3
Retinitis pigmentosa and neuropathy	3
IDIOPATHIC (TOTAL)	43 (30.1%)

HMSN = hereditary motor sensory neuropathy

HSN = hereditary sensory neuropathy

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Results

The clinical, electrophysiological and thermal studies on these patients are summarised in Table 11. Abnormality of thermal thresholds were considered to be present if values exceeded the 99th percentile (Table 4). To follow the convention in the contemporary literature, abnormality of NC studies was considered to be present if values exceeded the 95th percentile of the corresponding normal mean. This slightly less stringent significance level was used to permit comparison with previously published reports on nerve conduction. Normal values for the thermal thresholds are summarised in Table 4. Normal values for NC studies are summarised in Table 12.

One hundred and nine of the 143 patients studied (76%) had one or more symptom known to be associated with neuropathy (Thomas 1984) while 114 (79.7%) showed some abnormality of sensation on clinical examination for one or more of the modalities tested. Clinical examination of temperature sensitivity showed abnormality in 61 patients (42%). EMG and/or NC studies were abnormal in 127 (88.8%) patients, of whom 103 (72%) had an abnormality of the amplitude, duration and/or latency of one or more of the SNAPs determined. In 40 patients (28%) all of these parameters (amplitude, duration and latency) of the ulnar, median and sural SNAPs were within the normal range. Sixty-eight of the 143 (47.5%) showed abnormalities in the ulnar and/or median SNAP. Ninety-five of the 143 (66%) showed abnormalities in the sural nerve SNAP.

One or more of the thermal thresholds determined were abnormal (outside the 99th percentile) in 141 patients (98.6%). Only one patient, a recently diagnosed case of Friedreich's ataxia, with abnormal sural SNAP had normal thermal thresholds. The other patient, a female aged 17 years also with a recently diagnosed Friedreich's ataxia, had both the thermal threshold values and the SNAP studies within normal limits. Abnormalities of thermal

TABLE 11: Clinical Conventional Electrophysiological and thermal threshold assessment of 143 patients with neuropathy

Evidence for neuropathy		Number and percentage	
ONE OR MORE SYMPTOMS OF NEUROPATHY (TOTAL)		109	(76%)
pain		53	
paraesthesia		86	
numbness		63	
weakness and/or fasciculation		81	
autonomic		42	
altered thermal feeling		69	
ONE OR MORE SIGNS OF NEUROPATHY (TOTAL)		114	(79.7%)
abnormal touch		77	
abnormal vibration		76	
abnormal pinprick		94	
abnormal thermal		61	
weakness, wasting and/or fasciculation		80	
ABNORMAL EMG AND/OR NC STUDIES (TOTAL)		127	(88.8%)
abnormal one or more SAP		103	
abnormal sural SAP		95	
abnormal ulnar and/or median SAP		73	
ABNORMAL ONE OR MORE THERMAL THRESHOLD (TOTAL)		141	(98.6%)
Abnormal ankle	: HT	125	
	CT	127	
	HT & CT	114	
	CT or HT	141	
Abnormal wrist	: HT	88	
	CT	70	
	HT & CT	56	
	HT or CT	102	
Abnormal ankle HT & CT and wrist HT & CT		55	

EMG & NC : electromyography and nerve conduction

SNAP : sensory nerve action potential

HT : heat threshold

CT : cold threshold

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TABLE 12: Normal nerve conduction values for 42 healthy subjects at skin temperature of 34 ± 1°C

I Normal SNAP values

NERVE	Latency Mean ms	Latency SD ms	Amplitude Mean µV	Amplitude SD µV	Duration Mean ms	Duration SD ms
Median	2.92	0.26	17.8	7.4	1.26	0.16
Ulnar	2.87	0.25	12.0	5.5	1.16	0.17
Sural	3.62	0.44	6.8	2.0	2.17	0.42

II Normal FMCV and SDML values

NERVE	SDML Mean ms	SDML SD ms	FMCV Mean m/s	FMCV SD m/s
Common peroneal	3.6	0.5	50.5	4.6
Median	3.5	0.3	58.6	4.8

SNAP : sensory nerve action potential (orthodromic, surface recording)

FMCV : fastest motor conduction velocity

SDML : shortest distal motor latency

SD : standard deviation

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thresholds were generally more marked at the ankle (98.6%) than the wrist (71.3%). It is noteworthy that in nine asymptomatic patients with unequivocal abnormalities on EMG, known to have diseases predisposing to neuropathy, there was no abnormality on NC studies. These nine patients were found to have significant abnormalities of one or more of the thermal thresholds. Among 40 patients with normal SNAP studies in the median, ulnar and sural nerves (Figure 12), 34 (85%) had ankle HT and CT outside the 99th percentile while 20 (50%) had abnormal wrist HT and CT values. One or more thermal threshold was abnormal in 39 (97.5%) of the 40 patients. Figure 13 from 70 patients with normal ulnar and median SNAPs shows control wrist HT and CT values expressed in multiples of the standard deviation (x SD) outside the normal mean. In 42 (60%) of these, one or both wrist thermal threshold values were abnormal. Figure 14, from 48 patients who had normal sural SNAP, shows ankle HT and CT values. These thermal threshold values were abnormal in 86% of the patients.

The SNAP parameters, indices of the functional integrity of the large diameter afferent fibres (Buchthal et al 1984) and the thermal thresholds, indices of the functional integrity of the small diameter afferent fibres, were compared. Patients with absent SNAP, all of whom had abnormal thermal threshold values, were excluded. SNAP latencies and amplitudes of the R median and sural nerve were compared with HT and CT of the wrist and the ankle respectively. To facilitate this comparison each value was expressed as a figure representing the xSD outside the corresponding normal mean and the histograms plotted (Figure 15). Again the SD used is that of the corresponding control parameter. None of the SNAP amplitude values were more than 3 xSD outside the normal mean and few had their SNAP latency values outside this value. the majority of patients had their thermal threshold values in excess of 3 xSD above the normal mean (Figure 15). This emphasises the sensitivity of the technique in assessing patients with

Figure 12 Ankle and wrist thermal thresholds in 40 patients with normal sensory median, ulnar and sural nerve studies on conventional electrophysiology; vertical axis = number of patients; horizontal axis = multiples of standard deviation (x SD) from normal control mean; open histogram = distribution of normal control values; of normal control values; solid vertical line = mean value for normal controls; dashed vertical line = 3 x SD above normal control mean; HT = heat threshold; CT = cold threshold.

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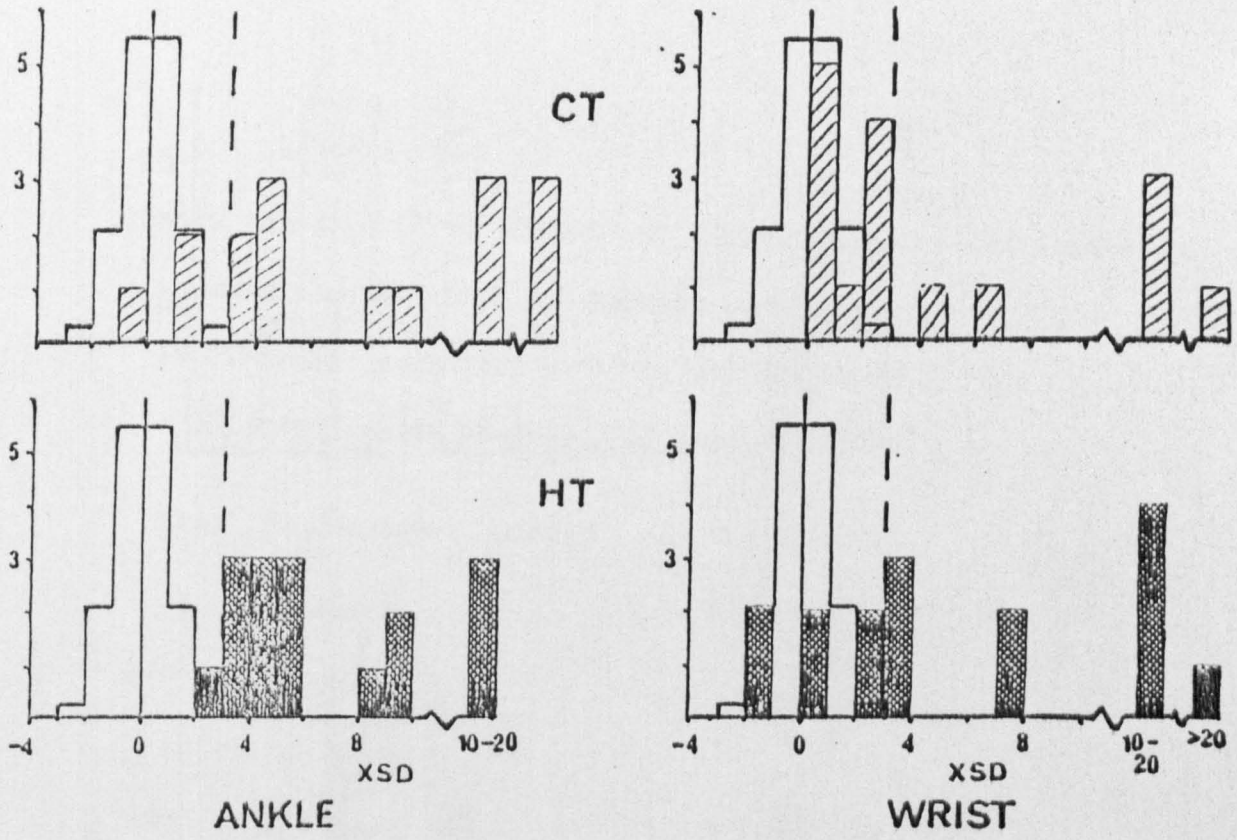
CT
HT
5
3
-4
0
4
8
10-20
>20
XSD
ANKLE
WRIST

Figure 13 Wrist thermal thresholds in 70 patients with peripheral neuropathy with normal sensory ulnar and median nerve studies on conventional electrophysiology; symbols as in Figure 12.

(Jamal et al, 1985b, reproduced with permission.)

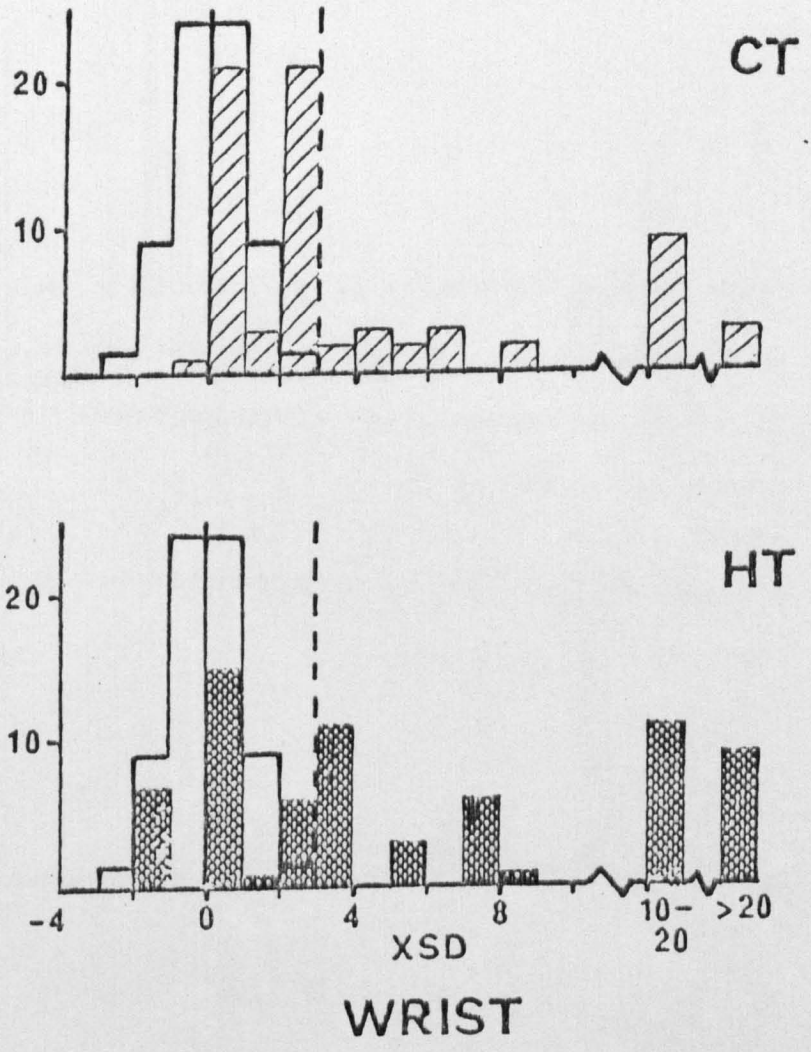
CT
20
10
HT
20
10
-4
0
4
8
10-
20
>20
XSD
WRIST

Figure 14 Ankle thermal thresholds in 48 patients with peripheral neuropathy, normal sensory sural potential on conventional electrophysiology; symbols as in Figure 12.

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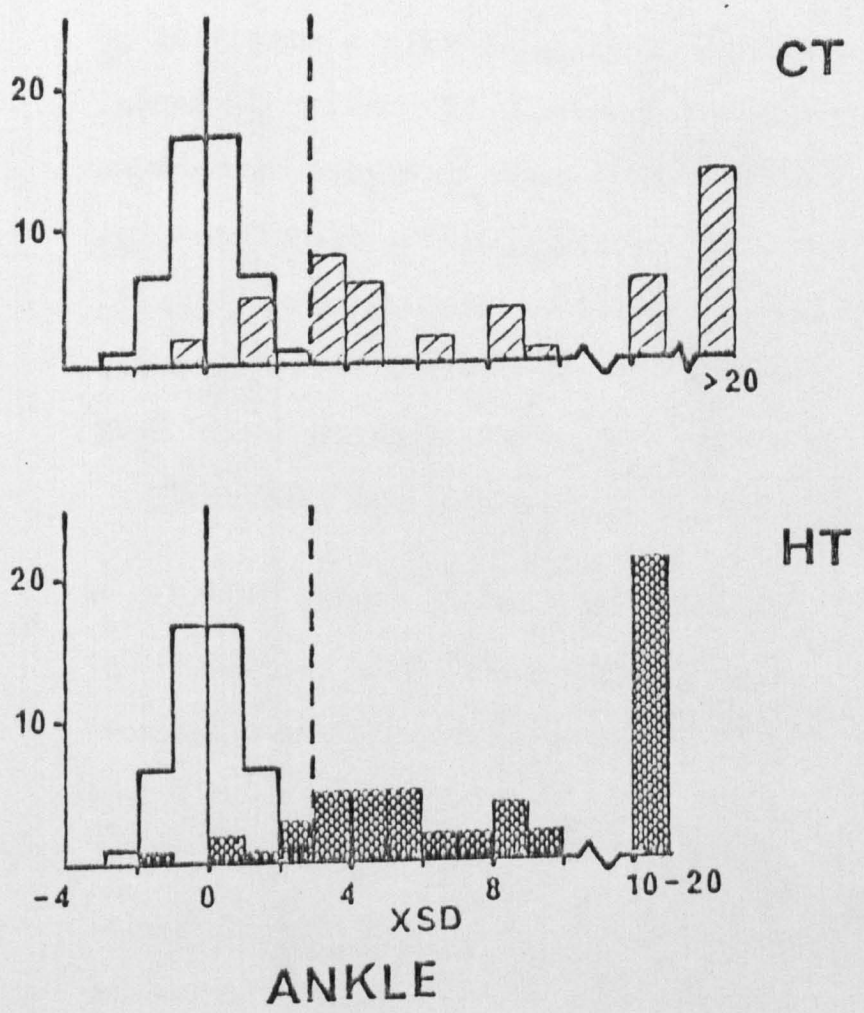
CT
20
10
>20
HT
20
10
-4
0
4
8
10-20
XSD
ANKLE

Figure 15 Comparison of conventional sensory electrophysiological studies and thermal thresholds in patients with peripheral neuropathy[+]. Vertical axis = number of patients; horizontal axis = multiples of standard deviation (x SD) outwith the normal control mean[*]; solid vertical lines = mean value for normal controls; dashed vertical lines = 3 x SD above normal control mean; LAT = latency of the sensory nerve actional potential (SNAP); AMP = amplitude of the SNAP; CT = cold threshold; HT = heat threshold.

[+] patients with absent median SNAP (when compared with wrist thermal thresholds) and those with absent sural SNAP (when compared with ankle thermal thresholds) are excluded.

[*] negative values are on the right side of zero in the AMP histogram as these represent abnormalities of amplitude.

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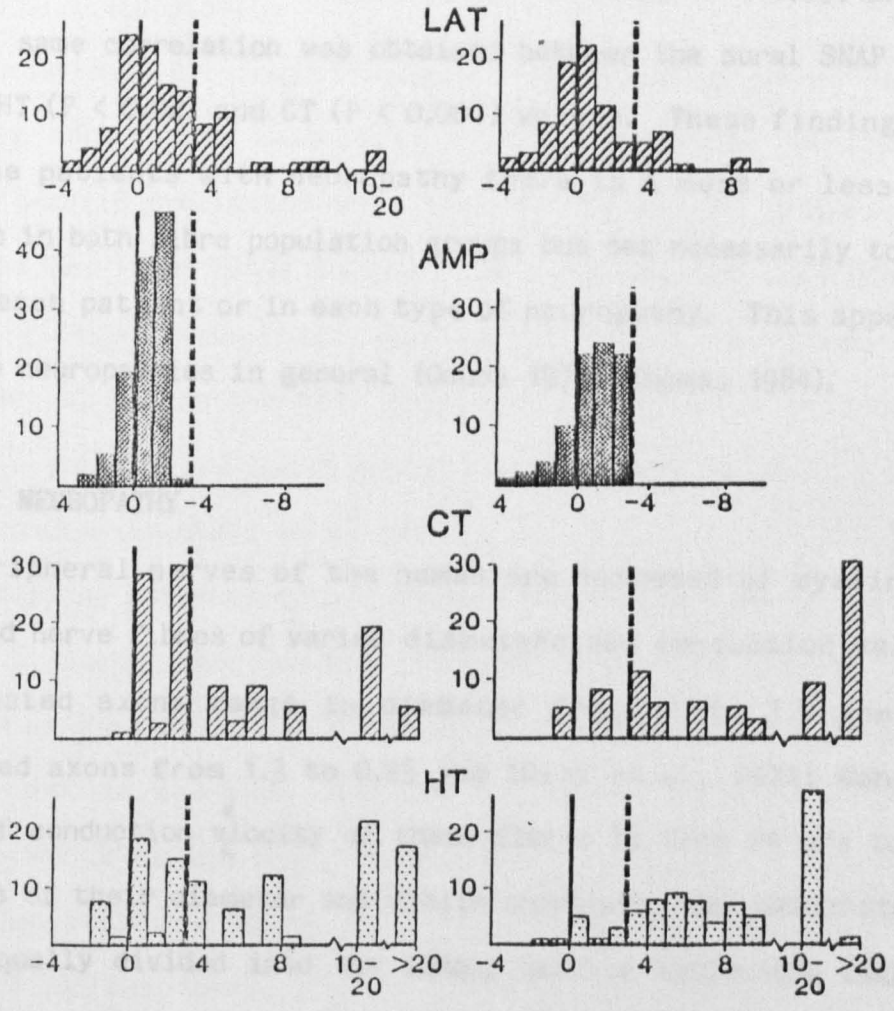

LAT
AMP
CT
HT
20
10
40
30
-4
0
4
8
10-
20
>20
MEDIAN N. - WRIST (N=116)
SURAL N. - ANKLE (N=85)

peripheral neuropathy.

The thermal thresholds for wrist and ankle were also correlated with the corresponding SNAP parameters. Patients with absent SNAP were again excluded. The most consistently significant correlation was with the SNAP amplitude, a measure of loss of large afferent fibres in neuropathy (Buchthal et al 1984). A reduction in the median (or ulnar) SNAP amplitude was accompanied by an elevation of the wrist HT ($P < 0.05$) and CT ($P < 0.05$). The same correlation was obtained between the sural SNAP amplitude and ankle HT ($P < 0.02$) and CT ($P < 0.001$) values. These findings suggest that in the patients with neuropathy there is a more or less parallel dysfunction in both fibre population groups but not necessarily to the same degree in each patient or in each type of neuropathy. This appears to be true of the neuropathies in general (Ochoa 1978; Thomas 1984).

SMALL FIBRE NEUROPATHY

The peripheral nerves of the human are composed of myelinated and unmyelinated nerve fibres of varied diameters and conduction velocities. the myelinated axons range in diameter from 14 to 1.3 /um and the unmyelinated axons from 1.3 to 0.25 /um (Dyck et al, 1971; Ochoa 1978). The range of conduction velocity of these fibres is from 84 m/s to 0.4 m/s. On the basis of their diameter and myelin thickness, the myelinated fibres are about equally divided into the large, heavily myelinated ($A\alpha\beta$) fibres with a mean diameter of about 8 /um and the thinly myelinated ($A\Delta$) fibres with a mean diameter of 2-2.5 /um (Dyck et al, 1971). In human cutaneous nerves, such as the sural, the unmyelinated C fibres are at least 4-5 times more numerous than the myelinated axons (Dyck et al, 1971; Ochoa and Mair 1969; Ochoa 1978).

Preferential involvement of these small or large nerve fibre populations does occur in neuropathies and this leads to the occurrence of specific symptom patterns (Dyck et al 1971; Ochoa 1978; Asbury and Gilliatt

1984; Thomas 1984). Predominant large myelinated fibre dysfunction causes abnormalities of two-point discrimination, touch-pressure, proprioception, vibration sense together with diminution of deep tendon reflexes and a variable degree of motor weakness (Asbury and Gilliatt 1984). Loss of function in the thinly myelinated (AΔ) and unmyelinated (C) fibres produces disturbance of temperature and pain sensation and of autonomic function (Asbury and Gilliatt 1984).

The conventional electrophysiological estimation of motor, sensory and mixed nerve conduction velocities reflects activity in the fastest conducting, heavily myelinated nerve fibres, only a small proportion of the total (Ochoa and Mair 1969; Dorfman 1984; Jacobs and Love 1985). The AΔ and C fibres, numerically the largest group of fibres in human cutaneous nerves (Ochoa and Mair 1969) are not tested by this technique. Motor, sensory and mixed nerve conduction studies are usually normal in this circumstance (Buchthal et al 1984).

By quantifying activity in the thermal fibres which are contained among the AΔ and C fibres, the Glasgow Thermal System is likely to give a quantitative assessment of the function of the small fibre population as a whole. The method was used to study a group of patients suspected on clinical grounds of having small nerve fibre dysfunction. In addition, EMG and NC studies supplemented by measurement of the vibration perception threshold using the technique of Goldberg and Lindblom (1979) were undertaken to assess the function of the large peripheral nerve fibre population.

The same standard techniques for EMG and NC studies were used to measure the fastest motor nerve conduction velocities (FMNCVs) and the shortest distal motor latencies (SDMLs) for the R common peroneal nerve (CPN) and R median nerve. Similarly SNAPs in the R median, ulnar and sural nerves were recorded and their amplitudes, latencies and durations were

measured. Concentric needle EMG studies were also performed on the R first dorsal interosseous, the R tibialis anterior and the R extensor digitorum brevis muscles. Hoffman (H) (Hoffman 1922) and F responses were also measured using established methods (Kimura 1983a,b).

Vibration perception thresholds (VPTs) were measured on the dorsal aspect of the middle of the R second metacarpal bone and the dorso-medial aspect of the middle of the R first metatarsal bone where the overlying subcutaneous tissue is thin (Goldberg and Lindblom 1979). Briefly, the vibration stimulus intensity is assessed directly as the amplitude of displacement of the skin. The degree of displacement of the skin in the repetition movement is the physiological stimulus to the vibration-sensitive receptors (Lindblom and Lund 1966; Goldberg and Lindblom 1979). The apparatus(SOMEDIC AB VIBRAMETER type III) consists of an electromagnetic vibrator with a 13 mm diameter probe which vibrates at right angles to the skin at a frequency of 100 Hz. The amplitude of the skin displacement (the vibration amplitude) is measured by an accelerometer and displayed on a digital meter. Vibration amplitudes in the range of 0-399.9 /um can be produced. The vibrator is held against the skin with a force of 500 ± 100 g by reference to a force indicator on the vibrameter. The subject is placed in a comfortable position with the R leg supported by pillows to prevent stimulus spread. A suprathreshold test is applied to familiarise him/her with the sensation produced. The apparatus can deliver two standardised rates of increase in stimulus intensity, slow or fast. The amplitude of vibration is increased using one of these alternatives and the subject is instructed to indicate when he/she feels the stimulus. The vibration amplitude is repeated at the alternative rate of increase of stimulus intensity. The average of three trials is taken as the VPT. In cases where there is more than 10% variation between the values, further trials are performed until three consecutive readings are within the 10% limit. Skin temperature is maintained at 34 ± 1°C with a thermostatically

controlled heat source. On average, less than 5 minutes is required for each VPT determination. For HT and CT measurements, the two distal sites, the R wrist (site a) and the R ankle (site c) were selected and the thresholds were determined using the standard method described in Chapter 4.

Twenty-five patients were studied (18 male and 7 female) aged 22 to 65 (mean = 46.5, SD = 12) years. In each patient, a peripheral neuropathy was suspected on clinical grounds by the referring neurologist. The study was confined to patients in whom conventional electrophysiological indices of the large fibre population (FMNCVs, SDMLs, SNAPs, H and F wave latencies and VPT studies) were within the normal range. The values of these neurophysiological tests from the patients were compared with normal values derived from different control groups. Control values for the thermal thresholds were obtained from 61 subjects aged 35 to 73 (mean = 45.5, SD = 11.8) years. For the EMG and NC studies the control group consisted of 21 healthy subjects aged 23 to 69 (mean = 46; SD = 12) years and for the VPT measurement, 27 subjects aged 17 to 64 (mean = 46.2; SD = 11.5) years. No significant difference between the age of the patients and any of these control groups was found.

In all patients, sensory symptoms had been present for at least six months (range from 6 to 28, mean = 10; SD = 5.8 months) with a peripheral distribution in the limbs suggestive of peripheral neuropathy. Table 13 lists the principal clinical findings in the 25 patients studied. The predominant clinical involvement of pain and temperature sensation and autonomic function is suggestive of an abnormality in the AΔ and C fibres (Dyck et al 1971; Ochoa 1978; Asbury and Gilliatt 1984). No attempt was made to grade the clinical severity of the symptoms. Care was taken not to ask leading questions.

Pain of the following types were described (1) Lancinating pain arising

TABLE 13

Summary of clinical and neurophysiologic data of 25 patients with small fibre generalised peripheral neuropathy

	Number	%
Objective sensory signs (total)	22	88
Abnormal pinprick	22	88
Abnormal fine touch	5	20
Abnormal vibration	0	0
Abnormal sense of position (proprioception)	0	0
Abnormal deep tendon reflexes	0	0
Muscle weakness and/or wasting	0	0
Abnormal nerve conduction studies	0	0
Abnormal vibration threshold studies	0	0
Abnormal thermal threshold studies (total)	25	100
Abnormal ankle HT	22	88
Abnormal ankle CT	18	72
Abnormal ankle HT and/or CT	24	96
Abnormal wrist HT	13	52
Abnormal wrist CT	7	28
Abnormal wrist HT and/or CT	15	60

	Number	%
Underlying cause		
Diabetes mellitus	13	52
Alcohol abuse	2	8
Unknown	10	40
Somatic sensory symptoms (total)	25	100
Pain (total)	25	100
sharp, shooting pain	23	92
dull, continuous pain	13	52
continuous burning pain	10	40
Abnormal spontaneous sensation of heat	15	60
Abnormal spontaneous sensation of cold	16	64
Contact dysesthesia	7	28
Tingling (prickling)	12	48
Numbness	7	28
Autonomic symptoms (total)	25	100
Disturbance of sweating	14	56
Impotence or retrograde ejaculation	13	52
Postural dizziness or fainting	6	24
Urinary bladder	5	20
Gastrointestinal	2	8

in the feet and shooting upwards to the legs below the knees for a variable distance. (2) Dull, deep seated aching pain in the feet. (3) A constant burning pain, situated superficially in the skin mainly in the soles of the feet, worse at night. Pain with these descriptions is associated with dysfunction of the small peripheral nerve fibre population (Asbury and Fields 1984; Asbury and Gilliatt 1984). Subjective abnormalities of thermal sensation were described as episodic sensations of heat/cold lasting from a quarter to 3 hours. All patients were assessed clinically for symptoms suggestive of autonomic symptom dysfunction, but formal tests of autonomic function were not performed.

Abnormal sensory signs were present in 22 patients. In 16 patients pinprick sensation was reduced in the toes and/or feet. In 6 patients, pinprick sensation was reduced in the hands and feet. In 5 of the 22 patients, light touch sensation was also mildly diminished in the feet but in a smaller area of skin. All patients had one or more features of autonomic dysfunction (Table 13). In 3 of the 25 subjects there was no objective abnormality of sensation. Two were diabetic with 6 and 12 months history of autonomic and sensory symptoms (pain of the three kinds and subjective abnormalities of thermal sensation identical to the features described above). In the third, a 51 year old man with similar but more severe symptoms for 12 months, no cause was identified.

In 13 patients, the peripheral nerve dysfunction was due to diabetes mellitus, 3 insulin dependent and 10 non-insulin dependent. The duration of diabetes ranged from 2 months to 14 years (mean = 7.1; SD = 5.2) years. In the few months preceding the onset of symptoms, the diabetes was under good control. In two patients, the peripheral nerve dysfunction was thought to be due to excessive consumption of alcohol. In the remaining 10 patients no cause was identified at the time of investigation. There was no evidence of malnutrition or peripheral vascular disease and none of the patients had a known exposure to any neurotoxin.

The clinical presentation of symptoms and signs in these 25 patients involving pain, temperature and pinprick sensations and autonomic function suggests involvement of the small nerve fibre populations. Clinical abnormalities of pain and temperature senses and of autonomic function have been reported in a number of diseases in which histology reveals exclusive involvement of unmyelinated (C) and thinly myelinated (Aδ) nerve fibres eg hereditary amyloidosis (Dyck et al 1971; Thomas and King 1974), Tangier disease (Kocen and Thomas 1970; Kocen et al 1973; Ohnishi and Dyck 1974), familial dysautonomia (Aguayo et al 1971) and some forms of hereditary sensory neuropathy (Dyck 1984). A pattern of dissociated sensory involvement and autonomic dysfunction similar to that of these patients has been noted in patients with diabetes mellitus (Brown et al 1976; Said et al 1983). Both qualitative (Martin 1953; Thomas 1973) and quantitative (Brown et al 1976; Said et al 1983) abnormalities of Aδ and C fibres have been found in these patients. The sensation of pinprick, disturbed in the majority of these patients, is also thought to be served by the Aδ and C fibres (Zotterman 1939; Fruhstorfer et al 1974; MacKenzie et al 1975).

In evaluating the results of this study, again thermal thresholds outside the 99th percentile and motor and sensory conduction and VPT values above the 95th percentile were considered abnormal. Group means for the control groups of the various neurophysiological tests and those of the 25 patients are summarised and compared using student's 't' test in Table 14. Thermal thresholds at ankle and wrist were significantly higher in the patients than in controls. In all 25 patients HT and/or CT were abnormal at ankle and/or wrist and these abnormalities were more frequent and severe at the ankle (96%) than at the wrist (60%) (Figure 16). One patient had the ankle thermal thresholds within the 99th percentile but abnormal HT at the wrist and in addition he had a qualitative abnormality of heat sensation at threshold level at ankle.

TABLE 14: Comparison of neurophysiological parameters between normal control groups and patients with small fibre neuropathy

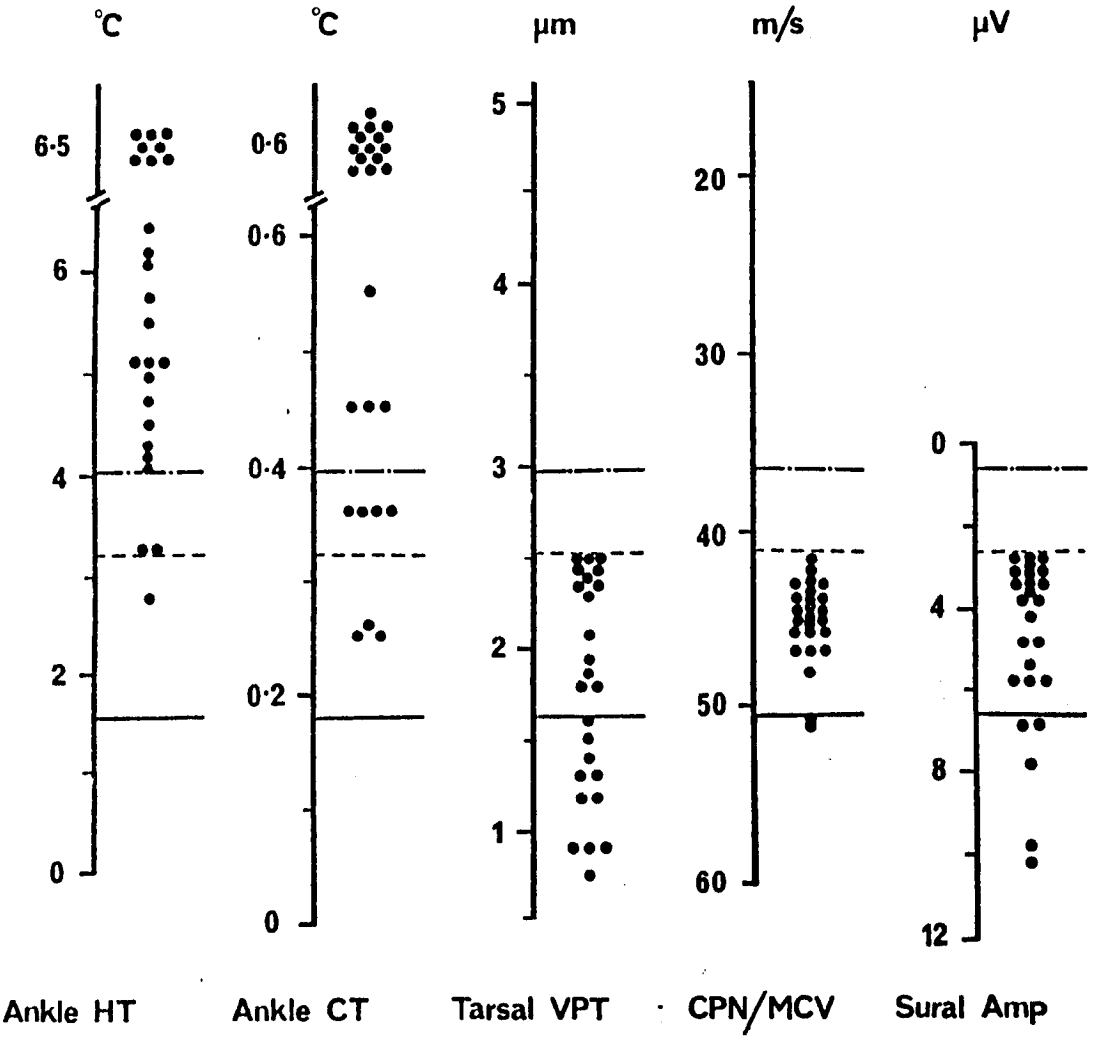
Parameter	units	Group	N	Mean	SD	P
Ankle HT	[°C]	Normal	52	1.59	0.82	< 0.001
		SFN	25	6.08	2.10	
Ankle CT	[°C]	Normal	52	0.18	0.07	< 0.005
		SFN	25	1.64	2.25	
Wrist HT	[°C]	Normal	52	0.23	0.07	< 0.02
		SFN	25	0.65	0.81	
Wrist CT	[°C]	Normal	52	0.16	0.05	< 0.005
		SFN	25	0.33	0.25	
SDML for CPN	[ms]	Normal	21	3.59	0.44	< 0.002
		SFN	25	4.05	0.44	
SDML for median nerve	[ms]	Normal	21	3.54	0.35	< 0.05
		SFN	25	3.77	0.42	
FMNCV for CPN	[m/s]	Normal	21	50.5	4.6	< 0.001
		SFN	25	45.5	2.6	
FMNCV for median nerve	[m/s]	Normal	21	58.6	4.8	< 0.001
		SFN	25	53.6	3.9	
Sural SNAP amplitude	[;V]	Normal	21	6.8	2	< 0.02
		SFN	25	5.1	2.29	
Median SNAP amplitude	[;V]	Normal	21	17.8	7	< 0.02
		SFN	25	12.6	6.5	

Abbreviations:

N : number
SD : standard deviation
SFN : small fibre neuropathy
HT : heat threshold
CT : cold threshold
SDML : shortest distal motor latency
FMNCV: fastest motor nerve conduction velocity
CPN : common peroneal nerve
SNAP : sensory nerve action potential

Figure 16 The distribution of values of the neurophysiological tests in the lower limbs performed in 25 patients with small fibre neuropathy. The scales are drawn so that control means (horizontal solid lines) and control SDs (2SD : broken lines, 3SD : semi-broken lines) coincide to make comparison easy. The axes of the common peroneal nerve (CPN), motor conduction velocity (MCV) and sural amplitude are reversed so that abnormalities are shown as shifts in upward direction for all the neurophysiological parameters.

Abbreviations: HT : heat threshold
CT : cold threshold
VPT : vibration perception threshold.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40
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60
0
4
8
12
Ankle HT
Ankle CT
Tarsal VPT
CPN/MCV
Sural Amp

Subjective descriptions of qualitative abnormalities of thermal sensation were reported by 12 patients. The thermal thresholds, however, were measured at that point where a sensation of any type was appreciated in response to the thermal stimulus. In these patients further increase in the stimulus intensity did produce a recognisable thermal sensation. The initial subjective response to the thermal stimulus was recorded as the thermal threshold to prevent bias of the results towards abnormal values. It is possible that the threshold so meausred was lower than the true thermal threshold in such patients.

In all 25 patients the individual NC and VPT values were within the normal range and their EMG studies did not show any abnormality. However, a comparison of the group mean values for the patients and control subjects showed significant differences (Table 14).

Friedreich's Ataxia

In contrast to small fibre neuropathy, a selective loss of large fibre population in Friedreich's ataxia has been shown in quantitative histologic studies (Dyck et al 1968,1971; McLeod 1971). NC studies in these patients shows either absent or abnormaly severe reduction in the amplitude of SNAPs of upper and lower limb nerves (Dyck and Lambert 1968; McLeod 1971; Bouchard et al 1979). In vitro compound action potential measurement of the excised sural nerve of patients with Friedreich's ataxia has shown a great reduction in the $A\alpha$ potential amplitude with normal latency indicating a loss of the large myelinated fibres with normal $A\Delta$ and C potentials at the early stages of the disease (Dyck et al 1971,1984). Quantitative sensory studies on individual patients have supported these findings and revealed the presence of a dissociated sensory loss involving vibration, proprioception and fine touch while pain and temperature sensations are spared early in the course of the disease (Dyck et al 1971,1984). It is only in advanced cases that a slight reduction of the

amplitude of the small fibre population of the in vitro compound action potential (Dyck et al 1971) and mild abnormality of temperature sensation (Dyck et al 1971,1984) might occur.

Ten patients with definite Friedreich's ataxia were studied (4 male and 6 female) aged 17 to 37 (mean = 23.6; SD = 10) years. The duration since the time the disorder was first noticed and/or diagnosed ranged between 0.5 to 22 (mean = 6.2; SD = 8) years. The principal clinical findings in the 10 patients are summarised in Table 15. Using the same standard techniques described above, EMG and NC studies were performed in all the patients and FMNCV and SDML were measured for the R CPN and median nerves. SNAP studies were also performed on the R ulnar, median and sural nerves. Hoffman (H) and F responses were recorded using the same method as for the SFN patients. VPT values were determined for the R foot (the dorso-medial aspect of the middle of the R first metatarsal bone). HT and CT values were also determined for the R wrist and R ankle. The normal values for these tests came from control groups with similar mean age to that of the patients. Control values for the thermal thresholds were obtained from 45 subjects aged 6-35 (mean = 24; SD = 10.5) years. For the EMG and NC studies the control group consisted of 20 healthy subjects aged 17-36 (mean = 24; SD = 11.2) years and for the VPT measurement 16 subjects aged 17-37 (mean = 23.4; SD = 11) years.

Thermal threshold value above the 99th percentile and motor and sensory conduction and VPT values outside the 95th percentile were considered abnormal. In all 10 patients (100%), abnormalities of SNAP and VPT were present (Table 15). Only two patients, aged 30 and 37 years, with advanced Friedreich's ataxia showed a mild abnormality of HT or CT at ankle. Both had blunting of pinprick sensation of the toes of both feet (Table 15). None of the patients had abnormal wrist thermal thresholds. The distribution of the values for various neurophysiological tests is shown in Figure 17 and

TABLE 15: Summary of clinical and neurophysiological data of 10 patients with Friedreich's ataxia

	Number	%
Family history (total)	9	90
Friedreich's ataxia	2	20
Pes cavus	9	90
Cerebellar ataxia	10	100
Skeletal deformities	10	100
Optic atrophy	2	20
Somatic sensory symptoms (total)	5	50
numbness	5	50
tingling	1	10
Objective sensory signs (total)	10	100
abnormal vibration	10	100
abnormal proprioception	10	100
abnormal fine touch	9	90
abnormal pinprick	1	10
Abnormal deep tendon reflexes	10	100
Absent H reflex	10	100
Distal muscle wasting and/or weakness	5	50
Abnormal nerve conduction (total)	10	100
abnormal median SNAP	10	100
abnormal ulnar SNAP	10	100
abnormal sural SNAP	10	100
abnormal median SDML and/or FMNCV	6	60
abnormal CPN SDML and/or FMNCV	8	80
Abnormal PT (foot)	10	100

Abnormal thermal thresholds (total)	2	20
abnormal ankle HT	2	20
abnormal ankle CT	2	20
abnormal wrist HT	0	0
abnormal wrist CT	0	0

Abbreviations:

HT : heat threshold

CT : cold threshold

SNAP : sensory nerve action potential

SDML : shortest distal motor latency

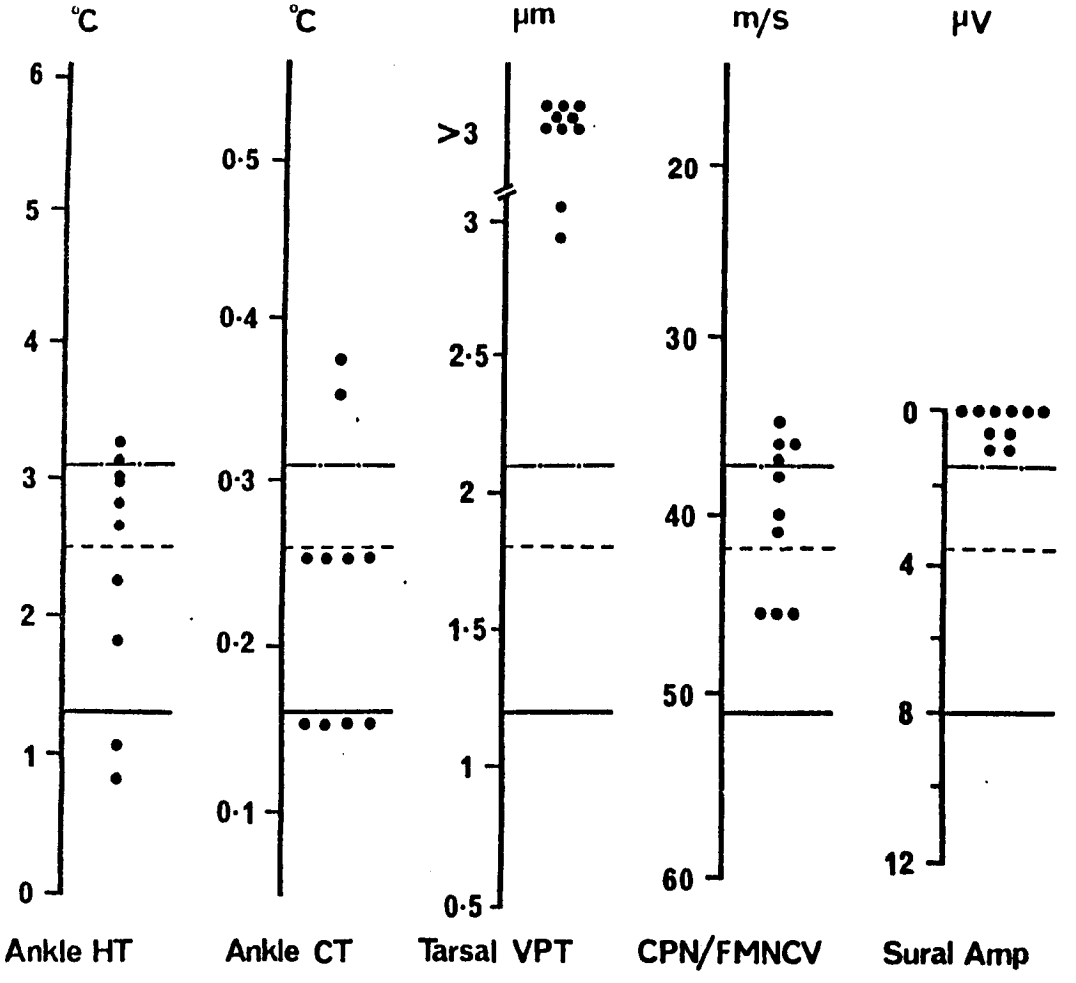
FMNCV : fastest motor nerve conduction velocity

CPN : common peroneal nerve

VPT : vibration perception threshold

Figure 17 The distribution of values of the neurophysiological tests performed in 10 patients with Friedreich's ataxia. The scales are drawn so that control means (horizontal solid lines) and control SDs (2SD : broken lines, 3SD : semi-broken lines) coincide to make comparison easy. The axes of the common peroneal nerve (CPN), fastest motor nerve conduction velocity (FMNCV) and sural amplitude are reversed so that abnormalities are shown as shifts in upward direction for all the neurophysiological parameters.
small fibre neuropathy.

Abbreviations: as in Figure 16.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1
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30
40
50
60
0
4
8
12
Ankle HT
Ankle CT
Tarsal VPT
CPN/FMNCV
Sural Amp

TABLE 16: Comparison of neurophysiological parameters between normal control groups and patients with Friedreich's ataxia (FA)

Parameter	Units	Group	N	Mean	SD	P
Ankle HT	[°C]	Normal	54	1.3	0.6	< 0.01
		FA	10	2.3	0.95	
Ankle CT	[°C]	Normal	54	0.16	0.05	< 0.05
		FA	10	0.23	0.09	
Wrist HT	[°C]	Normal	54	0.23	0.05	NS
		FA	10	0.26	0.06	
Wrist CT	[°C]	Normal	54	0.15	0.05	NS
		FA	10	0.17	0.03	
VPT (foot)	[/um]	Normal	16	1.2	0.3	< 0.001
		FA	10	7.6	4.3	
FMNCV for CPN	[m/s]	Normal	20	51	4.6	< 0.001
		FA	10	39	2.8	
FMNCV for median	[m/s]	Normal	20	59	4.7	< 0.001
		FA	10	45	3.6	
Sural SNAP amplitude	[/uv]	Normal	20	8	2.2	< 0.001
		FA	10	0.3	0.4	
Median SNAP amplitude	[/uv]	Normal	20	20.2	6.2	< 0.001
		FA	10	1.8	1.1	
Ulnar SNAP amplitude	[/uv]	Normal	20	16	5	< 0.001
		FA	10	1.3	0.9	

Abbreviations as in Table 15

Table 16. All mean values for the NC and VPT for the patients were significantly different from their corresponding values for the control groups. Mean ankle HT and CT for the 10 patients with Friedreich's ataxia were also significantly higher (Table 16).

Patients with Acromegaly

The association of median nerve entrapment at the wrist with acromegaly is well known (Woltman 1941; Kellgren et al 1952; Schiller and Kolb 1954; Johnston 1960; Skanse 1961) and is probably due to compression of the nerve by hypertrophic connective tissue (Brain et al 1947; Kellgren et al 1952; Sullivan et al 1963). Thus, unilateral or bilateral carpal tunnel syndrome (CTS) is one of the first symptoms in 12% of patients with acromegaly (Pickett et al 1975) and later in the course of the disease the incidence may rise to as high as 35-47% (O'Duffy et al 1973; Pickett et al 1975). Generalised neuropathy, however, is a much less recognised complication and only occasional reports of individual patients have appeared (Humberd 1937; Stewart 1966; Dinn 1970; Lewis 1972; Lucey 1972; Low et al 1974; Sandbank et al 1974; Khaleeli et al 1984). This neuropathy was found to be predominantly sensory in nature (McLeod and Pollard 1984) from clinical and NC studies although severe muscle weakness and wasting have been described in one patient (Lewis 1972).

In this study, evidence of a generalised neuropathy was looked for in 24 patients with definite diagnosis of acromegaly and the relative frequency of involvement of small versus large fibre afferent pathways was assessed using the thermal technique along with EMG and NC studies and VPT measurements. FMNCVs and SDMLs for the R CPN and median nerves, SNAPs for the R median and sural nerves, VPTs for the R hand (the dorsal aspect of the middle of the R second metacarpal bone) and R foot (the dorso-medial aspect of the middle of the R first metatarsal bone) and HT and CT values for the R wrist and ankle (sites a and c) were measured and compared to

those of control groups. There were 61 control subjects for the thermal thresholds aged 35 to 73 (mean = 45.5; SD = 11.8) years. The control group for the EMG and NC studies contained 21 healthy subjects aged 23 to 69 (mean = 46; SD = 12) years and for the VPT 27 subjects aged between 17 to 64 (mean = 46.2; SD = 11.5) years.

Twenty-four patients with clinical, radiological and biochemical evidence of acromegaly attending the Department of Medicine at the Western Infirmary, Glasgow, were included in this study. Their ages ranged from 26 to 78 (mean = 48; SD = 15.4) years. There were 14 female and 10 male patients. Any patient with excessive alcohol intake or taking any drug likely to cause peripheral nerve dysfunction was excluded from the study. All patients had received some treatment for acromegaly. This and other relevant clinical features are shown in Table 17 which includes, when available, the hormonal status both at diagnosis and at the time of the neurophysiological studies. A full biochemical and endocrinological evaluation of all patients were performed by admitting them to hospital prior to the neurophysiological evaluation (these were performed by Dr Davies at the Gardiner Institute, Western Infirmary, Glasgow). These included a standard 50 g oral glucose tolerance test, human growth hormone (HGH) day curve, standard intravenous thyrotrophin-releasing hormone test with measurement of the thyroid stimulating hormone (TSH) and HGH (Ormston et al 1971) and measurement of the total exchangeable body sodium (Nae) (Davies and Robertson 1973).

Clinical evidence of generalised neuropathy was present in eight patients. Two other patients had typical distal sensory symptoms but without objective clinical evidence (Table 17). In 10 patients, mostly with clinical evidence of neuropathy, the ulnar and/or the common peroneal nerves were considered to be palpably enlarged (Table 17). The results of the neurophysiological assessments of the control subjects and the patients

TABLE 17: SUMMARY OF THE IMPORTANT CLINICAL DATA IN 24 PATIENTS WITH ACROMEGALY AT DIAGNOSIS AND AT THE TIME OF THE NEUROPHYSIOLOGICAL ASSESSMENT

Case No.	Sex	Age (yr)	Clinical* polyneuropathy	CTS	Clinical nerve hypertrophy	At Diagnosis			At present					Treatment	
						mean 'HGH day curve'	Nae	GTT	Mean 'HGH day curve'	Nae	GTT	Mean HGH during GTT	TRH Test	Type	Duration (Yr)
1	F	68	+	+	+	43	147	N	6.1	125	Abn	3.9	Abn	H	5
2	F	48	+	-	+	67	126	N	9.3	107	N	16	N	H & I	4
3	F	38	-	-	+			N	1.8	96	N	1.9		H	6
4	M	52	+	-	+			N	1.8	109	N	1.9		H & I	19
5	M	30	+	+	+			N	1.6		N	0.8	N	H & I	10
6	M	46	-	-	-	39	133	N	7	112	Abn	6.8	Abn	H & I	3
7	M	66	+	-	+	17	126	Abn	4.1	125	Abn	3.2	Abn	H	10
8	F	30	-	+	+			N	4.5	121	N	4.5	Abn	H	2
9	F	68	+	-	-			N	22.2	138	N	20.4	Abn	H	14
10	M	26	-	-	-	618	118	N	115.8	115	N	24.6	Abn	I	6
11	M	43	-	-	-	135	132	N	11.4	107	N	11.3	Abn	H	11
12	F	52	-	-	-	19	120	N	4.2	111	N	4.4	Abn	I	10
13	F	62	-	-	-			N	2.9	93	N	1.4	N	I	10
14	F	29	-	-	-	36	114	N	29.2	109	N	40	Abn	H	6
15	M	30	-	+	-		139	N	17.3	118	Abn	15.8	Abn	H & I	8
16	F	56	-	+	-	63	134	N	6.7	115	N	6.2		H	2
17	F	65	-	+	-	109	134	N	2.4	107	N	2	Abn	H & I	8
18	F	54	-	+	-	97	120	N	2.5	111	Abn	2.7	N	H	6
19	M	65	+	+	+	140	155	Abn	2.2	128	Abn	1.6	Abn	H	7
20	F	42	-	-	+	36	108	N	21.8		N	18.8		H	12
21	M	78	+	+	+	80	153	N	17	144	N	28	N	H	30
22	M	37	-	+	-	38	131	N	8	119	N	9.2	N	H & I	3
23	F	35	-	-	-	29	115	N	1.2	93	N	1.2		H	10
24	F	33	-	-	-	16	107	N	2.9	93	N	1.6	N	H	5

* All patients with (+) had signs of weakness and/or wasting of small muscles of the foot and hyposensation to one or more of the following in a stocking-glove distribution: pinprick, light touch, vibration with or without symptoms (paraesthesiae, numbness, abnormal heat or cold sensation) of a generalised neuropathy.

Abbreviations:

F = female
M = male
\+ = present
\- = absent
N = Normal
Abn = Abnormal
H = Hypophysectomy
I = Irradiation
CTS = Carpal Tunnel syndrome
Nae = Total exchangeable body sodium
GTT = Glucose tolerance test
HGH = Human growth hormone
TRH = Thyrotrophin-releasing hormone

with acromegaly are summarised and compared in Table 18. The statistical significance of the results was evaluated using student's 't' test. It is clear from Table 18 that all of the neurophysiological parameters are significantly abnormal in the patients with acromegaly. The mean values of the upper and lower limbs thermal and vibration thresholds and the SDML for the CPN and median nerve were all significantly higher than corresponding means for the control groups. The mean values of the FMNCV for the CPN and median nerve and the median and sural SNAP amplitude were significantly lower than those of the control group.

The distribution and relative frequencies of the abnormalities for the neurophysiological tests are shown in Figure 18. Table 19 demonstrates that the SDML and/or the FMNCV for the CPN were abnormal in 50% of the patients, the sural SNAP amplitude and/or latency were abnormal in 14% of the patients and the VPT at foot was abnormal in 37% of patients with acromegaly. For these tests values above the 95th percentile were considered abnormal while thermal threshold values in excess of the 99th percentile were taken as abnormal. Thermal thresholds for ankle were abnormal in 62% of the patients. In short, the highest evidence of abnormality in these patients was found using the thermal threshold measurement technique. A smaller number of patients had abnormalities of the sensory and/or motor median nerve conduction studies (29%), of the carpal VPT (12%) and of the wrist thermal thresholds (42%).

The diagnosis of carpal tunnel syndrome (CTS) was made on both clinical and electrophysiological evidence. The clinical criteria of CTS included one or more of the following features: paraesthesiae in the distribution of the median nerve; wasting and/or weakness of the abductor pollicis brevis muscle and sensory impairment in the median nerve distribution of the hand. The electrophysiological criteria of CTS included one or more of the following abnormalities: a prolonged median nerve SDML; a prolonged median SNAP latency and a reduced median SNAP amplitude at the wrist. These

TABLE 18: Comparison of neurophysiological parameters between normal control groups and patients with acromegaly

Parameter	Group	N	Mean	SD	Units	P
Ankle	Normal	40	1.59	0.82	°C	< 0.001
	Acromegaly	24	4.17	2.16		
Ankle CT	Normal	40	0.18	0.07	°C	< 0.001
	Acromegaly	24	0.43	0.28		
Wrist HT	Normal	40	0.23	0.07	°C	< 0.02
	Acromegaly	24	0.55	0.62		
Wrist CT	Normal	40	0.16	0.05	°C	< 0.03
	Acromegaly	24	0.26	0.21		
Carpal VPT	Normal	27	0.8	0.41	um	NS
	Acromegaly	24	1.21	1.51		
Tarsal VPT	Normal	27	1.63	0.45	um	< 0.05
	Acromegaly	24	4.42	9.13		
Median SDML	Normal	21	3.54	0.35	ms	< 0.02
	Acromegaly	24	3.98	0.77		
Median FMNCV	Normal	21	58.6	4.8	m/s	< 0.05
	Acromegaly	24	54.8	7.66		
Median SNAP latency	Normal	21	2.92	0.26	ms	< 0.01
	Acromegaly	24	3.52	0.99		
Median SNAP amplitude	Normal	21	17.8	7	uV	< 0.01
	Acromegaly	24	11.7	8		
SDML for CPN	Normal	21	3.59	0.44	ms	< 0.001
	Acromegaly	24	4.5	0.9		
FMNCV for CPN	Normal	21	50.5	4.6	m/s	< 0.001
	Acromegaly	24	45.9	3.4		
Sural SNAP latency	Normal	21	3.62	0.44	ms	NS
	Acromegaly	24	3.53	0.42		
Sural SNAP amplitude	Normal	21	6.8	2	uV	< 0.005
	Acromegaly	24	4.8	2.15		

Abbreviations:

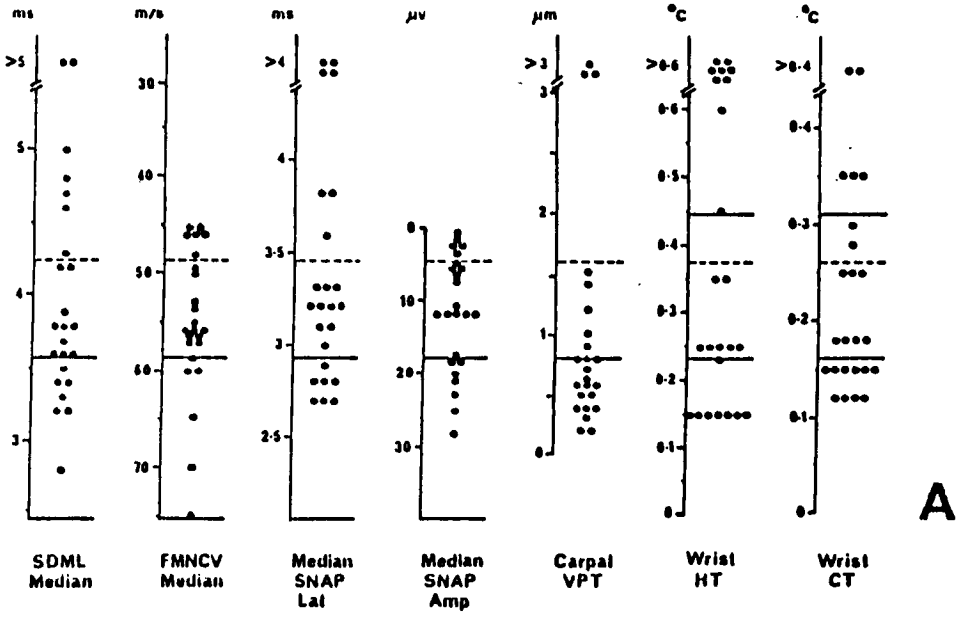
HT : heat threshold
CT : cold threshold
VPT : vibration perception threshold
SDML : shortest distal motor latency
FMNCV : fastest motor nerve conduction velocity
SNAP : sensory nerve action potential

TABLE 19: Frequency of abnormality of neurophysiological Parameters in 24 patients with acromegaly

Neurophysiological parameter(s)	Criteria of abnormality	Patients with abnormal values	
		No.	%
Ankle HT	99%CL	14	58
Ankle CT	99%CL	9	37
Wrist HT	99%CL	9	37
Wrist CT	99%CL	5	21
Tarsal VPT	95%CL	9	37
Carpal VPT	95%CL	3	12
Median SDML	95%CL	7	29
Median FMNCV	95%CL	6	25
Median SNAP latency	95%CL	7	29
Median SNAP amplitude	95%CL	5	21
SDML for CPN	95%CL	11	46
FMNCV for CPN	95%CL	3	12
Sural SNAP latency	95%CL	1	4
Sural SNAP amplitude	95%CL	3	12
HT and/or CT at ankle	99%CL	15	62
HT and/or CT at wrist	99%CL	10	42
HT and/or CT at wrist and/or ankle	99%CL	16	67
Carpal and/or Tarsal VPT	95%CL	9	37
SDML and/or FMNCV for CPN	95%CL	12	50
Sural SNAP latency and/or amplitude	95%CL	4	17
Abnormal CPN and/or sural NC studies	95%CL	12	50

Abbreviations: As in Table 18

Figure 18 The distribution of values of the neurophysiological tests performed on 24 patients with acromegaly; (A) in the upper limb; (B) in the lower limb. The scales are drawn so that control means and control SDs coincide to render comparison easy. The axes of the median and sural SNAP amplitudes and the CPN and median FMNCVs are reversed so that abnormalities are shown as shifts in upward direction for all the neurophysiological parameters.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m/s
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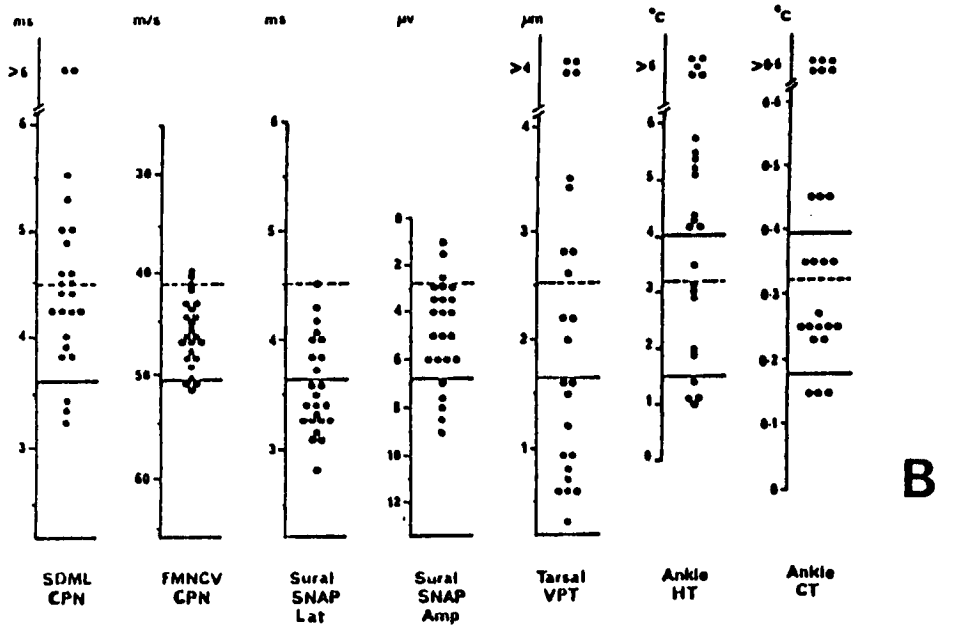
SDML Median
FMNCV Median
Median SNAP Lat
Median SNAP Amp
Carpal VPT
Wrist HT
Wrist CT
A


ms
m/s
ms
μv
μm
°C
°C
SDML CPN
FMNCV CPN
Sural SNAP Lat
Sural SNAP Amp
Tarsal VPT
Ankle HT
Ankle CT
B

criteria had to occur in the presence of normal ulnar nerve and proximal median nerve conduction studies. Ten patients had both clinical and electrophysiological criteria of CTS (42%). In five patients, two of whom had bilateral CTS, this was the only abnormality in their neurophysiological tests. In the remaining five of those with carpal tunnel syndrome there was also evidence of a widespread subclinical dysfunction of the peripheral nerves and their endorgans from one or more neurophysiological test performed on the lower limbs especially the ankle thermal thresholds which were abnormal in all (Table 20).

There was no significant correlation between the neurophysiological measurements and values of fasting blood glucose, two-hour post-prandial glucose, the area under glucose curve during GTT, human growth hormone (HGH), mean 'HGH day curve' and TSH levels at 20 and 60 minute intervals during the thyrotrophin-releasing hormone test. The neurophysiological parameters also did not correlate with these endocrinological data performed at the time of the diagnosis of acromegaly. Significant correlation, however, was found between most of these neurophysiological tests and the exchangeable sodium (Nae) (Table 21). No correlation was noticed between known duration of acromegaly and the neurophysiological parameters. It is accepted, however, that the lack of correlation may be due to the difficulty of estimation of the actual duration of this disorder.

DISORDERS OF THERMAL SENSATION IN PATIENTS WITH CENTRAL NERVOUS SYSTEM LESIONS

The Glasgow Thermal technique was also applied to a few patients with relatively rare, but relevant lesions of the CNS. These included two patients with syringomyelia, two with tabes dorsalis and one with partial Brown-Sequard syndrome from a stab wound (hemisection of spinal cord).

TABLE 20: SUMMARY OF SOME OF THE NEUROPHYSIOLOGICAL TESTS IN 10 PATIENTS WITH ACROMEGALY ASSOCIATED CARPAL TUNNEL SYNDROME.

PATIENT NO.	MEDIAN NERVE				SURAL		LPN	THERMAL THRESHOLDS				VPT	
	MOTOR		SNAP		SNAP			WRIST		ANKLE			
	SDML ms	FMNCV m/s	Lat ms	Amp uV	Lat ms	Amp uV	FMNCV m/s	HT °C	CT °C	HT °C	CT °C	CARPAL um	TARSAL um
15	4.7	50	4.5	5	4.5	3	44.2	0.15	0.15	2.85	0.25	0.4	0.6
16	4.3	49.5	3.2	12	4	5	45	0.15	0.15	2.95	0.75	0.6	2.2
17	5	53.5	3.8	5	3.3	6	46	0.15	0.15	1.35	0.25	0.2	0.9
18	4.8	49	6.5	0.5	3.4	5	44	0.15	0.15	3.45	0.35	0.8	1.5
22	3.6	50	3.6	12	3.8	6	50	0.25	0.15	3.15	0.25	0.6	1.6
1	6	46	5.4	3.5	4.3	4	43.4	0.35	0.25	5.65	0.35	5.7	45
7	4.2	54.3	4.5	3	3.6	3.5	41.7	1.45	0.95	6.75	1.15	5.6	10.6
9	4.6	60	3.3	7	3.3	3	46.4	0.65	0.28	7.35	0.45	0.7	3.5
19	3.8	55	3.8	4	3.3	3.5	43	1.45	0.35	5.25	0.65	0.8	5.6
21	5.4	46	5.5	2	4.0	4	46	0.35	0.25	4.20	0.75	0.9	2.6

Abbreviations: As for Table 18.

Abnormal values for VPT and thermal thresholds are underlined

TABLE 21: Correlations referred to in text between total exchangeable body sodium and the neurophysiological parameters

Neurophysiological Parameter	At the time of diagnosis of acromegaly		At present	
	r	P	r	P
Ankle HT	0.69	< 0.001	0.455787	0.02
Ankle CT	0.4347	< 0.05	0.428333	0.02
Tarsal VPT	0.4282	< 0.05	0.290966	NS
Median SDML	0.689	< 0.001	0.584923	0.01
Median SNAP Latency	0.4397	< 0.05	0.447054	0.02
Median SNAP amplitude	- 0.6677	< 0.001	- 0.2489	NS
Sural SNAP amplitude	- 0.679	< 0.001	- 0.424078	0.05
Sural SMAP latency	0.609	< 0.01	0.317485	NS
SDML for CPN	- 0.25	NS	- 0.157554	NS
FMNCV for CPN	- 0.4454	< 0.05	- 0.484736	0.02

Abbreviations: As in Table 18.

Syringomyelia

This is a disease of the spinal cord and brain stem of unknown cause associated with gliosis and cavitation of these structures. It is characterised clinically by loss of pain and temperature sensation but preservation of touch-pressure and vibration sensation in the affected parts of the body, that is, dissociated sensory loss. Pathologically there is central gliosis with cystic cavitation of the affected portion of the spinal cord. The irregular asymmetrical fluid filled cavity usually extends over many segments of the cord or even along its entire length but it is usually most extensive in the cervical segments (Larroche 1984). Contiguous structures, in particular the anterior horn cells, the sensory fibres decussating in the anterior commissure of the spinal cord (concerned with pain and thermal sensation) and the lateral corticospinal tracts are frequently destroyed. If the cavity, the so called syrinx, extends into the medulla, the nuclei of the lower cranial nerves may be involved (syringobulbia). In typical cases the cavity extends transversely across the cord involving the more posterior parts of the ventral horns and passing across the midline behind the central canal of the spinal cord.

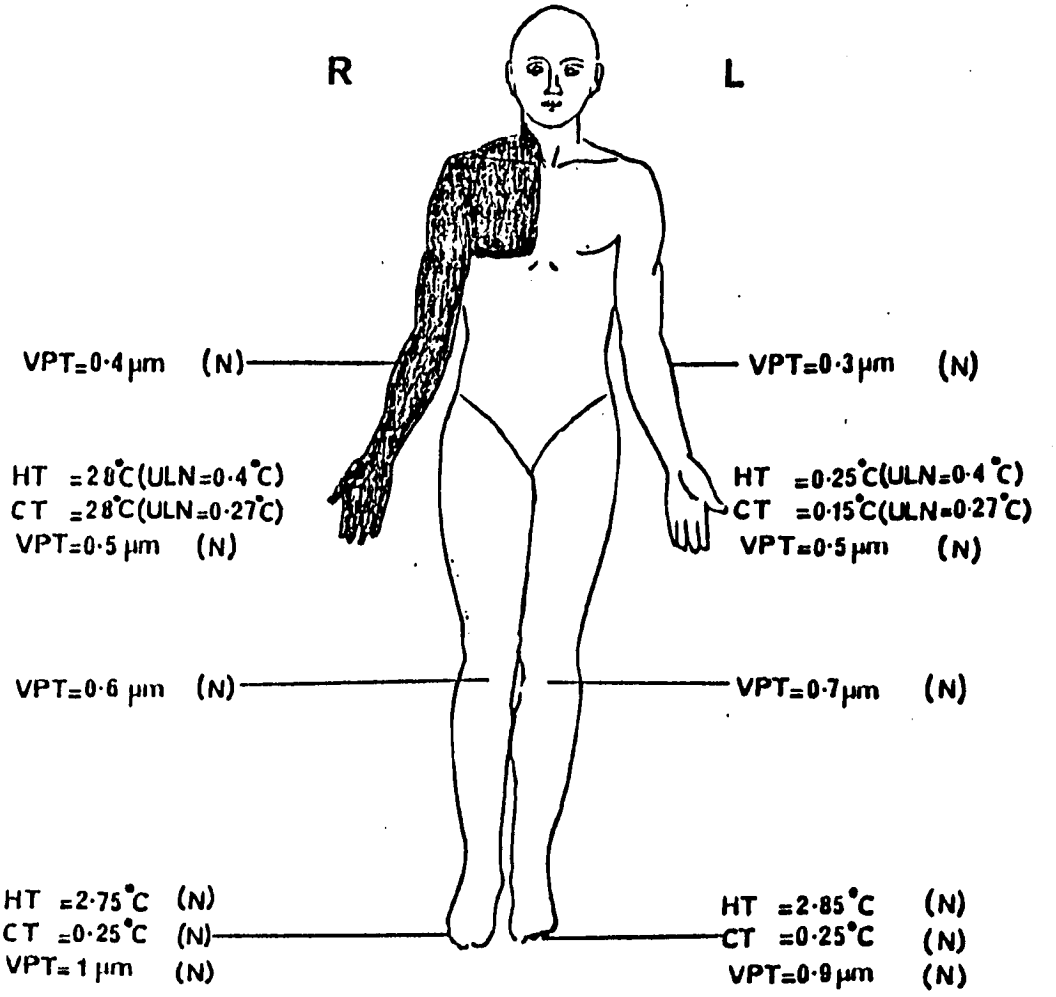
Two patients with established diagnoses of syringomyelia have been examined by the thermal technique. Patient 1 was a 45 year old female diagnosed as having this disorder 15 years prior to this examination. A summary of the clinical picture is diagramatically presented in Figure 19. She had reduced pinprick and temperature sensation in the R upper limb and R upper thorax to the level of T5 dermatome. Vibration, proprioception and two-point discrimination were all normal to clinical testing. There was wasting in the small hand muscles on the R side not accounted for by the median or ulnar nerves. The deep tendon reflexes were lost in the R arm, normal in the L arm and brisk in both lower limbs with bilateral upgoing toes and clonus.

Quantitative estimation of both vibration and thermal thresholds was

Figure 19 The shaded area represents the distribution of abnormality of pinprick and temperature sensation in a 45 year old female patient with syringomyelia (patient 1). Thermal threshold measurements are shown for the wrists (site a) and ankles (site c) and VPT measurements for the hands, forearms, tibial tuberosities and feet.

N = normal

ULN = upper limit of normal (at 95%CL for VPTs and 99%CL for the thermal thresholds).

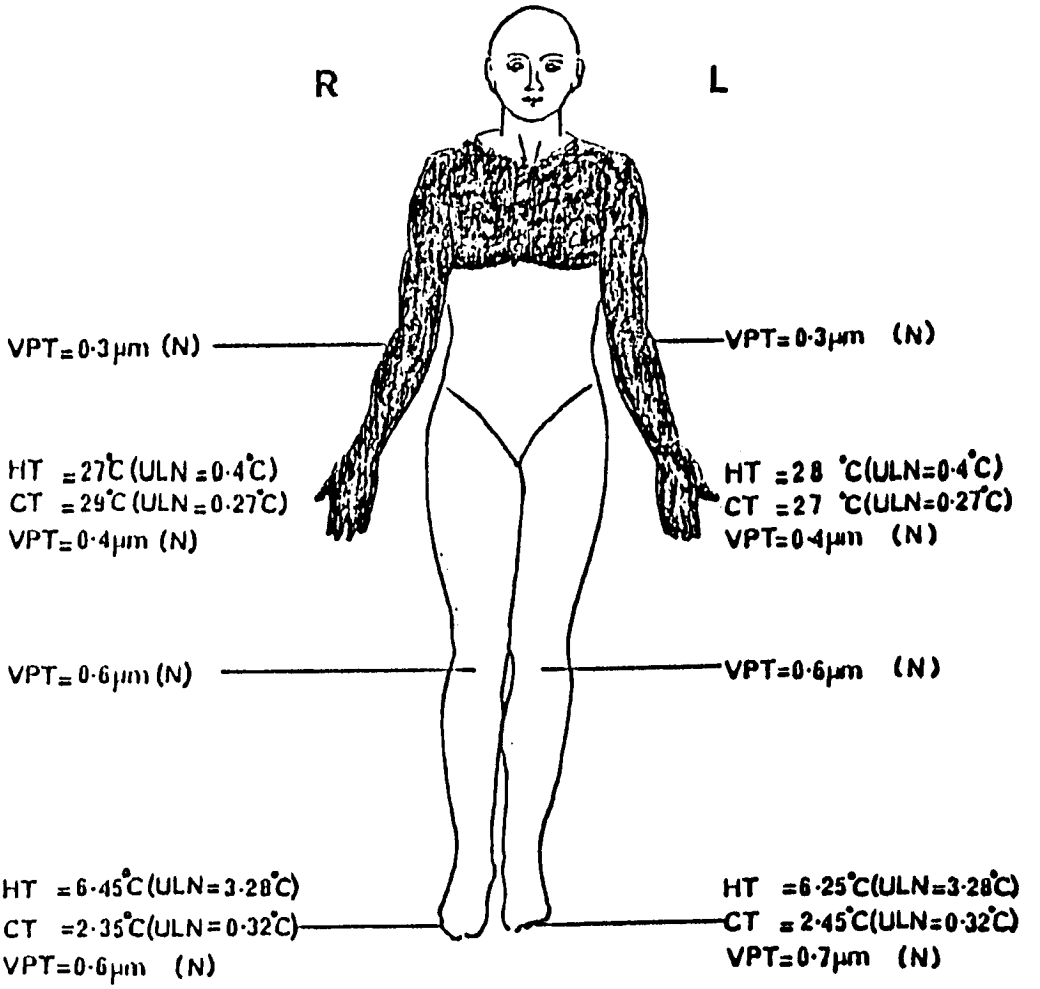

R
L
VPT=0·4 μm (N)
HT =2·8°C(ULN=0·4°C)
CT =2·8°C(ULN=0·27°C)
VPT=0·5 μm (N)
VPT=0·6 μm (N)
HT =2·75°C (N)
CT =0·25°C (N)
VPT= 1 μm (N)
VPT=0·3 μm (N)
HT =0·25°C(ULN=0·4°C)
CT =0·15°C(ULN=0·27°C)
VPT=0·5 μm (N)
VPT=0·7 μm (N)
HT =2·85°C (N)
CT =0·25°C (N)
VPT=0·9 μm (N)

performed on all four limbs and the results are summarised in Figure 19. VPTs were all within normal ranges for the feet (the middle of the postero-medial aspect of the first metatarsal bone), tibial tuberosities, hands (middle of the dorsal aspect of the second metacarpal bone) and the middle of the radius bones on the lateral aspect of both forearms. Thermal thresholds for the R wrist (site a) were very high [both HT and CT were greater than 10°C, that is, outside the range of the thermal threshold technique, but using the switch pressing method (Chapter 5) the patient could feel heating of 28°C and cooling stimulus of 28°C]. Both HT and CT values were within normal at the L wrist (site a on the left; HT = 0.25°C, CT = 0.15°C), R ankle (site c; HT = 2.75°C, CT = 0.25°C) and L ankle (site c on the left; HT = 2.85°C, CT = 0.25°C) [Chapter 5 for normal values]. These sites, however, showed no abnormality of sensation on clinical examination.

Patient 2 was a 62 year old lady with more than 35 years history of syringomyelia, confirmed radiologically and by CT scan, with progressive symptoms over the last two years. Sensory dissociation was found similar to that of patient 1 but involving both upper limbs and the upper part of the chest on both sides to the level of T6 dermatome (Figure 20). The patient had several scars of burns in both hands. Wasting of the small muscles of both hands, absent tendon reflexes in both upper limbs and brisk knee and ankle jerks with extensor plantar responses and fasciculations in both arm muscles were other clinical features. Sensations of vibration, proprioception and touch-pressure were intact. VPT values for the same sites as the previous patient were all within the normal range on both sides. The patient felt heat and cold stimuli applied to the wrists only when their values exceeded 20°C using the switch method. Ankle HT for the R (6.45°C) and the L (6.25°C) and ankle CT for the R (2.35°C) and the L (2.45°C) were abnormally increased. Both lower limbs, including ankles,

Figure 20 The shaded area represents the distribution of abnormality of pinprick and temperature sensation on clinical examination in a 62 year old woman with syringomeylia (patient 2). Thermal threshold measurements are shown for the wrists (site a) and ankles (site c) for the thermal thresholds and VPT measurements for the hands, forearms, tibial tuberosities and feet.

(Abbreviations as in Figure 19.)


R
L
VPT=0·3μm (N)
VPT=0·3μm (N)
HT =27°C (ULN=0·4°C)
CT =29°C (ULN=0·27°C)
VPT=0·4μm (N)
HT =28 °C(ULN=0·4°C)
CT =27 °C(ULN=0·27°C)
VPT=0·4μm (N)
VPT=0·6μm (N)
VPT=0·6μm (N)
HT =6·45°C(ULN=3·28°C)
CT =2·35°C(ULN=0·32°C)
VPT=0·6μm (N)
HT =6·25°C(ULN=3·28°C)
CT =2·45°C(ULN=0·32°C)
VPT=0·7μm (N)

showed no abnormality on clinical examination.

Tabes Dorsalis

The name of this disorder is derived from the shrunken appearance of the dorsal columns of the spinal cord as a result of the primary involvement of large myelinated axons at the posterior nerve root entry zone. The number of these fibres in the lumbo-sacral roots is diminished, cellular infiltration of the lumbo-sacral dorsal root ganglia and degeneration of the posterior columns are the essential pathological features of tabes dorsalis which results from syphilitic infection of these structures. Although in advanced cases all modalities of sensation may be involved, tabes dorsalis is characterised by marked proprioceptive ataxia and abnormality of touch and vibration sensations indicating predominant involvement of the large fibres in the dorsal roots. The peripheral nerves in tabes dorsalis are essentially normal (Dyck et al 1971).

Patient 3: A 68 year old female patient with a 36 years history of tabes dorsalis was examined. She had typical 'lightning pains' in the legs, gradually worsening ataxia which was worse on eye closure or in darkness, and bladder disturbances. All these symptoms increased during the six months before investigation. The patient was diagnosed as having syphilis in 1945 and was treated with a course of 'injections' for one month at Ruchill Hospital, Glasgow. On examination, she had typical Argyll Robertson pupils, sensory ataxia with positive Romberg's sign, steppage gait, intact pinprick but diminished vibration and proprioception in the lower limbs and normal reflexes in the arms but absent tendon reflexes in the lower limbs with mute plantar responses on both sides. Serological tests for syphilis were positive. EMG and NC studies, including the SNAPs for sural, median and ulnar nerves were all normal with the exception of H-reflexes which were absent on both sides. Somatosensory evoked potentials

(SSEP) showed normal peripheral but markedly abnormal central large fibre conduction velocities. Measurement of the VPTs showed abnormally high values for both feet (the middle of the dorso-medial aspect of the first metatarsal bones) and tibial tuberosities but normal values for both hands (the middle of the dorsal aspect of the second metacarpal bones). HT and CT values for both wrists (site a) and ankles (site c) were within the normal range (Figure 21).

Patient 4 was a 62 year old male patient who was diagnosed as having syphilis in the 1940s and treated with arsenicals. He had a history of tabes dorsalis for 30 years. The clinical picture in this patient was much the same as patient 3. Hoffman (H) reflexes were absent on both sides, the SSEP showed absence of the cortical responses on both sides on stimulation of posterior tibial nerves and the EMG and NC studies were normal on both sides. The VPTs were abnormal in the lower limbs but normal in the upper limbs. HT and CT values were abnormally increased at both ankles (site c) but within the normal range at both wrists (site a) (Figure 22).

Brown-Sequard Syndrome

This syndrome, named after the neurologist who described it in 1868 (Chapter 1), is the sequel of hemisection of the spinal cord. In the complete syndrome the following picture is observed.

(a) ipsilateral lower motor neurone paralysis in the segment of the lesion due to involvement of the anterior horn cells
(b) ipsilateral upper motor neurone lesion below the level of the pathology due to involvement of the corticospinal tract
(c) ipsilateral zone of cutaneous anaesthesia involving all modalities in the segment(s) of the lesion due to involvement of the afferent fibres at the level of the pathology

Figure 21 Patient 3: HT and CT values for the wrists (site a) an ankles (site c) and VPT values for the hands, forearms, tibial tuberosities and feet in a 68 year old woman with tabes dorsalis. Thermal thresholds are all normal while VPTs are increased in the lower limbs.

(Abbreviations as in Figure 19.)

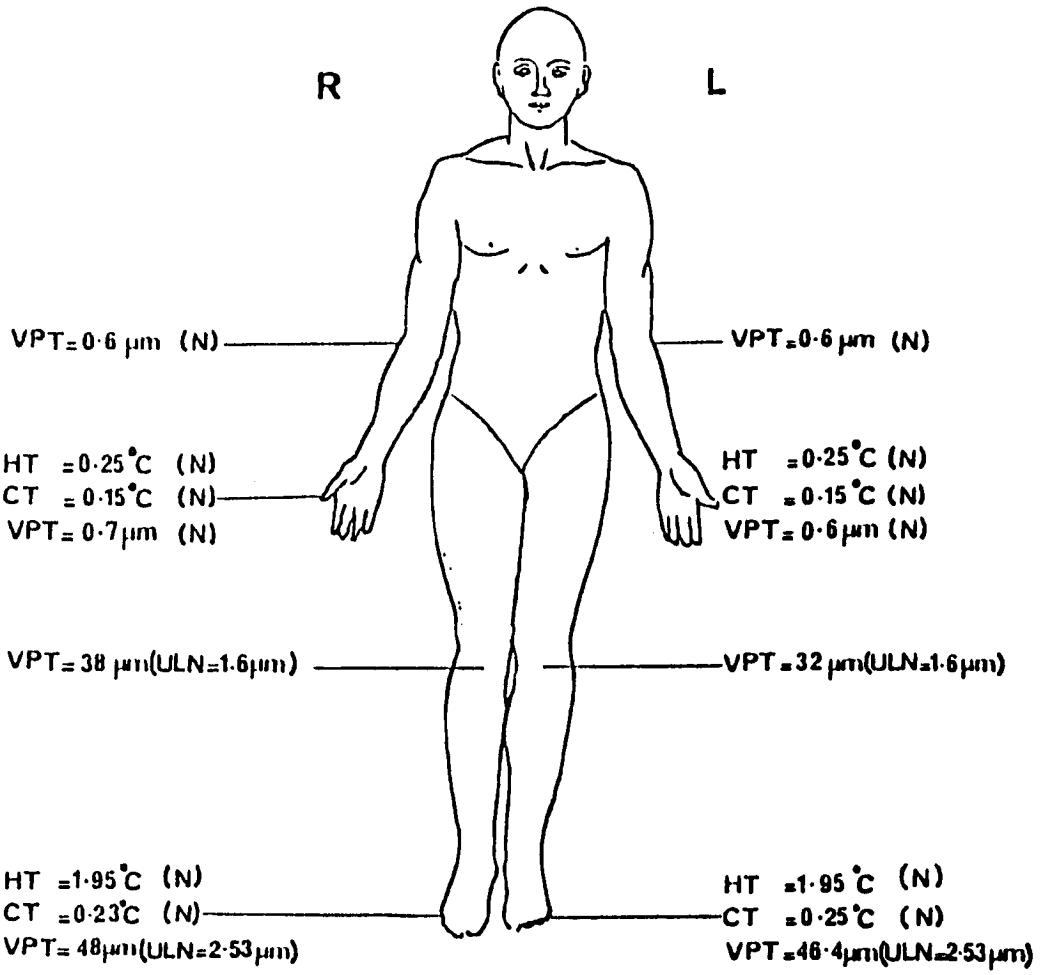
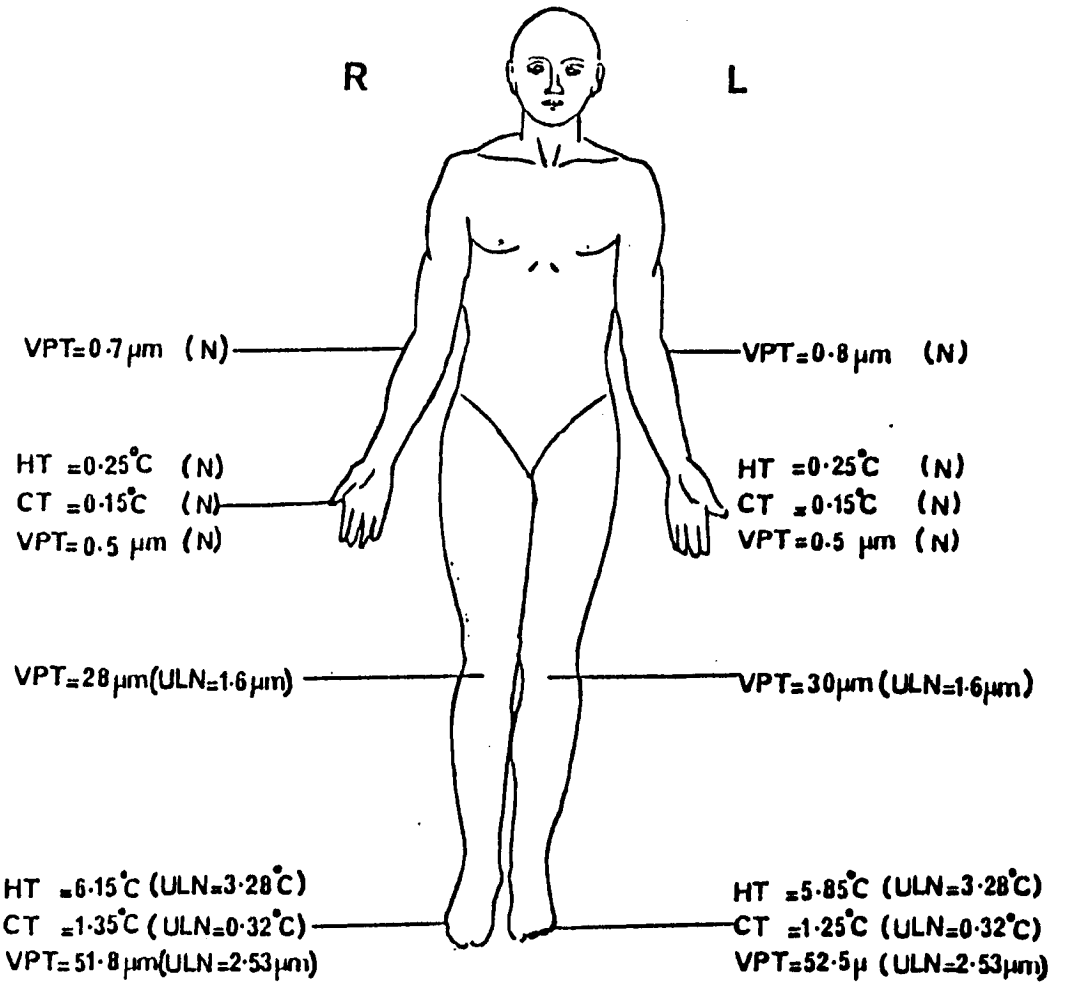

R
L
VPT=0·6 μm (N)
VPT=0·6 μm (N)
HT =0·25°C (N)
CT =0·15°C (N)
VPT=0·7 μm (N)
HT =0·25°C (N)
CT =0·15°C (N)
VPT=0·6 μm (N)
VPT=38 μm(ULN=1·6μm)
VPT=32 μm(ULN=1·6μm)
HT =1·95°C (N)
CT =0·23°C (N)
VPT=48μm(ULN=2·53μm)
HT =1·95°C (N)
CT =0·25°C (N)
VPT=46·4μm(ULN=2·53μm)

Figure 22 Patient 4: HT and CT values for the wrists (site a) and ankles (site c) and VPT values for the hands, forearms, tibial tuberosities and feet in a 62 year old man with tabes dorsalis. VPTs and thermal thresholds are abnormal in both lower limbs.

(Abbreviations as in Figure 19.)


R
L
VPT=0·7 μm (N)
VPT=0·8 μm (N)
HT =0·25°C (N)
CT =0·15°C (N)
VPT=0·5 μm (N)
HT =0·25°C (N)
CT =0·15°C (N)
VPT=0·5 μm (N)
VPT=28 μm(ULN=1·6 μm)
VPT=30 μm (ULN=1·6 μm)
HT =6·15°C (ULN=3·28°C)
CT =1·35°C (ULN=0·32°C)
VPT=51·8 μm(ULN=2·53 μm)
HT =5·85°C (ULN=3·28°C)
CT =1·25°C (ULN=0·32°C)
VPT=52·5 μ (ULN=2·53 μm)

(d) ipsilateral loss of proprioceptive, vibratory and two-point discrimination below the level of the lesion due to involvement of the uncrossed large fibre afferent pathway

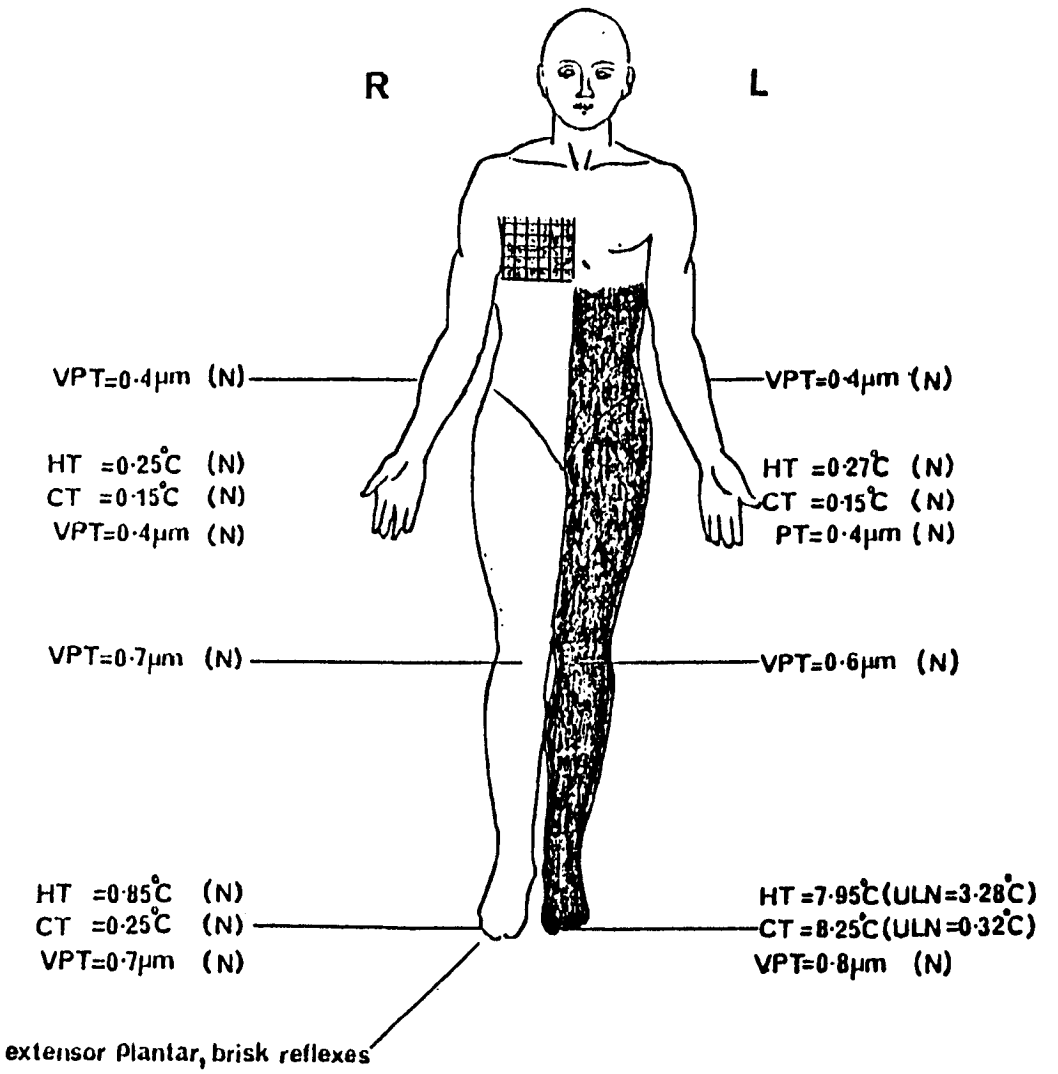
(e) contralateral loss of pain and temperature sensation below the level of the lesion due to involvement of the crossed spinothalamic tract.

A 42 year old male patient with incomplete Brown-Sequard syndrome was examined. He had been stabbed in the back about two inches to the right of the midline opposite the body of T4 vertebra immediately after which he was aware of a numb feeling in the left leg. There was also a numb area on the R side of the chest from anterior to posterior aspects. In these areas there was also a dull burning discomfort. He was not aware of any power loss in the legs and bladder function was normal. On examination, there was loss of pinprick below the level of T6 dermatome on the left side and from T6 to T4 on both the anterior and posterior aspects of the trunk. Touch sensation was also diminished in the same distribution on the chest on the R side but was normal in the legs and below the level of T6. Vibration and proprioceptive sensations were normal. Tendon reflexes were very brisk on the R with extensor plantar response while these were normal in the L leg and both upper limbs (Figure 23). SSEPs from stimulation of both median nerves and both posterior tibial nerves showed no abnormality, indicating that the posterior columns were intact, a finding in keeping with his clinical findings of normal vibration and proprioception. The clinical picture in this patient, therefore, pointed to a laceration of the spinal cord catching mainly the spinothalamic tract on the right but also causing some dysfunction in the corticospinal tract on that side manifested as reflex changes and extensor plantar response on that side without appreciable weakness.

Thermal thresholds measurements showed abnormal L ankle HT (7.95^{o}C) and CT (8.25^{o}C) values, but normal R ankle HT (0.85^{o}C) and CT (0.25^{o}C), R wrist

Figure 23 Patient 5: A summary of the clinical findings and the thermal threshold and VPT values in a 42 year old male patient with partial Brown-Sequard syndrome due to injury of the R half of the spinal cord by a stab wound. The cross-hatched area indicates the distribution of diminution of all modalities of sensation while the shaded area represents the distribution of reduced pinprick and temperature sensation on clinical examination.

(Abbreviations as in Figure 19.)


R
L
VPT=0·4μm (N)
HT =0·25°C (N)
CT =0·15°C (N)
VPT=0·4μm (N)
VPT=0·7μm (N)
HT =0·85°C (N)
CT =0·25°C (N)
VPT=0·7μm (N)
extensor Plantar, brisk reflexes
VPT=0·4μm (N)
HT =0·27°C (N)
CT =0·15°C (N)
PT=0·4μm (N)
VPT=0·6μm (N)
HT =7·95°C (ULN=3·28°C)
CT =8·25°C (ULN=0·32°C)
VPT=0·8μm (N)

HT (0.25°C) and CT (0.15°C) and L wrist HT (0.25°C) and CT (0.15°) values. VPTs were all within the normal range in the upper and lower limbs on both sides (Figure 23).

DISCUSSION

The results of the application of the Glasgow Thermal System to patients with both peripheral and central nervous system disorders underline its usefulness. In 143 patients with generalised neuropathy, thermal threshold abnormalities were detected in 141 (98.6%) compared to 79.7% on clinical examination of the sensory system and 72% on conventional sensory conduction studies (Table 11). While significant alterations of thermal thresholds were most often observed in patients with concomitant abnormalities on clinical and electrophysiological tests, they also occurred in isolation. Similar observations have been reported by other workers using different methods (Fruhstorfer et al 1976a). This technique, therefore, is a sensitive method for detection of disturbance of thermal sensation in patients with neuropathy. Figures 12,13,14,15 provide further evidence that the method is sufficiently sensitive to detect subclinical abnormality of sensation in generalised neuropathy.

Although abnormality within the CNS cannot be entirely excluded in these patients with peripheral neuropathy, with certain exceptions (for example hereditary neuropathies) one can assume that the abnormal thermal threshold values were mostly due to dysfunction of the peripheral fibre population serving thermal sensation and/or their endorgans. The observation that fewer patients had abnormal values at the wrist than at the ankle (Table 11) is compatible with the greater severity of dysfunction in the longest nerve fibres in peripheral neuropathy. It is, therefore, reasonable to assume that in these patients with established peripheral neuropathy, the technique assesses the function of the peripheral thermal

fibres and their endorgans, composed of A Δ and C fibres, an assessment which the conventional electrophysiological methods are unable to do (see below).

It is possible that the increased frequency of thermal threshold abnormality in the patients with neuropathy (98.6%) compared to abnormality detected on EMG and NC studies (89%) (Table 11) is at least in part due to the inherent limitation of the NC studies to detect large fibre involvement with adequate sensitivity as a substantial number of large nerve fibre loss must occur before a significant abnormality is noted on these tests (Buchthal et al 1984). The presence of significant correlations between abnormalities of thermal thresholds and the SNAP amplitudes in these patients (page 126) suggest that, in most neuropathies, a more or less parallel drop occurs in both fibre populations but not necessarily to the same extent in each type of neuropathy. This appears to be true in neuropathies of most type (Ochoa 1978; Adams and Victor 1981; Thomas 1984).

In the second study, thermal thresholds were abnormal in 100% of patients with selective small fibre neuropathy (n = 25) (Figure 16; Table 13). This study clearly demonstrates the usefulness of the technique in the documentation of dysfunction of the small nerve fibre population and could, therefore, act as an easy to use, reliable and quick method to study the function of the unmyelinated (C) and the thinly myelinated (AΔ) fibres. This is extremely important as all of the currently available methods to study the small fibre population have limited clinical application and other practical limitations. Morphometric histological studies have been useful in the assessment of size distribution of nerve fibre populations but the method is invasive (a piece of a peripheral nerve must be excised for histological examination). It is technically difficult and not infrequently correlates poorly with the clinical presentation (for review see Behse et al 1975; Ochoa 1978). In severe dysfunction, the in vitro electrophysiological method of compound action potential measurement of

Lambert and Dyck (1969) may detect abnormalities in the Aδ and C fibre potentials. This technique has many false negative results and is unable to distinguish between small fibres and immature axons of regenerating larger fibres. The method is also invasive, time consuming and requires sophisticated equipment and is difficult for the average clinician. Direct recordings of action potentials are possible from unmyelinated (C) and thinly myelinated (Aδ) fibres by microneurography using an intra-neural needle electrode (Vallbo and Hagbarth 1968; Vallbo et al 1979). When applied, however, to 28 patients with clinical frank neuropathy including symptoms suggestive of small fibre dysfunction, the technique failed to detect significant abnormality in the small fibre population (MacKenzie et al 1977) probably due to the limited sampling and limitations of the technique. These methods, therefore, while of value in the research laboratory are time consuming, invasive and of limited practical application in the clinical setting.

The more frequently detected abnormality of thermal thresholds at ankle in the 25 patients with small fibre neuropathy is similar to the observation in the 143 patients with peripheral neuropathy and is again consistent with the more severe abnormality of somatic sensation distally in generalised peripheral neuropathy. A coexistent abnormality in the central thermal pathways cannot be excluded entirely in these patients, but the circumstantial evidence available is strongly in favour of at least a significant peripheral contribution.

The results of the application of the technique to the 10 patients with Friedreich's ataxia are in keeping with these concepts. Both histological (Dyck et al 1968,1971) and electrophysiological (Dyck et al; 1971,1984) studies on excised sural nerves from patients with early Friedreich's ataxia have shown selective involvement of the large fibre population and

sparing of the Aδ and C fibres. In eight patients all below the age of 30 years with Friedreich's ataxia, the thermal threshold values were within the normal range (Table 15; Figure 17) while all had abnormality of VPTs. Similar findings were obtained by other workers using different methods (Dyck et al 1971,1984). In two patients, aged 30 and 37 years with advanced Friedreich's ataxia, there was mild abnormality of thermal thresholds at ankle (Table 15; Figure 17). Abnormality of thermal thresholds in two patients with advanced Friedreich's ataxia in whom small fibre abnormality was confirmed electrophysiologically has been reported by Dyck et al (1971,1984). From these two studies on patients with small fibre neuropathy and Friedreich's ataxia, therefore, the evidence is striking that thermal thresholds were abnormal in patients with selective small fibre neuropathy and normal in patients with early Friedreich's ataxia in which the large fibre pathway is selectively involved.

The significantly higher mean values of the CPN and median SDMLs, and the lower mean values of the CPN and median FMNCVs, the sural, median and ulnar SNAP amplitudes, and the tarsal VPTs in the 25 patients with small fibre neuropathy (though individual values were within the normal) indicate the presence of a mild and possibly subclinical dysfunction in the large fibre population (Buchthal and Rosenfalck 1971; Buchthal et al 1984). Conversely, the mean values of the ankle HT and CT and wrist HT and CT were significantly raised in the patients with Friedreich's ataxia (Table 16) indicating the presence of a subclinical involvement of the small fibre population. Both of these results support the consensus in the literature on peripheral neuropathies that predominant involvement of one fibre type is accompanied by less severe dysfunction in fibres of all type (Ochoa 1978; Thomas 1984).

Five of the 25 patients with small fibre neuropathy, showed mild abnormality of touch on clinical examination in addition to the more severe abnormality of pinprick sensation (Table 13). In these five patients,

VPTs were normal. It is generally believed that fibres serving touch sensation fall among the large myelinated population (Light and Perl 1984) but unmyelinated fibres have also been shown to convey impulses from some mechanoreceptors in mammals (Zotterman 1939; Douglas and Ritchie 1957; Iggo 1960; Iriuchijima and Zotterman 1960; Bessou and Perl 1969). There is as yet no evidence in man that Aδ or C fibres transmit impulses from mechanoreceptors. It is, therefore, not possible to identify whether the abnormality of touch sensation in these five patients is related to pathology of the large or the small fibre populations.

The first three studies (143 peripheral neuropathies, 25 small fibre neuropathies and 10 patients with Friedreich's ataxia), therefore, clearly demonstrate that the thermal technique is sensitive in diagnosing thermal sensation disturbances in patients with peripheral neuropathy and is a useful tool in documenting and quantifying the small fibre dysfunction in these patients where it may be the earliest or the only abnormality and also in assessing a concomitant dysfunction of small fibre population in somatic neuropathies in general. In combination with other neurophysiological methods testing the large fibre population function, the technique gives a good impression of the pattern of involvement of various fibre populations in peripheral neuropathies and lowers the threshold for diagnosis of these disorders.

The study on 24 patients with established acromegaly further demonstrates the sensitivity of the technique in detecting subclinical abnormality of thermal sensation. Contrary to the general belief that entrapment neuropathies are by far the most common neuropathies in acromegaly (see Introduction of Study 4), the results of this study demonstrate that generalised overt or subclinical neuropathy is more common (Table 19; Figure 18). Moreover, half of the cases with entrapment neuropathy have an underlying generalised disorder of the peripheral nerves

(Table 20). All neurophysiological tests used to investigate these patients with acromegaly showed changes in the direction indicating abnormality (Table 18, Table 19). In this context, however, the thermal technique showed much more frequent abnormality (67%) than nerve conduction studies (50%) and the VPT method (37%) (Table 19). It is, however, difficult to say whether this indicates an actual increased frequency of involvement of the small fibre versus large fibre populations or is due to greater sensitivity ofthe thermal technique for detection of dysfunction of the small fibre population compared to the techniques used for testing the integrity of the large fibre population. In addition to the neurophysiological evidence, 1/3 of the 24 patients with acromegaly showed clinical evidence of a generalised neuropathy (Table 17). Ten of the 24 patients (42%), including all but one with clinical generalised neuropathy, had evidence of hypertrophy of the peripheral nerves on clinical examination (Table 17). In the literature, several isolated cases of hypertrophic neuropathy have been described in association with acromegaly (Stewart 1966; Dinn 1970; Lewis 1972; Low et al 1974; Sandbank et al 1974). Sural nerve histology in some of these patients showed endoneural and subperineural tissue hypertrophy (Stewart 1966; Dinn 1970; Sandbank et al 1974). Low and his coworkers (1974) made histological studies on a small number of patients with acromegaly. They demonstrated a decrease in the density of unmyelinated and myelinated fibres with signs of segmental demyelination and remyelination. The more frequent abnormality encountered in the lower limbs with all three neurophysiological methods in these patients (Table 19; Figure 18) is consistent with the pattern of dysfunction in many other metabolic and toxic peripheral neuropathies where the most severe abnormality occurs in the longest nerve fibres.

No significant correlation was found between the neurophysiological measurements and the associated glucose intolerance, the plasma level of HGH, the mean 'HGH day curve', the mean HGH during the GTT and the 20 and

60 minute TSH hormone levels during the thyrotrophin-releasing hormone test. This is in agreement with Low et al (1974) and Pickett et al (1975) who found, in small numbers of patients with acromegaly, no correlation of the peripheral neuropathy with HGH levels and the associated diabetes mellitus. Total Nae is increased in acromegaly (Ikkos et al 1954; Snow et al 1977; Davies et al 1985) and may reflect disease activity since it correlates with HGH levels (Snow et al 1977) and with the duration of the disease process (Davies et al 1985) and it also falls following successful treatment but very gradually (Davies et al 1985). Most of the neurophysiological parameters showed a significant correlation with Nae; the higher the Nae, the more abnormal were these tests (Table 21). This may be interpreted as a generalised neuropathy which increases in severity with disease activity in patients with acromegaly.

The independence of the neurophysiological abnormalities from glucose intolerance and pituitary thyroid function suggests that the generalised neuropathy in acromegaly is not aetiologically similar to that of diabetes mellitus or hypothyroidism and the independence from the HGH levels in this heterogeneous group of patients may reflect the variable degree of success of their treatment regimens. The generalised peripheral neuropathy seems likely to be mediated by excessive HGH levels in acromegaly but the exact mechanism remains to be determined or that the neuropathy is not reversible by treatment of the hormonal disturbance.

Unilateral or bilateral carpal tunnel syndrome was present in 42% of the patients with acromegaly. This is in agreement with other published series (O'Duffy et al 1973; Pickett et al 1975). The results show that in half of the patients with acromegaly-associated CTS there is an underlying generalised peripheral neuropathy but equally there are 50% who develop the CTS independent of any measurable generalised process.

The results of the application of the thermal technique to five

patients with CNS diseases known to involve or to exclude thermal pathways underline its diagnostic usefulness. In patient 2 with syringomyelia, the normality of the VPTs and the SSEPs and the severe abnormality of thermal sensation in the areas involved are entirely in line with the pathological changes observed in this disorder. The mild, but abnormal increase in thermal thresholds in both lower limbs not detectable by clinical exmination (Figure 20) indicates the possibility of pressure, by the syrinx on both spinothalamic tracts to a degree not severe enough to produce changes detectable by bedside clinical examination but sufficient to be detected by the technique. This finding underlines the sensitivity of the Glasgow Thermal system as compared with conventional clinical examination in detecting subclinical dysfunction in the spinothalamic tract in disorders of the spinal cord. In the first patient with syringomyelia (Figure 19), no abnormality of thermal thresholds were detected in the clinically uninvolved area suggesting that the spinothalamic tracts are spared by the disease process.

In patients number 3 and 4 with tabes dorsalis, the neurophysiological tests of central large fibre pathways (SSEPs) showed abnormal values for central conduction. The abnormal VPT also indicates dysfunction of the same pathway (Goldberg and Lindblom 1979). These changes and the clinical features are in total agreement with the pathological changes observed in patients with this disorder which predominantly involve the large fibres in the dorsal roots and the posterior columns and commonly spare the small fibres (Adams and Victor 1981). Patient 4, unlike patient 3, had abnormal thermal thresholds at the ankles (Figures 21,22). Involvement of the unmyelinated and the thinly myelinated fibres in the dorsal roots can occur in tabes dorsalis leading to abnormality of pain and temperature sensation which could be severe to the extent of the development of Charcot joints (Adams and Victor 1981). At the root entry zone the large afferent fibres are grouped in a medial bundle and the small fibres in a discrete lateral

bundle. The abnormal thermal thresholds in patient 4 and the normal thermal thresholds in patient 3, therefore may suggest the involvement of the small fibre population within the dorsal roots in the former and their uninvolvement in the latter. In this context the application of the technique to various dermatomes of the lumbasacral region might help in mapping out the extent of involvement of these small fibres in the dorsal roots.

In patient 5, with partial Brown-Sequard syndrome, thermal thresholds, as expected, were highly abnormal in the sites supplied by the severed spinothalamic tract (Figure 23). The normal thermal thresholds on the same side below the lesion probably indicate the integrity of the contralateral spinothalamic tract. In this context, the technique may be a useful method to follow up such patients when there is a possibility of an expanding lesion from the development of a haematoma or scarring.

The results of the application of the thermal technique to these patients with disorders of the CNS suggest that the technique may be useful in the diagnosis of a subclinical involvement of central thermal pathways, in the delineation of the involvement of these structures by an established lesion and in the monitoring of a possible expansion of these lesions.

CHAPTER 8

EVIDENCE OF SENSORY DYSFUNCTION IN DISEASES PREVIOUSLY THOUGHT TO INVOLVE MOTOR SYSTEM EXCLUSIVELY

The findings of the application of the Glasgow Thermal System to diseases with expected involvement of thermal sensation do not differ in nature from those described by previous workers. However, this method (as demonstrated in Chapter 6) can detect much smaller alterations in thermal thresholds so it can be applied to examine for minor sensory abnormalities in disorders currently thought to involve motor system exclusively. This Chapter describes two studies performed on patients with established motor neurone disease and myotonic dystrophy.

As expected, no abnormality of thermal thresholds was detected in patients with limb girdle muscular dystrophy (n = 16), myasthenia gravis (n = 12), idiopathic polmyositis (n = 8) and myotonia congenita (n = 10) when compared with age-sex matched controls.

Motor Neurone Disease

Most authorities consider that motor neurone disease affects the motor system exclusively. Subjective sensory symptoms are however not uncommonly reported and variously described as paraesthesiae, coldness, prickling, numbness, aches and pains (Lawyer and Netsky 1953; Dyck et al 1975; Rowland and Layzer 1976; Walton, 1977; Mulder 1982). Objective sensory abnormalities in contrast are rare (Rowland and Layzer 1976; Walton 1977; Mulder 1982) but nevertheless occasional reports of objective dysfunction have appeared implicating all modalities including pain and temperature sensation (Wechsler et al 1929; Davison and Wechsler 1936; Friedman and Freedman 1950; Hudson 1980).

The above observations suggest that more sophisticated techniques for the quantification of sensation might provide further confirmation and a

higher incidence of dysfunction in the sensory pathways in patients with motor neurone disease. The purpose of this study was to use such a technique (The Glasgow Thermal System) to define thermal thresholds in motor neurone disease as an index of sensory dysfunction in the thermal system and to quantify the severity of this dysfunction.

Forty patients with motor neurone disease were investigated. Their age ranged between 36 and 73 (mean = 56.7; SD= 11.2) years. There were 25 male and 15 female patients. This sex ratio of 1.6:1 is in agreement with most other published series (Muller 1952; Lawyer and Netsky 1953; Mulder et al 1983). The duration of the symptoms varied between 2 - 72 (mean = 17.1; SD = 16.8) months. The diagnosis had been made on clinical grounds by the referring neurologist and was confirmed electrophysiologically (EMG and nerve conduction studies) using established criteria (Daube 1982). In particular, no patient with sensory abnormality on clinical testing or abnormality of sensory action potentials was included. Any cases which did not fully satisfy both the clinical and electrophysiological criteria were excluded from the study. All the patients were ambulant, well nourished and none of them had severe paresis of any limb. In wasted limbs, the possibility of entrapment neuropathy was excluded electrophysiologically. None had a family history of neuromuscular disease. The clinical data of the 40 motor neurone disease patients are summarised in Table 22.

The control group consisted of 40 healthy age, and sex-matched subjects. The age and sex distribution of the control and the motor neurone disease group is presented in Table 23.

Heat threshold (HT) and cold threshold (CT) values were determined for the volar aspect of the right (R) wrist just proximal to the distal wrist crease (site a) and for the medial aspect of the right ankle behind the medial malleolus (site c).

The mean and SD of HT and CT for the 40 healthy control subjects and the 40 motor neurone disease patients are presented in Table 24.

TABLE 22: Summary of clinical data of 40 MND patients

	Number		Percentage
Type Amyotrophic lateral sclerosis (ALS)		37	
Progressive muscular atrophy (PMA)		3	
Cramps (total)		34	85%
lower & upper limbs	27		67.5%
lower limbs (LL) alone	7		17.5%
upper limbs (UL) alone	0		
Muscle wasting (total)		33	82.5%
UL > LL	18		45%
LL > UL	6		15%
both nearly equal	9		22.5%
Bulbar weakness (total)		10	25%
mild	6		15%
moderate-severe	4		10%
Fasciculations (clinically overt)(total)		31	77.5%
tongue alone	1		2.5%
tongue (total)	16		40%
generalised	8		20%
Sensory symptoms (total)		19	47.5%
acne	15		37.5%
paraesthesia	10		25%
coldness of extremities	9		22.5%
abnormal heat	4		10%
numbness	7		17.5%

While some patients spontaneously volunteered the occurence of cramps and sensory symptoms, most did not but did confirm their presence on direct questioning. Sensory symptoms were recurrent and each bout lasted for about 15 minutes.

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TABLE 23: Age and sex distribution of Motor Neurone Disease patients and control subjects

		MND	Control
Total No.		40	40
Age range (yr)		36-73	36-73
Age groups	36-49(yr)	12	13
	50-59(yr)	8	9
	60-73(yr)	20	18
Mean Age (yr)		56.7	55.9
SD		11.2	10.9
Sex distribution	Male	25 (62.5%)	25 (62.5%)
	Female	15 (37.5%)	15 (37.5%)

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Table 24

Thermal threshold values for the MND patients and the normal control subjects

Thermal threshold		Normal subjects (40)		MND patients (40)		test of significance	
		mean	SD (°C)	mean	SD (°C)	t	p
wrist	HT	0.23	0.06	0.51	0.34	5.13	<0.0001
wrist	CT	0.17	0.05	0.26	0.14	3.83	<0.0001
ankle	HT	1.53	0.68	4.81	2.05	9.61	<0.0001
ankle	CT	0.18	0.06	0.67	1.03	3.00	<0.005

HT = heat threshold

CT = cold threshold

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Abnormality of thermal threshold was considered to be present when it exceeded the 99th percentile of the control series. Table 25 provides a summary of the thermal thresholds testing in the 40 motor neurone disease patients. Thirty-two of the 40 patients (80%) had an abnormality of one or more thermal thresholds. All patients with abnormal wrist HT and CT had abnormal ankle thresholds. Abnormalities of thermal thresholds were more frequent at ankle (80%) than at wrist (55%) (see Table 25).

Figure 24 shows HT and CT values in motor neurone disease patients for wrist and ankle expressed in multiples of the standard deviation (xSD) from control mean values. Ankle HT values were more than 3 x SD above the normal mean in 50% of the patients and ankle CT values were more than 3 x SD above the normal mean in 55% of the motor neurone disease patients. At the wrist, 45% had HT values more than 3 x SD above the normal mean while 12.5% had CT values 3 x SD above normal mean.

At necropsy, degeneration of posterior columns (Davison and Wechsler 1936; Engel et al 1959; Smith 1960; Holmes 1969; Brownell et al 1970; Hughes and Jerrome 1971; Dyck et al 1975; Lawyer and Netsky 1976) and anterior and lateral columns of the spinal cord outwith the corticospinal tract (Wechsler et al 1929; Smith 1960; Holmes 1969; Brownell et al 1970; Pallis 1977), loss of neurones in the posterior horns (Engel et al 1959; Smith 1960; Holmes 1969; Kawamura et al 1981), abnormalities in the parietal lobe (Lawyer and Netsky 1953), degeneration in the thalamus (Brownell et al 1970) and abnormalities in the posterior root ganglia and dorsal roots (Dyck et al 1975; Kawamura et al 1981) have been described. Pathological abnormalities in peripheal sensory pathways have also been found (Dyck et al 1975) and Dayan et al (1969) have demonstrated primary Schwann cell damage in sensory nerves. Shahani et al (1971) found evidence of abnormal resistance of peripheral sensory nerves to ischaemia in most patients with motor neurone disease. The literature, therefore, supports

Table 25

Summary of thermal thresholds testing results in 40 patients with MND

	number	percentage
One or more TT abnormal	32	80%
Ankle HT and/or CT abnormal	32	80%
Wrist HT and/or CT abnormal	22	55%
Ankle HT abnormal	24	60%
Ankle CT abnormal	22	55%
Wrist HT abnormal	18	45%
Wrist CT abnormal	5	12.5%

TT = Thermal thresholds

HT = Heat threshold

CT = Cold threshold

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Figure 24 Thermal thresholds in 40 control subjects and 40 patients with motor neuron disease. (A) Heat threshold (HT) and cold threshold (CT) values for the wrist, (B) HT and CT values for the ankle. Each thermal threshold value is expressed as a figure representing the number of standard deviations (xSD) from the mean control value. Vertical axis = number of patients or controls. Horizontal axis = number of SDs greater or less than the normal control mean.

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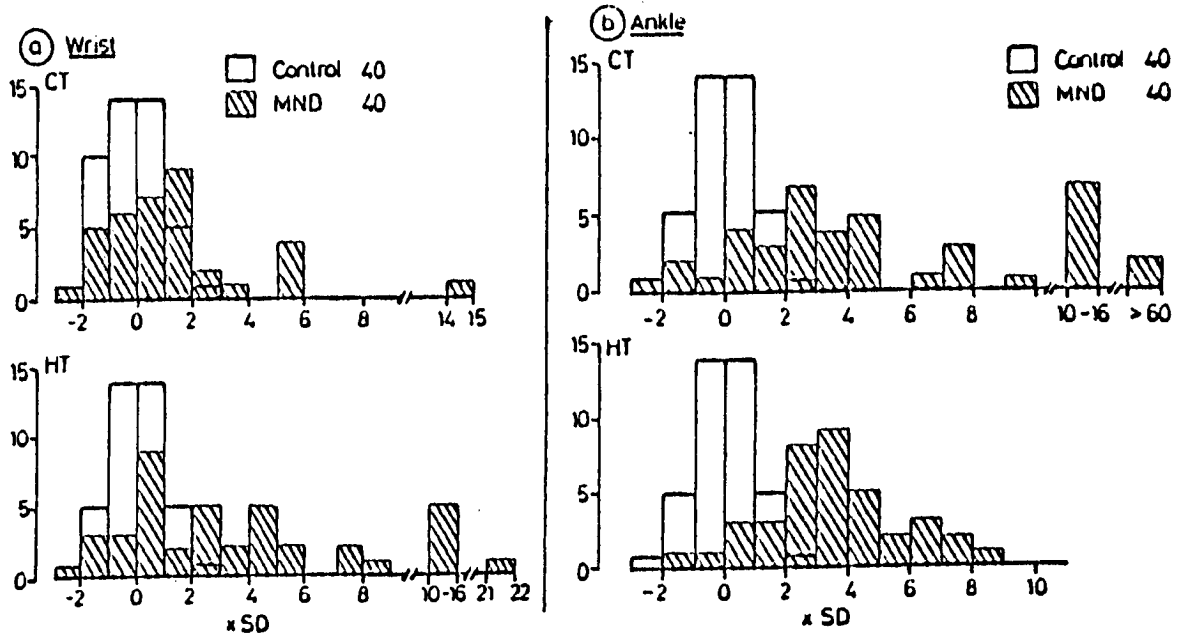
a Wrist
Control 40
MND 40
CT
HT
15
10
5
0
-2
0
2
4
6
8
14
15
10-16
21
22
x SD
b Ankle
Control 40
MND 40
CT
HT
10
-2
0
2
4
6
8
10-16
>60
10
x SD

the possibility of both peripheral and central sensory abnormalities in these patients, albeit mild when compared with those of the motor system. They are as a rule of insufficient severity to produce clinically detectable changes of sensation (Rowland and Layzer 1976; Walton 1977; Mudler 1982) or significant abnormalities using conventional electrophysiological techniques (Lambert 1959; Willison 1962). In a single study, however, one of 13 patients with motor neurone disease had an absent median sensory nerve action potential as an isolated finding and minimal impairment of vibration sense and two point discrimination (Fincham and Van Allen 1964).

More sophisticated quantitative techniques have demonstrated abnormalities of touch-pressure, vibration and thermal cooling sensations in a small number of patients (Dyck et al 1975; Mulder et al 1983). In a recent study (Matheson et al 1983), two-thirds of motor neurone disease patients had abnormalities of somatosensory evoked potentials and in one-third of these the abnormalities were thought to arise in the peripheral sensory pathways.

Brownell et al (1970) reported a case in their series of patients with motor neurone disease where loss of pain and thermal sensation was noted clinically, and at necropsy there was evidence of anterior and lateral column degeneration, extending outwith the pyramidal tract. The same authors found degeneration of the central nuclear complex of the thalamus in 53% of their cases while 56% without sensory symptoms had evidence of anterior and lateral column degeneration. Other motor neurone disease patients with abnormality of thermal and pain sensation have been described by Wechsler et al (1929), Hudson (1980) and Drake (1983). Posterior column degeneration has been much more widely reported (Davidson and Wechsler 1936; Lawyer and Netsky 1953; Engel et al 1959; Smith 1960; Holmes 1969; Brownell et al 1970; Hughes and Jerrome 1971; Dyck et al 1975) as a rule unaccompanied by clinical symptomatology.

The results indicate that dysfunction in the small fibre thermal pathways is a frequent occurrence in motor neurone disease. Of the 19 patients with sensory symptoms, 18 (95%) had abnormal thermal thresholds while 14 of 21 without sensory symptoms showed qualitatively similar abnormalities. Since the Glasgow method tests the integrity of both peripheral and central thermal pathways the site of dysfunction cannot be determined.

It is unlikely that thermal thresholds are influenced by the degree of muscle wasting in these patients as in general wasting was not severe, the sites of thermal testing did not overlie sites of marked muscle wasting and wasting was more severe in the upper limbs in which abnormalities of the thermal thresholds were least marked. In a separate study of four patients (two with spinal muscular atrophy and two with old poliomyelitis) where there was severe muscle wasting, thermal thresholds were normal. Finally, no correlation between the severity of abnormality of thermal thresholds and the age of the patient or the duration of clinical symptoms was found.

It is concluded that whether arising centrally or peripherally, abnormalities of thermal thresholds are common and are indicative of involvement of the afferent pathway of thermal sensation in patients with motor neurone disease.

Myotonic Dystrophy

This genetic disorder is characterised by dystrophy of striated muscles (in a typical distribution), iterative action potentials with retarded muscular relaxation (myotonia) following muscle contraction, cataract of a specific type, gonadal atrophy and cardiac and other smooth muscle abnormalities (Harper 1979). Dystrophic changes have been observed in the central nervous system and eosinophilic inclusion bodies have been found in the thalamus (for review see Jamal et al 1986d; Appendix 3).

The muscular wasting has been regarded as myopathic in aetiology on the evidence of both electrophysiological (Simpson 1973; Buchthal 1977) and pathological (Dubowitz and Brooke 1973) studies. The hypothesis that myotonic dystrophy is a pure myopathic disorder has been increasingly challenged and an additional neuropathic component has been postulated in recent years (McComas et al 1971; Ballantyne and Hansen 1975; Panayiotopoulos and Scarpalezos 1975). A number of clinical observations and other evidence lend support to the presence of a neuropathic influence (for review see Jamal et al 1986d; Appendix 3).

Minor sensory loss has been reported in patients with myotonic dystrophy (Maas 1938; Kalyanaraman et al 1973; Pilz et al 1974; Borenstein et al 1977; Olson et al 1978; Harper 1979). Slowing of conduction in both peripheral and central large fibre afferent pathways has also been reported (Caccia et al 1972; Lieberman and O'Brien 1972; Hideo et al 1973; Moniga and Lundervold 1975; Borenstein et al 1977; Thomson et al 1983; Bartel et al 1984), while histological studies have shown both normal (Pollock and Dyck 1976) and reduced (Kito et al 1973; Borenstein et al 1977) numbers of sensory axons in sural nerve biopsies.

In addition to the application of the Glasgow Method to measure HT and CT for R wrist (site a), and R ankle (site c) three independent neurophysiological methods were also used to investigate these patients. These included the method of Goldberg and Lindblom (1979) to measure the VPT at the R carpal and R tarsal site (the same sites as that used for the studies reported in Chapter 7). Motor and sensory nerve conduction and EMG studies and the technique of motor unit number estimation and motor unit potential parameters measurement in the R extensor digitorum brevis (EMG) muscle (Ballantyne and Hansen 1974a,b).

Twenty-four patients, 12 male and 12 female, with definite myotonic dystrophy were included in this study. Their age ranged from 15 to 63

(mean = 45.7; SD = 11.8) years. The duration of clinical symptoms varied from 0.2 to 22 (mean = 8.4; SD = 6.5) years. The clinical features of these patients are described in the report of Jamal et al (1986d) and are summarised in Table 26. Subjective sensory symptoms in the form of paraesthesiae, numbness, feeling of coldness or heat were present in the extremities in 13 (54%) patients. Five patients volunteered these symptoms and 8 agreed their presence on direct questioning. One patient alone of the 13 (4%) had hypoalgesia to pinprick, touch, and vibration in a stocking distribution.

The results of thermal threshold measurements and the other three neurophysiological methods are summarised in Table 27 and the distribution and the relative frequencies of the abnormalities are shown in Figure 25 . The transverse solid lines represent the control means and the broken lines represent the values of twice the standard deviation and three times the standard deviation above the control means for the neurophysiological parameters shown (Figure 25). Thermal thresholds at one or both sites were abnormal in 20 of the 24 patients studied (83%). Thermal threshold abnormalities were generally more marked and more frequent at the ankle (79%) than at the wrist (50%). The percentages of abnormalities in the other neurophysiological parameters are shown in Table 28 at 99% CL*. Thermal threshold values significantly correlated with values of all other neurophysiological parameters measured in the direction of abnormality (Table 29). No correlation was found between age or duration of symptoms and the thermal threshold values or values for other neurophysiological parameters studied in the myotonic dystrophy patients. The duration of symptoms is notoriously difficult to estimate in these patients and may account in whole or part for the lack of correlation.

* Unlike the rest of the studies the level of 99%CL was taken on the insistence of the Editor of "Brain" (Jamal et al 1986d).

TABLE 26: Summary of clinical data of 24 patients with myotonic dystrophy

	Number		Percentage
Family History (FH)			
positive FH (total)		15	62.5%
In parents or siblings	13		
In aunts or uncles	2		
negative FH (total)		9	37.5%
negative FH of myotonic dystrophy but positive FH of cataract and/or frontal baldness	4		
Muscle weakness and/or wasting (total)		23	96%
mild muscle wasting	16		
moderate-severe muscle wasting	3		
distal muscle weakness	23		
distal and proximal muscle weakness	7		
Absent or diminished reflexes (total)		21	87%
absent or diminished ankle jerk	21		
" " brachioradialis jerk	20		
" " biceps/triceps jerk	18		
" " knee jerk	10		
Myotonia on clinical examination (total)		22	92%
myotonia of grip	22		
myotonia of eyelids	8.		
Myotonia on EMG examination (total)		24	100%

TABLE 26 (cont)

Subjective sensory symptoms (total)		13	54%
paraestnesiae	10		
numbness	9		
abnormal heat or cold sensation	2		
Objective sensory signs (total)		1	3.7%
pinprick	1		
touch-pressure	1		
vibration	1		
Ptosis (total)		10	42%
bilateral ptosis	10		
Abnormal ECG (total)		13	54%
cardiomyopathy (total)	7		
cardiomyopathy alone	3		
conduction defect (total)	10		
conduction defect alone	6		
cardiomyopathy and conduction defects	4		

EMG = electromyography

ECG = electrocardiography

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TABLE 27: Comparison of neurophysiological parameters between normal control groups and patients with myotonic dystrophy

Parameter		Group	N	Mean	SD	P
Ankle HT	[°C]	Normal	106	1.35	0.73	< 0.0001
		MYD	24	5.1	1.63	
Ankle CT	[°C]	Normal	106	0.17	0.06	< 0.002
		MYD	24	0.49	0.41	
Wrist HT	[°C]	Normal	106	0.23	0.06	< 0.005
		MYD	24	0.47	0.37	
Wrist CT	[°C]	Normal	106	0.15	0.05	< 0.0001
		MYD	24	0.26	0.10	
Sural SNAP amplitude	[/uV]	Normal	21	6.8	2	< 0.0001
		MYD	24	3.5	2.2	
Sural SNAP latency	[ms]	Normal	21	3.62	0.44	< 0.0002
		MYD	24	4.3	0.64	
Median SNAP amplitude	[/uV]	Normal	21	17.8	7	< 0.03
		MYD	24	13.9	6.8	
Median SNAP latency	[ms]	Normal	21	2.92	0.26	NS
		MYD	24	3.0	0.3	
Ulnar SNAP amplitude	[/uV]	Normal	21	12	5.5	< 0.02
		MYD	24	8.7	4	
Ulnar SNAP latency	[ms]	Normal	21	2.87	0.25	NS
		MYD	24	2.82	0.5	
Vibration threshold (foot)	[/um]	Normal	27	1.63	0.45	< 0.05
		MYD	24	2.43	1.73	

Parameter		Group	N	Mean	SD	P
SDML (CPN)	[ms]	Normal	21	3.59	0.44	< 0.0005
		MYD	24	4.42	0.77	
FMNCV (CPN)	[m/s]	Normal	21	50.5	4.6	< 0.0001
		MYD	24	42.2	6.2	
MUN (EDB muscle)		Normal	21	200	54	< 0.0001
		MYD	24	106	41	
Mean MUP latency	[ms]	Normal	21	4.62	0.66	< 0.002
		MYD	24	5.56	1.12	
Mean MUP amplitude	[/uV]	Normal	21	60.5	12.7	NS
		MYD	24	74.7	44.9	
Mean MUP duration	[ms]	Normal	21	9.4	1.2	< 0.0002
		MYD	24	12.6	3	
Mean MUP area		Normal	21	17.0	4.0	< 0.01
		MYD	24	23.3	10.4	

HT = heat threshold
CT = cold threshold
MYD = myotonic dystrophy
SNAP = sensory nerve action potential
SDML = shortest distal motor latency
FMNCV = fastest motor nerve conduction velocity
CPN = common peroneal nerve
EDB = extensor digitorum brevis
MUP = motor unit potential
MUN = motor unit number

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Figure 25 The distribution of neurophysiological measurements on 24 patients with myotonic dystrophy in their R lower limbs. The scales are drawn so that control means (CMs) and control standard deviations (SDs) coincide. The axes of the sural sensory nerve actional potential (SNAP) amplitude, the fastest motor nerve conduction velocity (FMNCV) for the R common peroneal nerve and the motor unit number (MUN) in the R extensor digitorum brevis muscle are reversed so that abnormalities are shown as shifts in upwards direction for all the parameters.

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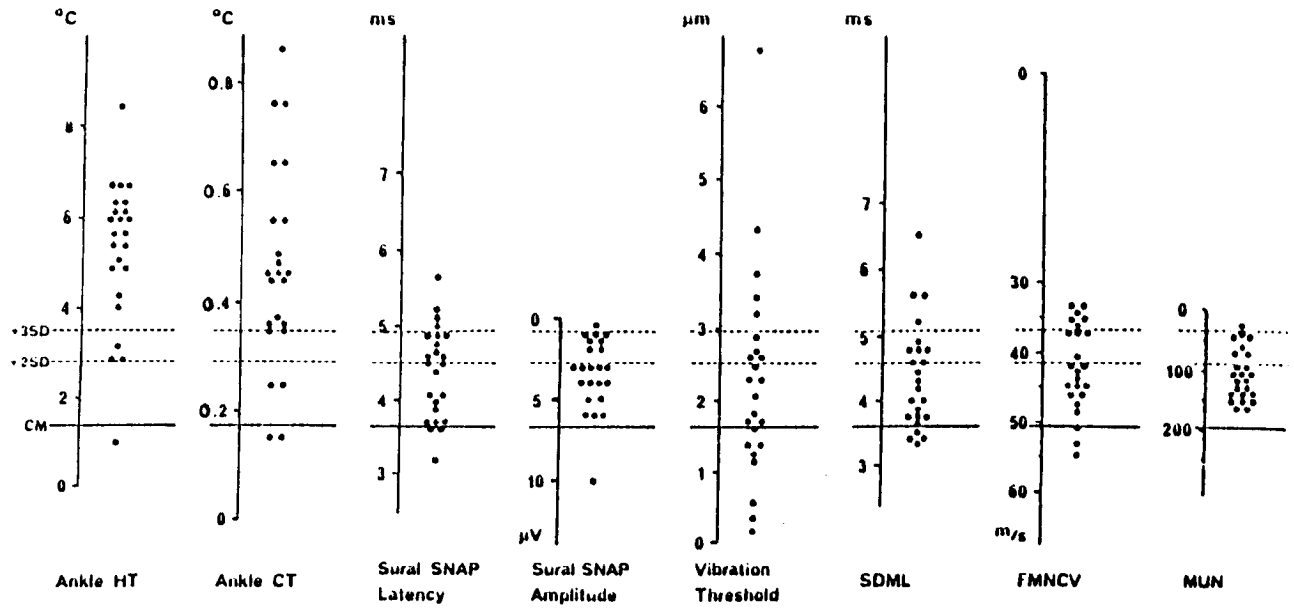
°C
°C
ms
µm
ms
+3SD
+2SD
CM
µV
m/s
Ankle HT
Ankle CT
Sural SNAP Latency
Sural SNAP Amplitude
Vibration Threshold
SDML
FMNCV
MUN

TABLE 28: Frequency of abnormality* of neurophysiological parameters in 24 patients with myotonic dystrophy

Neurophysiological parameter(s)	No. of patients with abnormal values	% of patients with abnormal values
Ankle HT	19	79
Ankle CT	18	75
Wrist HT	10	42
Wrist CT	7	29
Vibration threshold	5	21
Sural SNAP amplitude	1	4
Sural SNAP latency	4	17
FMNCV (LPN)	6	25
SDML (LPN)	4	17
MUN (EDB muscle)	1	4
HT and/or CT at wrist and/or ankle	20	83
HT and/or CT at ankle	19	79
HT and/or CT at wrist	12	50
Sural SNAP amplitude and/or latency	4	17
FMNCV and/or SDML of LPN	8	33

*Values in excess of the 99th percentile were considered abnormal for all the tests.

Abbreviations: As in Table 27

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TABLE 29: Correlations referred to in text

Correlation between			r	P
Ankle HT	-	Sural SNAP amplitude	-0.671	< 0.01
Ankle HT	-	MUN (EDB muscle)	-0.604	< 0.01
Ankle CT	-	Sural SNAP amplitude	-0.429	< 0.05
Ankle CT	-	MUN (EDB muscle)	-0.422	< 0.05
Vibration thresnold	-	Sural SNAP amplitude	-0.410	< 0.05
Vibration threshold	-	Sural SNAP latency	0.433	< 0.05
MUN (EDB muscle)	-	Mean MUP latency	-0.668	< 0.01
MUN (EDB muscle)	-	Mean MUP amplitude	-0.496	< 0.02
MUN (EDB muscle)	-	Mean MUP duration	-0.467	< 0.05
MUN (EDB muscle)	-	Mean MUP area	-0.563	< 0.01
FMNCV (LPN)	-	SDML (LPN)	-0.788	< 0.01
FMNCV (LPN)	-	Mean MUP area	-0.449	< 0.05
FMNCV (LPN)	-	Mean MUP latency	-0.805	< 0.01
FMNCV (LPN)	-	Mean MUP duration	-0.605	< 0.01
SDML (LPN)	-	Mean MUP latency	0.887	< 0.01
SDML (LPN)	-	Mean MUP duration	0.769	< 0.01

Abbreviations: As in Table 27.

(Jamal et al 1986d, reproduced with permission)

The results of the application of the Glasgow method to this group of 24 patients indicate the presence of significant abnormality of thermal sensation in myotonic dystrophy. Although there have been occasional reports of minor sensory loss implicating all modalities (see Jamal et al 1986d; Appendix 3 for review), this is the first report of the presence of abnormality of thermal sensation in 80% of a large group of patients with myotonic dystrophy. Abnormalities of both peripheral and central large fibre sensory pathways, abnormality of vibration sense and abnormalities of peripheral motor nerves have been demonstrated in these 24 patients and in other patients reported by other authors (Jamal et al 1986d; Appendix 3). Histological abnormalities of sural nerve have also been reported (Kito et al 1973; Borenstein et al 1977).

The Glasgow method examines the small fibre thermal afferent pathways as a whole and cannot distinguish between peripheral and central involvement (Jamal et al 1985b). However, the greater frequency of abnormalities of thermal thresholds at the ankle (83%) compared to the wrist (42%) is similar to the pattern of somatic sensory abnormalities found in patients with peripheral neuropathy. The findings of the other neurophysiological studies and their significance are discussed in detail in the report of Jamal et al (1986d) (Appendix 3). They support the suggestion that myotonic dystrophy has a peripheral neuropathy component which includes involvement of small afferent fibres.

CHAPTER 9

PROSPECTS FOR FUTURE WORK

These will be discussed under the following headings:

1. Future studies and those still in progress using the Glasgow Thermal System.
2. Glasgow Thermal System Mark 2.
3. Introduction of an automated system for quantification of vibration sense.
4. Thermal cortical evoked responses.

Studies in Progress or to be performed using the Glasgow Method

Several studies are still in progress and utilise this method. A summary of these is as follows:

1. **Diabetic Neuropathy:** These patients are studied by the Glasgow method and in addition their VPTs and nerve conduction velocities are measured in upper and lower limbs to determine the frequency and severity of involvement of various nerve fibre populations. These neurophysiological values are also correlated with indices of metabolic derangement. The relative sensitivity of these neurophysiological methods to diagnose and to characterise patients with this disorder is to be assessed. A target of at least 100 patients is sought.

2. The Glasgow method is currently used in two major clinical trials in diabetic neuropathy:

   i) <u>The Sorbinil trial</u> (Aldose reductase inhibitor): The effect of this drug on diabetic neuropathy is being studied. The use of the Glasgow method is to assess the response of the small nerve fibre population while NC and VPT measurements are used to assess the response of the large nerve fibre population to this treatment in patients with diabetes. The study is double blind of two years'

duration during which the patients are assessed serially.

(ii) The γ-Butyric Linolenic Acid trial: The effect of this substance is being studied on patients with diabetic neuropathy. Initial results of a double blind study of six months' duration in which the patients are assessed before and after treatment have shown some significant changes of both nerve conduction and thermal thresholds on repeated studies (Jamal et al, 1985c). A two-year double blind study is planned.

3. **Toxic effects of certain drugs** on the peripheral nerves are also studied:

(i) The potential neurotoxic effects of large doses of metronidazole used in the treatment of patients with Crohn's disease are assessed using the Glasgow method and other conventional neurophysiologic methods. The response of those patients who develop neuropathy to stopping the treatment is also evaluated.

(ii) Patients taking Amiodarone (a potent cardiac antiarrhythmic drug) are all examined neurophysiologically (with the Glasgow method and VPT and NC studies) before and at intervals of three months after the start of the treatment to assess the potential neurotoxic effect of this drug. A neuropathy associated with its use has recently been reported. More information, however, is required as to the incidence, severity, frequency of involvement of various nerve fibre populations and the response of this neuropathy to stopping the drug.

4. **Guillain-Barré Syndrome:** A two year follow-up study of patients with this syndrome using the thermal technique and VPT, EMG and NC studies to determine the frequency of involvement of the sensory system, the small fibre population and axons in this disorder and the incidence and

rate of improvement of these structures.

5. **Entrapment neuropathy:** Patients with the diagnosis of meralgia paraesthetica (compression of the lateral cutaneous nerve of the thigh at, above or below the inguinal ligament) are examined by the Glasgow method and nerve conduction studies. Those with underlying subclinical generalised neuropathy are excluded. Involvement of large versus small fibres are then assessed in this entrapment neuropathy. The clinically uninvolved side is also examined to detect subclinical changes. The relative sensitivity of the two methods will also be assessed in the early diagnosis of entrapment neuropathy. Patients with meralgia paraesthetica were chosen because of the size of the thermode.

In addition to these studies currently in progress, it is planned to apply the Glasgow method in other studies; examples include:

1. Can the technique be used for the screening of the neurotoxic effects of various industrial and agricultural products with potential danger to the nervous system?

2. It is planned to apply the technique in combination with the somatosensory evoked response, the visual evoked response and the brainstem auditory evoked response studies to a large number of patients with definite multiple sclerosis (McAlpine criteria) to assess the frequency of overt and subclinical involvement of thermal sensation in these patients. The method is also to be applied to patients with probable and possible multiple sclerosis [illegible] and to follow-up these patients and compare the results of thermal threshold measurements with the other techniques used in order to investigate the possible use of this method as an additional tool in the diagnosis of

multiple sclerosis through the identification of subclinical lesions in the central thermal pathways. This would add another spatial dimension in the investigation of multiple sclerosis and would act as an extra tool for the ssessment of response of this disease to therapeutic regimens. It has been shown that the SSEP is often abnormal in multiple sclerosis but this is largely a test of the posterior columns and large fibre pathways. The thermal thresholds will give a measure of the function of the lateral spinothalamic tracts and the rest of the central thermal pathways, hitherto not amenable to electrophysiological testing non-invasively.

Mark 2 of the Glasgow Thermal System

At present, work is progressing to produce a new version of the system including some changes in both hardware and software. These modifications are planned to bring about the following main changes in the system:

(a) Three different sized thermodes could be used to cover all body areas including distal sites. In addition to the 12.5 cm^2 size used in the existing system, thermodes of either 6.5 cm^2 or 1.84 cm^2 stimulating surface areas could be plugged into the machine and be used.

(b) The accuracy and the maximum values of the current driving the Peltier thermode and hence the accuracy of fixing the rate of change of the stimulating temperature will be increased. A new S100 processor board will be used which will enable the current to be sampled every 50 ms (100 ms in the existing equipment).

(c) A more strict control of the basic skin temperature between the trials is achieved by automatically driving a current with a feedback system to keep the basic skin temperature at the specified level with a 0.1°C accuracy.

(d) A printer format will be added to the system which puts down the

patient's identification, age, sex, date and the values of the thermal thresholds at the sites tested.

(e) Further modification of the UDTR will be made to allow a more efficient approach to the threshold level further reducing the testing time without eroding the accuracy of the threshold measurements.

Quantification of Vibration Sense

Plans are well ahead for the introduction of an automated system to quantify the sense of vibration in a sensitive, accurate and reproducible way. Vibration sensation is served by the large fibre pathway (Goldberg and Lindblom 1979). This system, therefore, will be complementary to the thermal method in covering the whole range of fibre populations and their central pathways. Previous workers in this field have had limited success with techniques in which the vibraiton stimulus is scaled by the measure of the voltage applied to the stimulator (Goldberg and Lindblom 1979). It is, however, well documented that displacement of the skin and hence of the receptors is a much closer measure of the actual stimulus to the mechanoreceptors (Lindblom and Lund 1966). This correct physiological principle is incorporated into the technique of Goldberg and Lindblom (1979). The latter, however, uses a switch pressing method which introduces errors due to subject's response bias and reaction time into the measurement of the VPT. The importance of these factors has been demonstrated in the case of thermal sensation. In collaboration with the originators of this method, it is planned to incorporate the vibrator stimulator of their apparatus in the hardware used for the Glasgow Thermal System and the psychophysical forced-choice method and the modified UDTR to produce a system with much improved accuracy, sensitivity and reproducibility.

Thermal Evoked Cortical Responses

Interest has been developed recently in recording cortical evoked responses to rapidly rising heat and cold stimuli. The work is in the preliminary stage and only a summary of the method adopted and some few data obtained are presented. The work if completely successful is planned to be expanded and the qualities of recordings to be improved. The method then will be an additional and complementary tool in the investigation of thermal pathways both in clinical situations and in research.

Review of previous work in this context has shown some inconsistencies. While Duclaux et al (1974) successfully recorded cortical evoked responses from the application of cold stimuli to the human hand at a mean latency of 324 ms, Chatt and Kenshalo (1979) have recorded such potentials in two subjects at a mean latency of 175 ms, almost 150 ms shorter latency than those recorded by Duclaux et al (1974). Duclaux and his co-workers (1974) however recorded successfully from only eight out of the 10 subjects they examined on stimulation of the hand. Fruhstorfer et al (1976c) were successful in recording cortical responses following cold stimulation of the hand in 13 out of 15 subjects. Stimulation of the lip produced more consistent findings (Duclaux et al 1974; Fruhstorfer et al 1976c; Chatt and Kenshalo 1979).

Many attempts to record cortical responses to heat stimulation have failed (Fruhstorfer et al 1973; Duclaux et al 1974; Carmon 1976). Fruhstorfer and others (1976c), however, succeeded in a later attempt to record heat evoked cortical responses, but only from 44 out of 57 normal subjects to lip stimulation and from 8 out of 15 normal subjects to hand stimulation. Chatt and Kenshalo (1977) reported heat evoked cortical response from three normal subjects. The latency of the evoked responses reported by Fruhstorfer et al (1976c) (602 ± 146 ms), however, was almost twice that reported by Chatt and Kenshalo (1977) (range, 280-356 ms). Our

research aims at obtaining more consistent results by modifying both stimulating and recording conditions. Although, some early success has been obtained, the method is still under development.

A special stimulator capable of delivering thermal stimuli without tactile cues with a well defined onset and a short rising time, which was modified from that used by Hensel et al (1951), was used. Peltier based stimulators were not used as they are incapable of delivering thermal stimuli at the required rate of change of temperature. Figure 26 shows a diagrammatic simplification of the method. The stimulator, with a 12.5 cm^2 stimulating surface area, is made of a thin copper box, the size of which was kept at an optimal minimal value to keep the heat capacity of the thermode as low as possible and hence to deliver a fast rising thermal stimulus. The thermode is connected, through separate circuits, to two different thermostatically controlled waterbaths at different temperatures. When no stimulus is applied, water from the first waterbath, set at the desired basic skin temperature (reference temperature) circulates through the thermode via the first circuit (broken lines, Figure 26). Stimulation is achieved by the activation of solenoid valves R and S which instantaneously changes the water circulation to the second circuit (solid lines, Figure 26) so that water from the stimulating bath now passes through the thermode. By adjusting the temperature of the stimulating waterbath and the duration of the solenoid valves activation, the magnitude and rate of change of the stimulating temperature can be set to optimal levels. Heat stimuli of $8^{o}C$ at a rate of $21^{o}C/s$ and cold stimuli of $6^{o}C$ at a rate of $20^{o}C/s$ both with clear onset can be obtained. The onset of the thermal stimulus is 370 ms after activation of the solenoid valves, representing the time required for water from the second circuit (solid lines, Figure 26) to fill the piece of tube common to both circuits. The electrical pulse which activates the solenoid valves provides the trigger for the sweep of the signal averager. The signals from the scalp are

Figure 26 Components of the thermal evoked potential system.

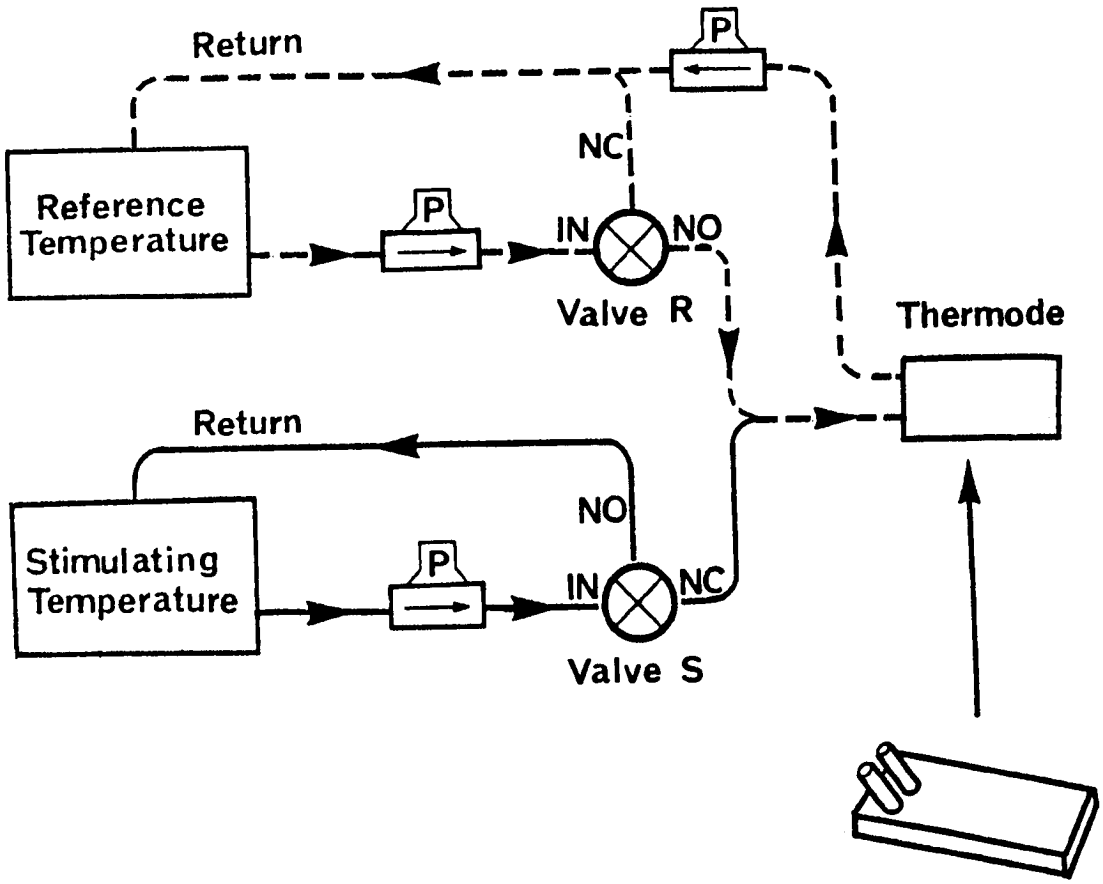
S and R are solenoid valves

NO: normally open (closes when the solenoids are activated)

NC: normally closed (opens when the solenoids are activated)

IN: Water flowing in

P: Water pump


Return
P
NC
Reference Temperature
P
IN
NO
Valve R
Thermode
Return
NO
Stimulating Temperature
P
IN
NC
Valve S

averaged on-line, after passing through amplifiers with a band pass betwen 0.3 to 30 Hz using a Medelec Sensor evoked potential system. Cortical responses are recorded from the scalp by using padded silver electrodes positioned according to the 10-20 international EEG system (Jasper 1958). Heat stimulation of the dorsal aspect of the R hand in all six subjects examined produced distinct cortical responses recorded from C3 position (Figure 27). These responses were in the shape of a large positive peak with a latency ranging from 278 to 350 (mean = 302.3; SD = 26.3) ms and an amplitude of 7.6 to 11 (mean = 8.8; SD = 1.2)/uv. These values are in close agreement with those reported by Chatt and Kenshalo (1977) for three subjects. This positive wave was followed by a large negative wave the study of which and other possible waves was not possible in the present investigation because of short recording time. Figure 28 shows the responses recorded simultaneously from positions C3, Cz, FP1 and O1 for one of the subjects on heat stimulation of the R hand. It shows the presence of a smaller response but of similar latency to that recorded from the contralateral sensory cortex. No consistent time-locked response was identified at positions FP1 and O1 (Figure 28). In three subjects an electrode over the ipsilateral sensory cortex (C4 position) picked up consistent responses of much smaller amplitudes (mean 4.3 /uv) and longer latencies (on average 45.3 ms) longer than those of the contralateral sensory cortex (C3) (Figure 29). Similar findings were reported by Chatt and Kenshalo (1977) in two normal subjects. Figure 30 shows cortical evoked responses from cold stimulation of the dorsum of the R hand in two normal subjects. In both subjects, reliable positive peaks could be reproduced at peak latencies of 200 ms (upper trace Figure 30) and 195 ms (lower trace Figure 30). In two normal subjects, Chatt and Kenshalo (1979) obtained latencies of 200 and 140 ms on cooling the hand. The values obtained by the latter authors and in the present study are, however, about

Figure 27 Heat evoked cortical responses recorded from C3 position on the stimulation of the R hand in 6 subjects reproduced on three occasions for each subject. Each recording represents average of at least 25 sweeps.

E: Onset of the electrical pulse which activated the solenoid valves

TS: Onset of the thermal stimulus

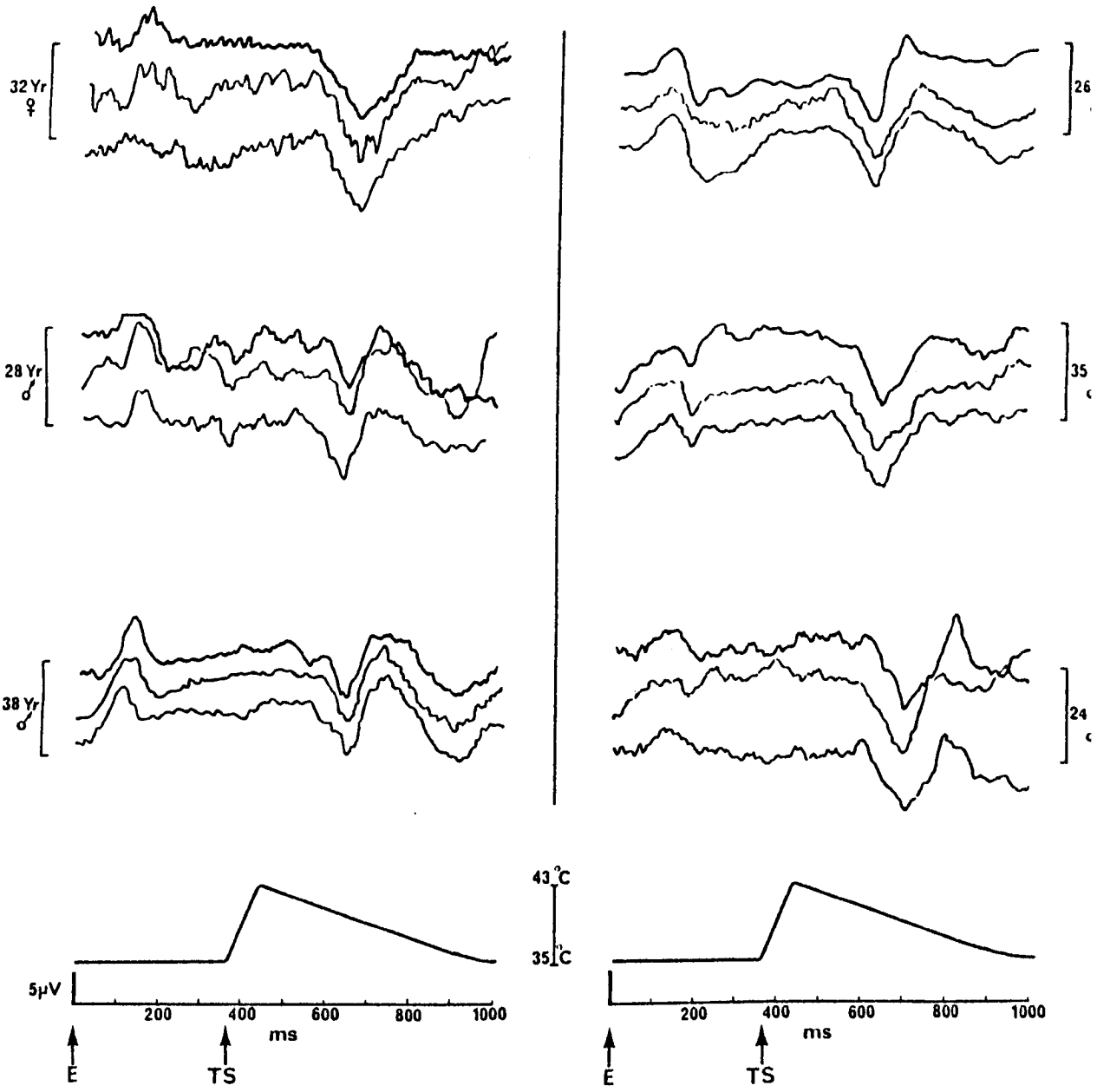

32 Yr ♀
28 Yr ♂
38 Yr ♂
26
35
24
43°C
35°C
5μV
200
400
600
800
1000
ms
E
TS

Figure 28 Heat stimulation evoked cortical responses from a 32 year female subject with recording electrodes at the positions shown. A time-locked consistent response of a smaller amplitude but similar latency could be recorded simultaneously from the vertex at Cz (in addition to the response at the contralateral sensory cortex). No consistent time-locked response could be determined at FP1 and O1 positions.

E: Onset of the electrical pulse which activated the solenoid valves

TS: Onset of the thermal stimulus

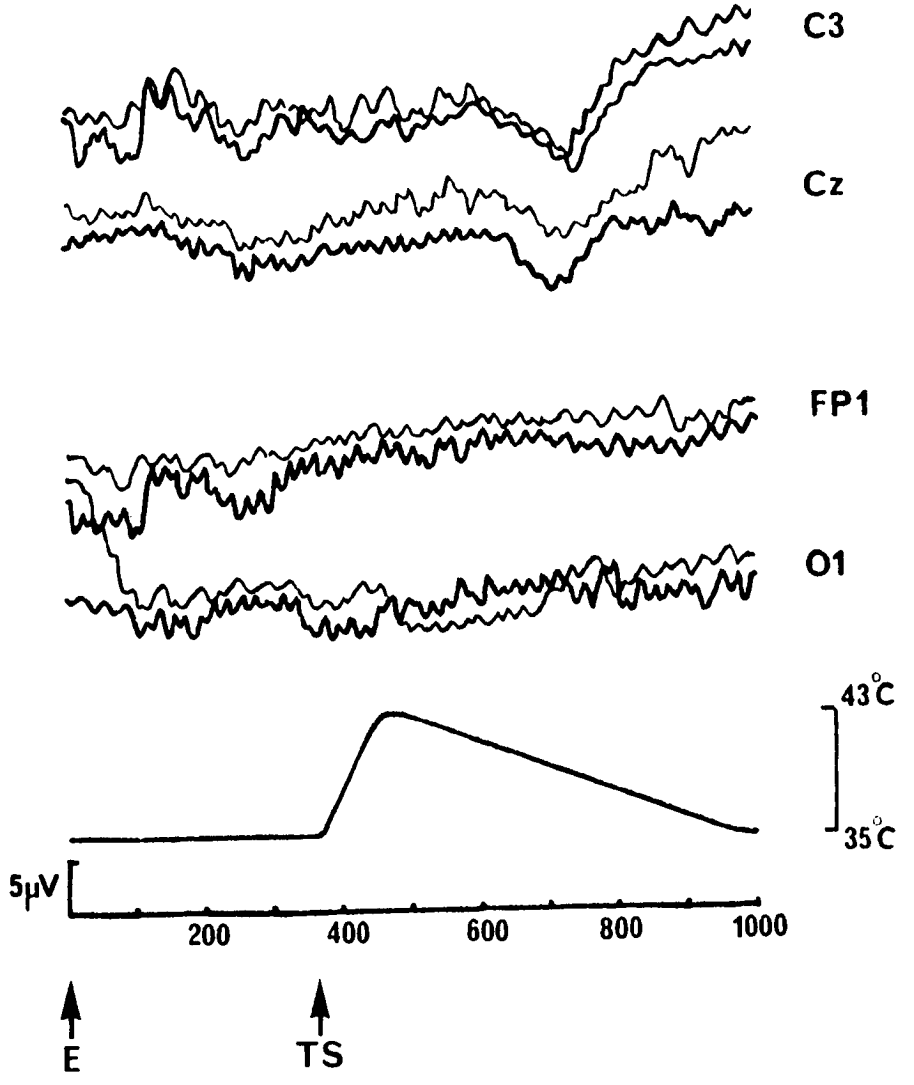

C3
Cz
FP1
O1
43°C
35°C
5μV
200
400
600
800
1000
E
TS

Figure 29 Contralateral (CL) and ipsilateral (IL) heat evoked cortical responses in 3 subjects to stimulation of the R hand. Responses from the scalp overlying the ipsilateral sensory cortex were smaller in amplitude and of longer latencies than those recorded from the sensory cortex contralateral to the side of stimulation.

E: Onset of the electrical pulse which activated the solenoid valves

TS: Onset of the thermal stimulus

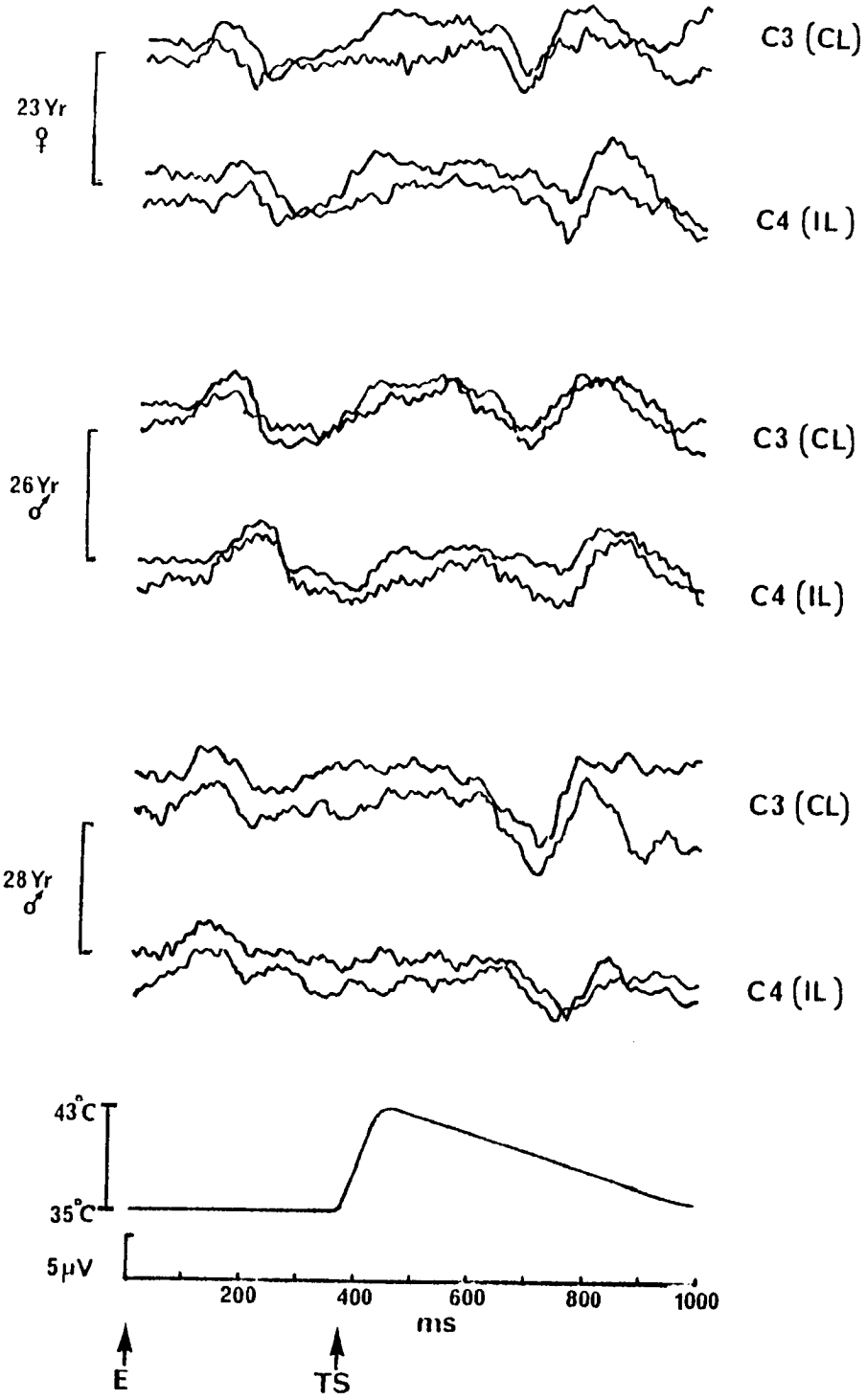
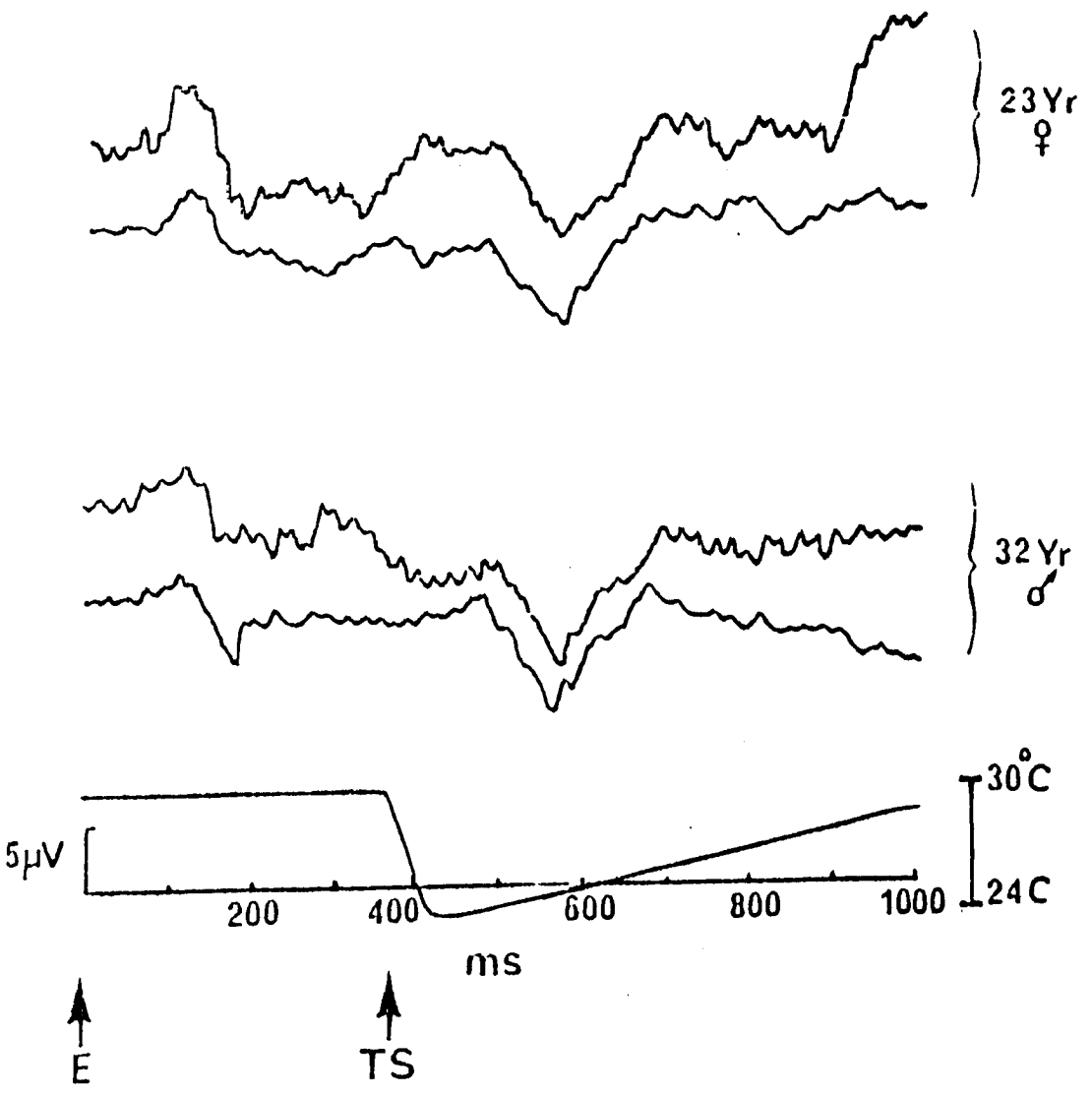

23 Yr
♀
C3 (CL)
C4 (IL)
26 Yr
♂
C3 (CL)
C4 (IL)
28 Yr
♂
C3 (CL)
C4 (IL)
43°C
35°C
5μV
200
400
600
800
1000
ms
E
TS

Figure 30 Cold stimulation evoked cortical responses from C3 position on stimulation of the R hand in two subjects reproduced on two occasions for each of the subjects. Each recording represents the average of at least 25 sweeps.

E: Onset of the electrical pulse which activated the solenoid valves

TS: Onset of the thermal stimulus


23Yr
♀
32Yr
♂
30°C
24C
5μV
200
400
600
800
1000
ms
E
TS

150 ms shorter than those obtained by Duclaux et al (1974). Whether this discrepancy is due to stimulation at different rates of change of temperature as suggested by Chatt and Kenshalo (1979) or due to other factors remains to be seen. In the study of Duclaux et al (1974) the rate of change of stimulating temperatures was 11°C/s versus 19°C/s in Chatt and Kenshalo (1979) and 20°C/s in the present study. Investigation of this point is planned with the present set-up. Figure 31 shows the recording from 4 positions in the scalp for one of the subjects tested for cold evoked cortical responses. A much smaller positive peak could be reliably reproduced from the ipsilateral side C4 but this wave had a peak latency 36 ms longer than that of the contralateral side. Bilateral responses to cooling stimuli similar to what is reported here have been found by other workers (Duclaux et al 1974; Chatt and Kenshalo 1979).

Application of the method to two patients with severe small fibre neuropathy (Figure 32) and syringomyelia (Figure 33) showed absent responses.

Recording of cortical evoked responses to pure thermal stimulation represents a new approach to the investigation of thermal sensation in man. This preliminary study confirms earlier observations that such potentials could be recorded from human scalp (Duclaux et al 1974; Chatt and Kenshalo 1977,1979; Fruhstorfer et al 1976). Heat evoked responses from the cortex are confirmed to have longer latencies than those evoked by cold stimulation. This finding is in good concordance with a number of other observations; that two kinds of specific receptors serve heat and cold sensations (Chapter 1), that the reaction time to heat stimuli is longer than that for cold stimuli (Fruhstorfer et al 1972), that conduction along heat specific fibres is slower than cold specific fibres (Darian-Smith et al 1971; Hensel and Iggo 1971; Sumino et al 1971; Chapter 1) and the observation that warm and cold sensations could be dissociated during regional anaesthesia of the peripheral nerves (Chapter 1).

Figure 31 Cold stimulation evoked cortical responses from a 23 year old female subject with recording electrodes at the positions snown. A smaller amplitude, longer latency response to that observed in the contralateral cortex (C3) could be detected in the cortex (C4) ipsilateral to the side of stimulation. No consistent time-locked responses were found at positions FP1 and O1

E: Onset of the electrical pulse which activated the solenoid valves

TS: Onset of the thermal stimulus

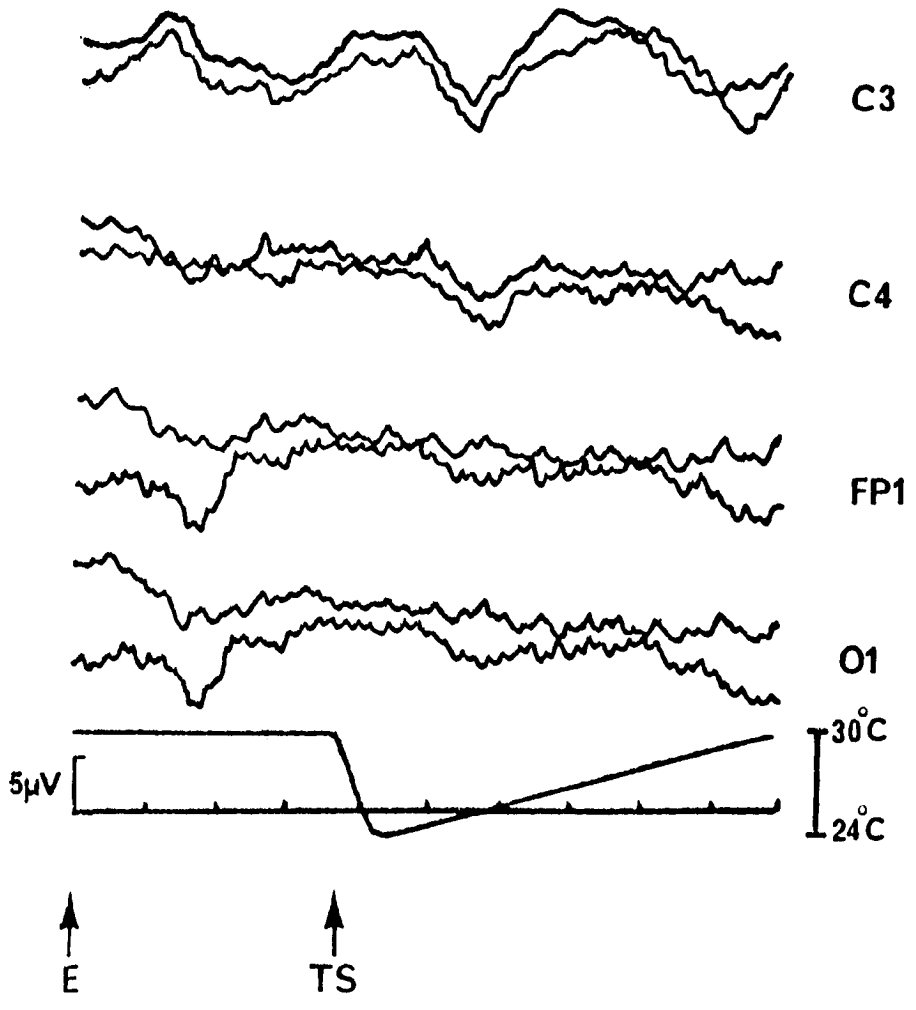

C3
C4
FP1
O1
5μV
30°C
24°C
E
TS

Figure 32 Cortical evoked responses to pure heat stimulation of the R hand in a 38 year old male patient with severe predominantly small fibre neuropathy and very high wrist thermal thresholds. No convincing time-locked reproducible response was noticed from the contralateral sensory cortex. Similar finding was noted for cold stimulation. Somatosensory evoked responses were normal in this patient.

E: Onset of the electrical pulse which activated the solenoid valves

TS: Onset of the thermal stimulus

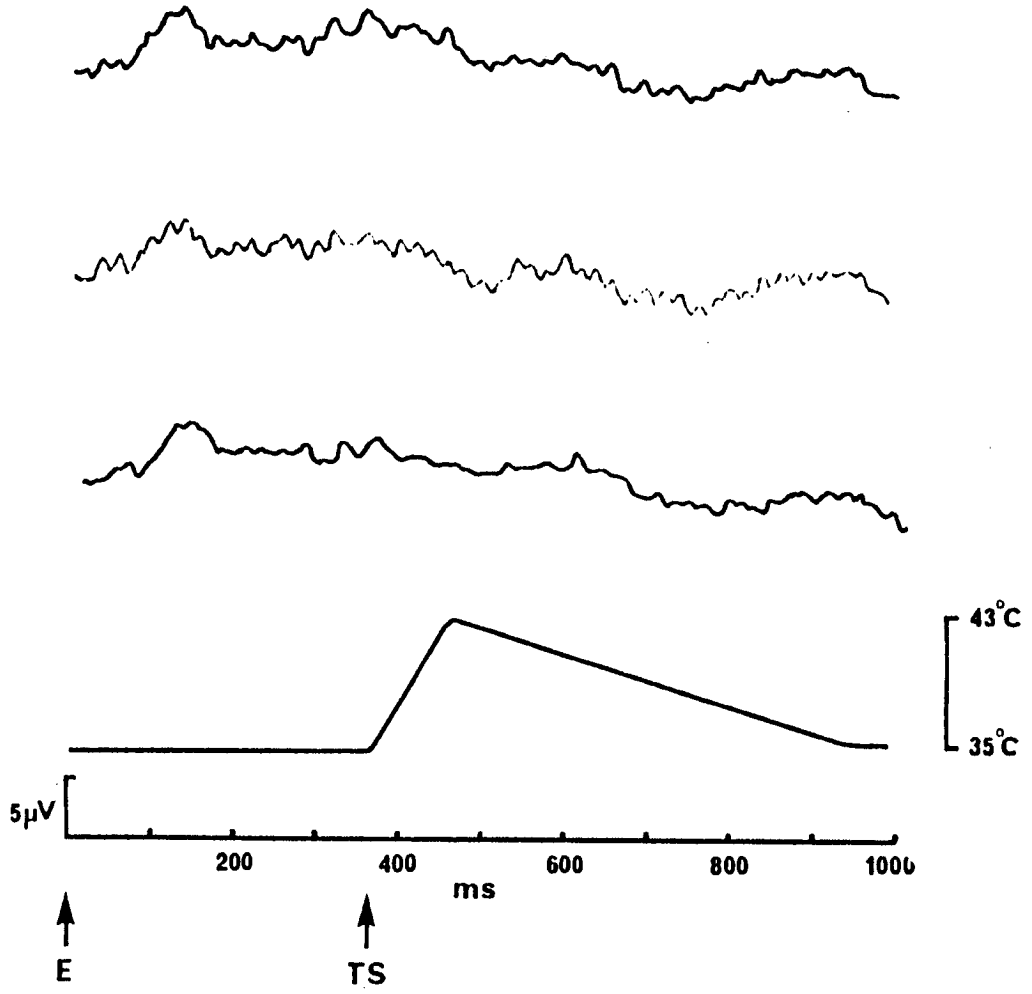
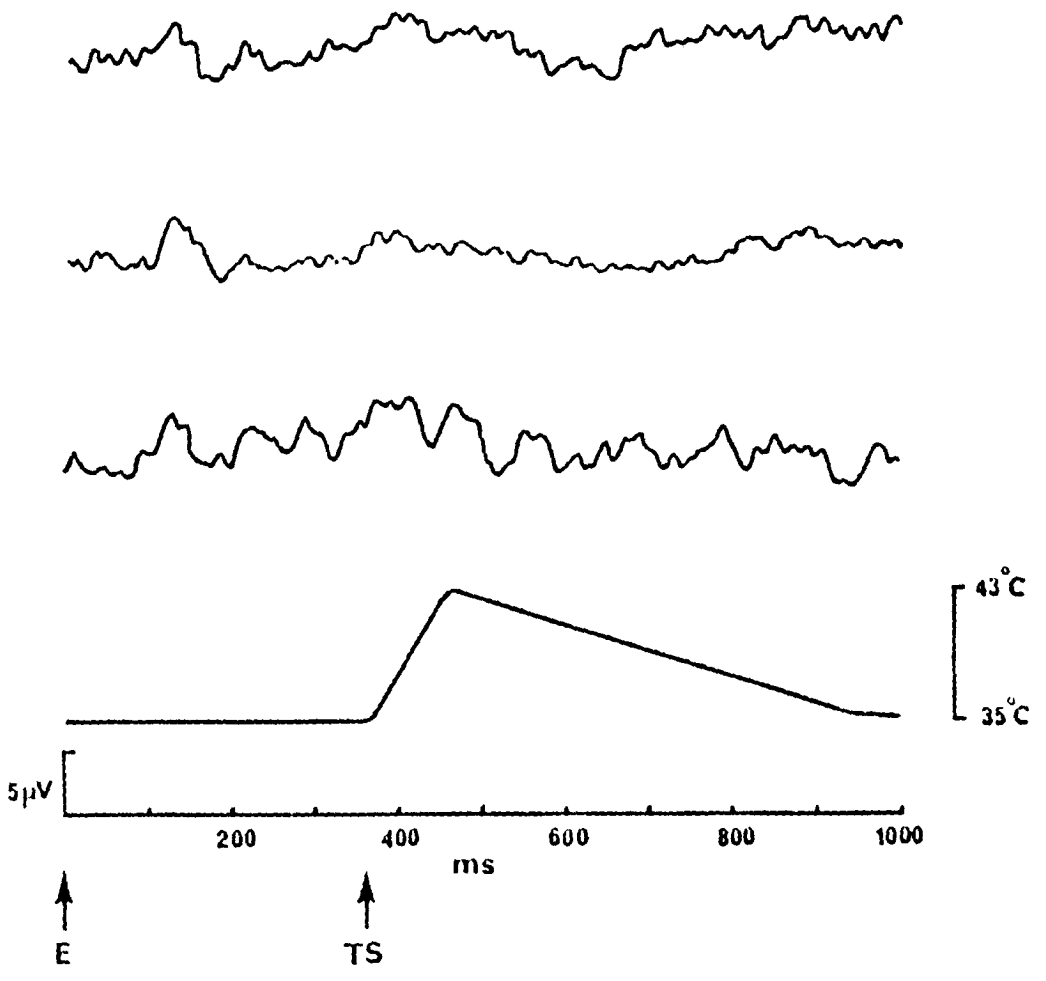

43°C
35°C
5μV
200
400
600
800
1000
ms
E
TS

Figure 33 Cortical evoked responses to pure heat stimulation of the R hand in a 45 old female patient with definite syringomyelia (same patient as in Figure 19) with very high thermal thresholds from the same hand. NO response could be detected, unlike normal subjects. Cold stimulation showed the same results. Somatosensory evoked responses from R median nerve stimulation were normal in this patient.

E: Onset of the electrical pulse which activated the solenoid valves

TS: Onset of the thermal stimulus


43°C
35°C
5μV
200
400
600
800
1000
ms
E
TS

Confirmation of the consistency of these cortical evoked responses in a large number of normal subjects is, however, necessary. It could be important in providing more information concerning thermal sensation in man as to whether the thalamic neurones project the input they receive to a localised area in the cortex and whether thermal sensation has a somatotopic organisation similar to that of tactile sensation (Franzen and Offenloch 1969; Stowell 1972). In addition, if completely successful, it could provide another diagnostic tool for the investigation of involvement of thermal pathway in diseases of the nervous system.

Modification of the system described in this report is planned so that (a) the rate of change of stimulating temperature is raised still higher, (b) recordings improved and artefacts eliminated, and (c) the possibility of recording these potentials from stimulation of the lower limb will be investigated.

CHAPTER 10

CONCLUSIONS

Clinical tests of thermal sensation are poorly quantified, inaccurate and not strictly modality specific. Many previous attempts to measure this sensation have failed to provide adequate accuracy, sensitivity and reproducibility in terms of both inter- and intra-individual measurements. This thesis describes a greatly improved method which is unrivalled by any of the previous methods. This was achieved through intensive review of the present knowledge of thermal sensation, minimisation of the effects of factors causing variability and elimination of serious errors in the measurement of thermal thresholds.

In a large group of healthy subjects (110), evaluation of the results of repeated measurements showed that a change in the thermal thresholds equivalent to one (in most sites tested) or two (in ankle) steps of stimulus intensity levels (each of $0.1^{o}C$), from an available scale of 90 levels, is enough to indicate a true change of these thresholds with a 99% probability.

The results of the application of the Glasgow Method to a large group of patients with peripheral neuropathy (143) of different aetiology and varied severity, demonstrated the superiority of the method to clinical testing in detecting involvement of thermal sensation. In this group of patients, abnormality of thermal thresholds, detected by the method was found to be more frequent than either abnormality of sensory system on clinical examination or of conventional EMG and nerve conduction velocity studies.

In 25 patients with clinical features suggestive of selective small fibre neuropathy selected for their normal conventional neurophysiology studies and VPT measurements, the technique scored abnormal results in 100% of these patients. Peripheral thermal afferent units fall exclusively among

the thinly myelinated (A) and the unmyelinated (C) fibre population. By the provision of a sensitive, accurate, quantitative and reproducible test of the integrity of thermal fibres, the Glasgow Method is, therefore, likely to reflect the state of function of the small fibre population in general. In keeping with this is the finding of normal values of thermal thresholds in 8 patients with early and mild Friedreich's ataxia in which selective involvement of the large fibre pathway occurs. Combination of the method with other neurophysiological tests for integrity of the large fibre pathway gives a good idea about the pattern of involvement of various fibre populations in peripheral neuropathy.

Application of the Glasgow method, along with other neurophysiological techniques to 24 patients with acromegaly supplied evidence for the presence of a generalised peripheral nerve dysfunction and that, unlike the present belief, this subclinical neuropathy is more common than localised entrapment neuropathy. Abnormality of thermal thresholds correlated significantly with values of nerve conduction velocities and VPTs. The neurophysiological abnormalities did correlate significantly with values of the total body exchangeable sodium, a measure of the longterm abnormality of human growth hormone levels.

In spinal cord lesions, the method yielded normal results in patients in whom the thermal pathway is expected to be spared (tabes dorsalis; the side ipsilateral and below a hemitransected cord) and highly abnormal results in patients in whom the thermal pathway is involved (syringomyelia; the side contralateral and below a hemitransected cord). The sensitivity of the method in detecting subclinical lesions in the spinothalamic tract is demonstrated by abnormal values obtained in the lower limbs in a patient with syringomyelia in whom clinical examination of the lower-limbs was normal. Abnormality of thermal thresholds in a patient with tabes dorsalis confirms clinical and discloses subclinical involvement of the lateral part

of the dorsal root entry zone. The method may prove to be of value in the follow-up of patients with expanding lesions of the spinal cord.

Comparison of results from the application of the Glasgow method to groups of patients with limb girdle muscular dystrophy, idiopathic polymyositis, myasthenia gravis and myotonia congenita with those from age and sex matched controls showed normal results supporting the consensus that the sensory system is spared in these diseases. In 40 patients with motor neurone disease and 40 age and sex matched control subjects, comparison of the results of the application of the Glasgow method showed the presence of significant abnormality of thermal sensation. This finding was supported by other evidence from the literature on this disease. The Glasgow method was also applied to 25 patients with definite myotonic dystrophy and the results, compared with those of a control group, showed significant abnormality of thermal sensation in this syndrome. The increase in the values of thermal threshold measurement significantly correlated with evidence of abnormality of three independent neurophysiological methods (nerve conduction studies, vibration threshold measurement and motor unit number estimation) in the same group of patients. The results suggested that, in addition to the myopathic component, patients with myotonic dystrophy have significant dysfunction of peripheral nerves and of large and small fibre sensory pathways (the findings were supported by evidence from previous work in the literature on myotonic dystrophy). Further modification of the technique is planned which may give further improvements in the accuracy of measurement of thermal thresholds. The addition of a system to quantify the sense of vibration with similar success could prove to be a useful companion to the Glasgow Thermal System.

Preliminary results of thermal evoked cortical response studies confirm recent reports in a small number of normal subjects. Cortical responses to pure thermal stimuli were obtained in six normal subjects. The findings of

abnormal thermal thresholds by the Glasgow method in two patients was supported by the absence of thermal evoked responses in these patients. Modification of the system for recording cortical responses to pure thermal stimuli and its application to a large number of normal subjects and to patients with neurological diseases is planned for future studies.

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APPENDIX I

THE GLASGOW THERMAL SYSTEM

OPERATING INSTRUCTIONS

POWER UP

Switch on the Visual Display Unit (VDU). Switch on the Thermode Interface Unit (TIU) and press SET/RESET button. Switch on water bath. Switch on computer.

Program starts on power up and on pressing reset button on front panel of computer. If first display after power up is corrupted then pressing reset button will restart with correct display. It may also be necessary to press reset button on the VDU.

The small black box with two LEDs and a push button is a visual indicator for the stimulus and the push button is used by the patient to signal pain threshold.

The small white box with push button is the ABORT button and when pressed disconnects the current from the Marstock stimulator.

A forced-choice trial consists of one period of stimulus (or no stimulus) followed by one period of no stimulus (or stimulus). The program randomly selects the order. The patient must reply with the period in which he felt the stimulus. The reply whether right or wrong increases or decreases the stimulus intensity and after six changes in direction the test is complete.

At the start of up-and-down transform rule (UDTR), the stimulus level is changed in large steps as noted below. A single correct reply is enough to decrease the stimulus. After the first wrong reply the stimulus level is changed in smaller steps and three correct replies are now required to decrease the level.

With a wrong reply the power or time is increased as below except that only one wrong reply, at any time, is required to increase the level.

	add or subtract
Large Step	1 s
Small Step	0.1 s

DISPLAYS

There are three main displays on the VDU.

1) Parameters for PELTIER element and TEST mode.

2) Action Options.

3) Parameters for selected options (if required).

In all displays typing 1 will return user to previous display. To change from default values in any of the displays the user types number at the start of the line, whereupon the present value will be displayed and the user asked for the new value. To enter new value type it (maximum of six digits plus decimal point, if required) followed by return (key 'CR'). The complete display will then be renewed with the updated value. If the new value is too large an error message will be displayed and user again asked for new value. Also if during heating or cooling the ABORT button is pressed, the program returns to the first display with the message '*RUN ABORTED*' at the top of the screen. The user can then continue, after resetting the TIU as described below.

FIRST DISPLAY

```
1.  SEEBECK COEFFICIENT     7.0     MW/A/DEG K
2.  THERMAL CONDUCTIVITY    180.0   MW/DEG C
3.  INTERNAL RESISTANCE      .340   OHM
4.  TEST MODE               FALSE
C.  TYPE C TO CONTINUE
```

Default values are as above and the first three options are parameters for the PELTIER element. For option 4 to change from false to true and vice versa user just types 4. To continue from here type 'C'. If option 4 TRUE, during UDTR, wnether tne stimulus is first or second, power value and time rare displayed wnile the test is in progress.

SECOND DISPLAY

Options here are the tests available.

REFERENCE TEMPERATURE XX.XX DEG C

1. RETURN TO START
2. HEATING OR COOLING HEATING
3. TEST STIMULUS
4. SENSATION (VARY HEAT)
5. SENSATION (VARY TIME)
6. PAIN
7. MEASURE REFERENCE TEMPERATURE
8. MINIMUM TIME BETWEEN TRIALS 30.0 S

Typing '2' will change from heating to cooling or vice versa (OPTIONS 3,4,5 and 6).

Typing '7' will measure reference temperature of the front surface of the thermode and display the value above the options as shown. Typing the number selects the option.

'8' is typed to alter the minimum time between trials.

Options 3,4,5 and 6 show further displays with the relevent default parameters for the option. The first line displayed tells user which option selected, whether heating or cooling and whetner test mode or not.

OPTION 3

Header Display

1. RETURN
2. POWER 2000.0 MW
3. TIME 6.0 S
4. START

Supplies a stimulus of known power and duration, measures and displays the rise (or fall) in temperature over this duration. The values displayed for power and time are used as default values for options 4 and 5 respectively.

Both LEDs are lit during stimulus. When test completed temperature change is displayed and 'C' is typed to return to start of option.

TEMPERATURE CHANGE = - -XX.XX DEG C

TYPE C TO RESTART

OPTION 4

Header Display

1. RETURN
2. TIME 5.0 S
3. START

CTRL C TO ABORT UDTR

Stimulation duration (TIME) is constant during experiment but may be altered prior to starting, the power is varied according to UDTR.

RESULTS DISPLAY

THRESHOLD TEMPERATURE IS - (+/-) X.XX DEG C

MEAN POWER XXXX.XX MW

TYPE C TO TO RESTART

OPTION 5

When options 5 and 6 are selected a stimulus of 2000 Mw is supplied for 6 seconds and the resulting temperature change used compute a calibration value (change in temp/time/power) which is used to calculate the power required to give the requested rate of temperature change.

During the six seconds COMPUTING POWER FACTOR is displayed.

Header display

TEMPERATURE CHANGE XX.XX DEG C

1. RETURN

2. RATE 1.0 D C/S POWER XXXX.X MW

3. START

CTRL C TO ABORT UDTR

The rate may be altered, prior to starting, and the power is then recalculated using the calibration value when option 5 first selected. Time is varied according to UDTR.

RESULTS DISPLAY

THRESHOLD TEMPERATURE IS (+/-) X.XX DEG C

MEAN POWER XXXX.XX MW

MEAN TIME XX.XX S

TYPE C TO RESTART

Mean power in this option is meaningless as power is kept constant.

In results displays 4 and 5 if ctrl 'C' was typed a further line is displayed:

N CHANGES IN DIRECTION (numbers of changes prior to aborting UDTR).

In option 4 the time is kept constant and the power varied and with option 5 the power kept constant and the time varied according to UDTR. On starting, a stimulus or non stimulus selected at random is delivered to the Peltier element for the time required and after a three second gap the

opposite stimulus or non stimulus delivered. The first period is indicated by the first LED being lit and the second by the second LED being lit. During the trial 'TEST IN PROGRESS' is displayed and when completed user asked to reply 1 or 2. Time between trial is started at end of test. User replies by typing 1 or 2 or ctrl 'C' (hold down CTRL key and type 'C' key) if wisned to abort UDTR.

If run aborted results displayed with current values. Otherwise UDTR continues until six changes in direction have occured. While in option five, if the time of stimulation is equal or less than one second, the LEDS remain lit for one second although the actual stimulus is less. When time between trials is finished the next trial is started.

If during any trial the TIU stimulator cannot deliver current calculated, current is set to a maximum or minimum value and a warning is displayed:

CURRENT OUT OF RANGE

OPTION 6

Power is calculated as noted in option 5.

Header display

TEMPERATURE CHANGE XX.XX DEG C

1. RETURN
2. RATE 1.0 DEG C PER XXXX.X MW
3. START

This option is used to find heating or cooling pain threshold. When started the Peltier element dissipates heat at constant power (to obtain specified rate of temperature change) until the button on the LED box is pressed, whereupon the display:

BUTTON PRESSED

is appended to tne above display. The power is reversed until the

temperature is within two degrees of the refrence temperature. Maximum or minimum temperature along with energy, calculated by displayed. User types 'C' to return to previous display.

RESULTS DISPLAY

PAIN TEMPERATURE	(+/-) XX.XX	DEG C
TIME TILL BUTTON PRESSED	XX.X	S
ENERGY	XXX.X	JOULES

TYPE C TO RESTART

APPENDIX 2

GENERALISED PERIPHERAL NERVE DYSFUNCTION IN ACROMEGALY: A STUDY BY CONVENTIONAL AND NOVEL NEUROPHYSIOLOGICAL TECHNIQUES

by

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SUMMARY

Twenty-four patients with clinical, radiological and biochemical evidence of acromegaly were investigated by a number of independent neurophysiological tests. Two-thirds of the patients showed evidence of generalised peripheral nerve dysfunction. A significant correlation was found between total exchangeable body sodium, an indicator of disease activity, and the severity of the neuropathy. The generalised peripheral nerve abnormality was found to occur independently of the associated carbohydrate intolerance human growth hormone levels and other endocrinological dysfunction in this disorder.

INTRODUCTION

The association of median nerve entrapment at the wrist with acromegaly is well known[1-5] and is probably due to compression of the nerve by hypertrophic connective tissue[3,6,7]. Unilateral or bilateral carpal tunnel syndrome (CTS) is one of the first symptoms in 12% of patients with acromegaly[8] and later in the course of the disease the incidence may rise to as high as 35-47%[8,9]. Generalised neuropathy is a much less recognised complication and only occasional reports of individual patients have appeared[10-17]. This neuropathy was found to be predominantly sensory in nature[18] although severe muscle weakness and wasting have been described[13].

Although believed to be related to the disease process, no correlation was found between this peripheral nerve dysfunction and indices of human growth hormone (HGH) secretion and the associated glucose intolerance[8,15]. This was not based on statistical analysis of this correlation in an adequate number of patients but rather on observations on individual patients.

We have looked for evidence of a generalised peripheral neuropathy in 24 patients with acromegaly and have correlated our findings with measurements of body composition, circulating HGH concentration, thyroid dysfunction, total exchangeable body sodium and other endocrine data. The relative frequency of involvement of large versus small fibre afferent pathways was assessed using conventional electromyography and nerve conduction studies, our recently introduced technique for the study of thermal thresholds[19] and the technique of Goldberg and Lindblom[20] for the quantitative measurement of vibration thresholds.

METHODS AND MATERIALS

THE NEUROPHYSIOLOGICAL TECHNIQUES

Electromyography and Nerve Conduction Studies

Electromyography (EMG) and nerve conduction (NC) studies were performed using a Medelec MS91 electromyograph. The fastest motor nerve conduction velocity (FMNCV) and the shortest distal motor latency (SDML) for the right (R) lateral popliteal nerve (LPN) and (R) median nerve were recorded from surface electrodes over the extensor digitorum brevis (EDB) and abductor pollicis brevis (APB) muscles respectively by conventional techniques[21]. The sensory nerve action potentials (SNAPs) were elicited orthodromically in the R median and sural nerves. For each SNAP measurement, 64 potentials were averaged. Sensory latencies were measured from the onset of the stimulus artefact to the peak of the negative deflection. Amplitudes were measured from peak to peak. For median SNAP studies, the method of Gilliatt and Sears[22] was followed. The sural nerve was stimulated at the lateral aspect of the foot immediately inferior and anterior to the lateral malleolus and the potential recorded by surface electrodes 12-14 cm proximal to the malleolus and lateral to the tendo achillis. The distance between the recording and the reference electrodes was 4 cm. Electromyographic studies were performed with concentric needle electrodes in the APB and the EDB muscles. The ambient room temperature was kept at 22 ± 2°C. Skin temperature of the limb was maintained at 34 ± 1°C using a thermostatically controlled heating lamp.

Thermal thresholds measurement

Thresholds for appreciation of heat (HT) and cold (CT) were determined for the volar aspect of the R wrist just proximal to the distal wrist crease and for the medial aspect of the R ankle behind the medial malleolus. These were expressed in temperature change from the basal skin

temperature (before application of the stimulus) using a microcomputer controlled system and the two-alternative forced-choice method of psychophysical analysis (The Glasgow Thermal System). The method has been described in detail elsewhere[19], but the following is a summary of the technique. The microprocessor system controls the stimulating probe (the thermode) and performs the forced-choice trials. The thermode is constructed from an array of semiconductor thermo-electric elements with a stimulating surface area of 12.5 cm^2 and operates on the Peltier principle. On the background of a constant skin temperature (34-35°C), the thermode applies a quantified thermal (heat or cold) stimulus to the skin tested. The subject is placed in a comfortable position and the thermode is applied to the area of the skin tested with a standard pressure. A number of trials are performed. In each trial, the subject is presented with two periods during which a null stimulus and an thermal stimulus are applied and the periods are indicated to him by two lights numbered 1 and 2 and illuminated in sequence. The order of assignment of the actual and the null stimuli to the periods is randomised by the microcomputer and is unknown to the subject and the examiner. At the end of each trial the subject must choose that period during which he/she felt or thought he/she felt the stimulus. Depending on the response, the computer will alter the stimulus strength applied during the next trial according to the up-and-down transform rule (UDTR)[23]. The stimulus power is kept constant such that the rate of change of temperature at the skin surface is 1°C/s. The strength of the thermal stimulus is altered by changing its duration of application. The threshold is calculated as the mean of at least 12 separate trial values in accordance with the UDTR. The investigation is carried out in a quiet room at a temperature of 22 ± 2°C. HT is determined first followed by CT. The time required to determine both HT and CT for one site is usually 15-20 minutes. All investigations were carried out by the same person (GAJ).

Vibration threshold measurement

Vibration perception threshold (VPT) was measured in all subjects on the dorsal aspect of the middle of the right second metacarpal bone and on the dorso-medial aspect of the middle of the R first metatarsal bone where the overlying subcutaneous tissue is thin. The technique, its physiological basis and normal values have been described[20]. Briefly, the vibration stimulus intensity is assessed from the displacement of the skin in micrometres and not from the voltage applied to the vibrameter. The degree of displacement of skin is the physiological stimulus to the vibration-sensitive receptors[20,24]. The apparatus (SOMEDIC AB VIBRAMETER type III) consists of an electromagnetic vibrator with a 13 mm diameter probe which vibrates at right angles to the skin. The amplitude of the skin displacement (the vibration amplitude) is measured indirectly by an accelerometer with continuous digital display. The vibrator is held against the skin with a force of 500 ± 100 g by reference to a force indicator on the Vibrameter. The subject is placed in a comfortable position, the R leg is supported by pillows to prevent stimulus spread and a suprathreshold test is applied to familiarise him/her with the sensation produced. The apparatus can deliver two standardised rates of increase in stimulus intensity, slow or fast. The amplitude of vibration is increased using one of these alternatives and the subject is instructed to indicate when he/she feels the stimulus. The vibration amplitude is repeated at the alternative rate of increase of stimulus intensity. The average of three trials is taken as the VPT. In cases where there is more than 10% variation between the values, further trials are performed until 3 consecutive readings are within the 10% limit.

Vibration amplitudes in the range of 0-399.9 micrometres at 100 Hz can be produced by the apparatus. The VPT determinations are made in a quiet room with a constant ambient temperature (22 ± 2°C). Skin temperature is

kept at 34 ± 1°C with a thermostatically controlled heat source. On the average less than 5 minutes is required for each VPT determination. All investigations were carried out by the same person (GAJ).

PATIENTS AND CONTROL SUBJECTS

The normal values for various tests come from different control groups. Healthy control groups were drawn from among the staff and their relatives of the Institute of Neurological Sciences, Southern General Hospital, Glasgow. There were 61 control subjects for the thermal thresholds aged 35-73 (mean = 45.5, SD = 11.8) years. The control group for the EMG and NC studies contained 21 healthy subjects aged 23-69 (mean = 46, SD = 12) years. The control group for the vibration threshold measurement consisted of 27 subjects aged 17-64 (mean = 46.2, SD = 11.5) years.

Patients

Twenty-four patients with clinical, radiological and biochemical evidence of acromegaly attending the Department of Medicine at the Western Infirmary, Glasgow, were included in this study. Their ages ranged from 26 to 78 (mean = 48, SD = 15.4) years. There were 14 female and 10 male patients. All the patients were informed about the nature and purpose of the study and agreed to participate. Those thought to have excessive alcohol intake or to be taking drugs likely to cause peripheral nerve dysfunction were excluded from the study. All patients had received some treatment for their acromegaly. This and other clinical details are shown in Table 1 which include, where available, the hormonal status both at diagnosis and at the time of the neurophysiological studies.

All patients had been admitted to hospital for full biochemical and endocrinological evaluation within 6 months prior to the neurophysiological measurements[25]. A standard 50 g oral glucose tolerance test was performed on each after an overnight fast. Blood samples (venous cannula) were taken at the time of glucose ingestion and at 30 minute intervals for two hours for blood glucose and HGH estimations. The areas under glucose and HGH curves during the glucose tolerance test were also measured. A 'HGH day

curve' from blood samples taken during one day at 800, 1100, 1300, 1700 and 1900 hours, was also performed to obtain the mean circulatory HGH concentration. HGH was measured by radioimmunoassay using the 1st international reference preparation (MRC 66/127; 1 mcg/l = 2 mu/l). Each patient, in addition, had a standard intravenous thyrotrophin-releasing hormone test[26] during which the thyroid stimulating hormone (TSH) and HGH were measured at intervals of 0, 20 and 60 minutes after intravenous administration of 200 /ug of synthetic thyrotrophin-releasing hormone. Total exchangeable body sodium (Nae) was determined by the method of Davies and Robertson[27] and was expressed as a percentage of that expected in a normal individual of the same body surface area and sex. Total body water was measured by tritium dilution.

RESULTS

Clinical evidence of a generalised neuropathy was present in 8 patients. Two other patients had typical distal sensory symptoms but without objective clinical evidence on examination (Table 1). In 10 patients, mostly with clinical evidence of neuropathy, the ulnar and/or the lateral popliteal nerves were considered to be enlarged clinically (Table 1).

The results of the neurophysiological assessments of the control subjects and the patients with acromegaly are summarised and compared in Table 2. The statistical significance of the results was evaluated using student's (t) test. It is clear from Table 2 that all but one (the sural SNAP latency) of the neurophysiological parameters are significantly abnormal in the patients with acromegaly compared with the normal control groups. The mean values of the upper and lower limbs thermal and vibration thresholds, the median SNAP latency, the SDML for the LPN and median nerve were all significantly higher than corresponding means for the control groups. The mean values of the FMNCV for the LPN and median nerve and the median and sural SNAP amplitude were significantly lower than those of the control group.

The figure shows the distribution and the relative frequencies of the abnormalities for the neurophysiological tests. Values above the 95th percentile were abnormal for sensory and motor conduction and vibration threshold studies while thermal threshold values in excess of the 99th percentile were considered abnormal. The SDML and/or the FMNCV for the LPN were abnormal in 50% of the patients. The sural SNAP amplitude and/or latency were abnormal in 14% of the patients with acromegaly. A smaller number of patients had abnormalities in the sensory and/or motor median nerve conduction studies (Table 3).

Thermal thresholds for one or both sites were abnormal in 67% of the patients studied. The thermal threshold abnormalities were generally more marked and more frequent at the ankle (62%) than at the wrist (42%) (Table 3). Abnormal VPT at the tarsal site was encountered in 37% of the patients while 12% had VPT abnormality at the carpal site (Table 3).

The diagnosis of carpal tunnel syndrome (CTS) was made on both clinical and electrophysiological evidence. The clinical criteria of CTS included one or more of the following features: paraesthesiae in the distribution of the median nerve; wasting and/or weakness of the APB muscle and sensory impairment in the median nerve distribution of the hand. The electrophysiological criteria of CTS included one or more of the following abnormalities: a prolonged median nerve SDML, a prolonged median SNAP latency and a reduced median SNAP amplitude at the wrist. These criteria had to occur in the presence of normal ulnar nerve and proximal median nerve conduction studies. Ten patients had both clinical and electrophysiological criteria of CTS (42%). In 5 patients, two of whom had bilateral CTS, this was the only abnormality in their neurophysiological tests. In the remaining 5, of the CTS patients, there was also evidence, from one or more of the neurophysiological tests performed on the lower limbs, of a widespread subclinical dysfunction of the peripheral nerves and their end organs (Table 4).

There was no significant correlation between the neurophysiological parameters and values of fasting blood sugar, two hour post-prandial glucose, the area under glucose curve during GTT, human growth hormone (HGH), mean HGH during the glucose tolerance test (GTT), the area under HGH curve during GTT, mean 'HGH day curve' and TSH levels at 20 and 60 minute intervals during the thyrotrophin-releasing hormone test. The neurophysiological parameters also did not corelate with these endocrinological data performed at the time of the diagnosis of acromegaly before treatment. Significant correlation, however, was found between

most of these neurophysiological tests and the Nae (Table 5). No correlation was noticed between duration of diagnosis of acromegaly and the neurophysiological parameters. It is accepted, however, that the lack of correlation may be due to the difficulty of estimation of the actual duration of this disorder.

DISCUSSION

The results obtained in this study using a number of independent neurophysiological techniques, indicate the presence of a generalised impairment of peripheral motor and sensory nerves in acromegaly. One-third had clinical and two-thirds had neurophysiological evidence of a generalised neuropathy. Local nerve entrapments were present in 42%.

Several isolated cases of hypertrophic neuropathy have been described in association with acromegaly[11-13]. In a small series of patients with acromegaly, 45% were found to have some hypertrophy of peripheral nerves clinically[15]. Sural nerve histology in some of these patients showed endoneurial and subperineurial tissue hypertrophy[11,12,14]. These findings were supported by Low and associates[15] who also demonstrated an increase in the fascicular areas of the sural nerves. Ten of our patients (42%) had clinical evidence of hypertrophy on examination.

The sural sensory action potential (SNAP), when measured to the peak, gives information in its latency about the modal peak of the conduction velocity of the unmyelinated nerve fibre velocity population[28]. The amplitude gives information about the number of nerve fibres stimulated with a wide variety of velocities[28]. This test was abnormal in 14% of the patients (Table 3). Abnormal tarsal vibration perception threshold was found in 37% of the patients, an indication of involvement of the large fibre afferent nerve pathway[20]. The abnormality of VPT was less severe and less frequent at the carpal site compared with the more distal tarsal position.

Thermal thresholds are an indication of function in the small nerve fibre afferent pathway[29]. In the acromegalic patients abnormalities of thermal thresholds were more severe at the ankle (67%) than at the wrist (42%). Sural nerve histological studies in acromegaly have demonstrated a decrease in the density of unmyelinated and myelinated fibres with signs of segmental demyelination and remyelination[15].

Our results suggest involvement of both small and large fibre pathways. In addition, the combination of all the neurophysiological and perceptual tests with the greater frequency of thermal and vibration sense abnormalities distally is similar to the pattern of involvement in many metabolic and toxic peripheral neuropathies where the most severe abnormality occurs in the longest nerve fibre.

No significant correlation was found between the values of the neurophysiological tests and the associated glucose intolerance, the level of HGH in plasma, the mean 'HGH day curve', the mean HGH during the glucose tolerance test and the 20 and 60 minute TSH hormone levels during the thyrotrophin- releasing hormone test. This is in agreement with Low et al[15] and Pickett et al[8] who found no correlation of the peripheral neuropathy with HGH levels and the associated diabetes mellitus in acromegaly. Total Nae is increased in acromegaly[25,30,31] and may reflect disease activity since it correlates with HGH levels[31] and with the duration of the disease process[25] and also falls following successful treatment[25]. Most of the neurophysiological parameters showed a significant correlation with Nae; the higher the Nae, the more abnormal were the neurophysiological tests (Table 5). This would reflect a generalised neuropathy which increases in severity with disease activity.

The independence of the neurophysiological data from the glucose in tolerance and the pituitary thyroid dysfunction suggests that the neuropathy is not aetiologically similar to that of diabetes mellitus or hypothyroidism. In view of the known correlation betwen Nae and HGH[25,31], the lack of an association between HGH and the neurophysiological data is difficult to explain but may be a different rate of change in the two variables following treatment in this heterogenous group of treated acromegalic patients. However, the generalised peripheral neuropathy seems likely to be due to an effect mediated through excessive human growth

hormone levels the exact mechanism, remains to be determined.

Unilateral or bilateral carpal tunnel syndrome was present in 42% of our patients. This is in agreement with other published series[8,9]. The results show that in 50% of patients with acromegaly associated carpal tunnel syndrome, there is an underlying generalised peripheral neuropathy but equally there are 50% who develop the entrapment neuropathy independent of any generalised process.

CONCLUSION

Generalised peripheral nerve dysfunction is common in patients with acromegaly. The peripheral nerve abnormality does not correlate with the associated diabetes mellitus, the circulating levels of growth hormone, and the pituitary thyroid function. A significant correlation exists between the presence and severity of the peripheral neuropathy and total exchangeable body sodium. Compression neuropathies either as part of the generalised dysfunction, or independent of it, occur frequently. The exact mechanism of this peripheral nerve dysfunction in acromegaly remains to be determined.

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LEGENDS

Figure 1 The distribution of the values of the neurophysiological tests performed in 24 patients with acromegaly.

A: in the upper limb

B: in the lower limb

The scales are drawn so that control means and control standard deviations coincide to render comparison easy. The axes of the median and sural SNAP amplitudes and the LPN and median FMNCVs are reversed so that abnormalities are shown as shifts in upward direction for all the parameters.

HT	: heat threshold
CT	: cold threshold
SNAP	: sensory nerve action potential
SDML	: shortest distal motor latency
FMNCV	: fastest motor nerve conduction velocity
LPN	: lateral popliteal nerve
VPT	: vibration perception threshold

TABLE 1: SUMMARY OF THE IMPORTANT CLINICAL DATA IN 24 PATIENTS WITH ACROMEGALY AT DIAGNOSIS AND AT THE TIME OF THE NEUROPHYSIOLOGICAL ASSESSMENT

						At Diagnosis			At present					Treatment	
Case No.	Sex	Age (yr)	Clinical* polyneuropathy	CTS	Clinical nerve hypertrophy	mean 'HGH day curve'	Nae	GTT	Mean 'HGH day curve'	Nae	GTT	Mean HGH during GTT	TRH Test	Type	Duration (Yr)
1	F	68	+	+	+	43	147	N	6.1	125	Abn	3.9	Abn	H	5
2	F	48	+	-	+	67	126	N	9.3	107	N	16	N	H & I	4
3	F	38	-	-	+			N	1.8	96	N	1.9		H	6
4	M	52	+	-	+			N	1.8	109	N	1.9		H & I	19
5	M	30	+	+	+			N	1.6		N	0.8	N	H & I	10
6	M	46	-	-	-	39	133	N	7	112	Abn	6.8	Abn	H & I	3
7	M	66	+	-	+	17	126	Abn	4.1	125	Abn	3.2	Abn	H	10
8	F	30	-	+	+			N	4.5	121	N	4.5	Abn	H	2
9	F	68	+	-	-			N	22.2	138	N	20.4	Abn	H	14
10	M	26	-	-	-	618	118	N	115.8	115	N	24.6	Abn	I	6
11	M	43	-	-	-	135	132	N	11.4	107	N	11.3	Abn	H	11
12	F	52	-	-	-	19	120	N	4.2	111	N	4.4	Abn	I	10
13	F	62	-	-	-			N	2.9	93	N	1.4	N	I	10
14	F	29	-	-	-	36	114	N	29.2	109	N	40	Abn	H	6
15	M	30	-	+	-		139	N	17.3	118	Abn	15.8	Abn	H & I	8
16	F	56	-	+	-	63	134	N	6.7	115	N	6.2		H	2
17	F	65	-	+	-	109	134	N	2.4	107	N	2	Abn	H & I	8
18	F	54	-	+	-	97	120	N	2.5	111	Abn	2.7	N	H	6
19	M	65	+	+	+	140	155	Abn	2.2	128	Abn	1.6	Abn	H	7
20	F	42	-	-	+	36	108	N	21.8		N	18.8		H	12
21	M	78	+	+	+	80	153	N	17	144	N	28	N	H	30
22	M	37	-	+	-	38	131	N	8	119	N	9.2	N	H & I	3
23	F	35	-	-	-	29	115	N	1.2	93	N	1.2		H	10
24	F	33	-	-	-	16	107	N	2.9	93	N	1.6	N	H	5

* All patients with (+) had signs of weakness and/or wasting of small muscles of the foot and hyposensation to one or more of the following in a stocking-glove distribution: pinprick, light touch, vibration with or without symptoms (paraesthesiae, numbness, abnormal heat or cold sensation) of a generalised neuropathy.

Abbreviations:

F = female
M = male
\+ = present
\- = absent
N = Normal
Abn = Abnormal
H = Hypophysectomy
I = Irradiation
CTS = Carpal Tunnel syndrome
Nae = Total exchangeable body sodium
GTT = Glucose tolerance test
HGH = Human growth hormone
TRH = Thyrotrophin-releasing hormone

TABLE 2: NEUROPHYSIOLOGICAL DATA: COMPARISON OF NORMAL AND PATIENT GROUPS

Parameter	Group	N	Mean	SD	Units	P
Ankle	Normal	40	1.59	0.82	°C	< 0.001
	Acromegaly	24	4.17	2.16		
Ankle CT	Normal	40	0.18	0.07	°C	< 0.001
	Acromegaly	24	0.43	0.28		
Wrist HT	Normal	40	0.23	0.07	°C	< 0.02
	Acromegaly	24	0.55	0.62		
Wrist CT	Normal	40	0.16	0.05	°C	< 0.03
	Acromegaly	24	0.26	0.21		
Carpal VPT	Normal	27	0.8	0.41	um	NS
	Acromegaly	24	1.21	1.51		
Tarsal VPT	Normal	27	1.63	0.45	um	< 0.05
	Acromegaly	24	4.42	6.13		
Median SDML	Normal	21	3.54	0.35	ms	< 0.02
	Acromegaly	24	3.98	0.77		
Median FMNCV	Normal	21	58.6	4.8	m/s	< 0.05
	Acromegaly	24	54.8	7.66		
Median SNAP latency	Normal	21	2.92	0.26	ms	< 0.01
	Acromegaly	24	3.52	0.99		
Median SNAP amplitude	Normal	21	17.8	7	uv	< 0.01
	Acromegaly	24	11.7	8		
SDML for LPN	Normal	21	3.59	0.44	ms	< 0.001
	Acromegaly	24	4.5	0.9		
FMNCV for LPN	Normal	21	50.5	4.6	m/s	< 0.001
	Acromegaly	24	45.9	3.4		
Sural SNAP latency	Normal	21	3.62	0.44	ms	NS
	Acromegaly	24	3.53	0.42		
Sural SNAP amplitude	Normal	21	6.8	2	uv	< 0.005
	Acromegaly	24	4.8	2.15		

Abbreviations:

HT : heat threshold
CT : cold threshold
VPT : vibration perception threshold
SDML : shortest distal motor latency
FMNCV : fastest motor nerve conduction velocity
SNAP : sensory nerve action potential
LPN : lateral popliteal nerve

TABLE 3: FREQUENCY OF ABNORMALITY OF NEUROPHYSIOLOGICAL PARAMETERS IN 24 PATIENTS WITH ACROMEGALY

Neurophysiological parameter(s)	Criteria of abnormality	Patients with abnormal values	
		No.	%
Ankle HT	99%CL	14	58
Ankle CT	99%CL	9	37
Wrist HT	99%CL	9	37
Wrist CT	99%CL	5	21
Tarsal VPT	95%CL	9	37
Carpal VPT	95%CL	3	12
Median SDML	95%CL	7	29
Median FMNCV	95%CL	6	25
Median SNAP latency	95%CL	7	29
Median SNAP amplitude	95%CL	5	21
SDML for LPN	95%CL	11	46
FMNCV for LPN	95%CL	3	12
Sural SNAP latency	95%CL	1	4
Sural SNAP amplitude	95%CL	3	12
HT and/or CT at ankle	99%CL	15	62
HT and/or CT at wrist	99%CL	10	42
HT and/or CT at wrist and/or ankle	99%CL	16	67
Carpal and/or Tarsal VPT	95%CL	9	37
SDML and/or FMNCV for LPN	95%CL	12	50
Sural SNAP latency and/or amplitude	95%CL	4	17
Abnormal LPN and/or sural NC studies	95%CL	12	50

Abbreviations: As in Table 2

TABLE 4: SUMMARY OF SOME OF THE NEUROPHYSIOLOGICAL TESTS IN 10 PATIENTS WITH ACROMEGALY ASSOCIATED CARPAL TUNNEL SYNDROME.

PATIENT NO.	MEDIAN NERVE				SURAL		LPN	THERMAL THRESHOLDS				VPT	
	MOTOR		SNAP		SNAP			WRIST		ANKLE			
	SDML	FMNCV	Lat	Amp	Lat	Amp	FMNCV	HT	CT	HT	CT	CARPAL	TARSAL
15	4.7	50	4.5	5	4.5	3	44.2	0.15	0.15	2.85	0.25	0.4	0.6
16	4.3	49.5	3.2	12	4	5	45	0.15	0.15	2.95	0.75	0.6	2.2
17	5	53.5	3.8	5	3.3	6	46	0.15	0.15	1.35	0.25	0.2	0.9
18	4.8	49	6.5	0.5	3.4	5	44	0.15	0.15	3.45	0.35	0.8	1.5
22	3.6	50	3.6	12	3.8	6	50	0.25	0.15	3.15	0.25	0.6	1.6
1	6	46	5.4	3.5	4.3	4	43.4	0.35	0.25	5.65	0.35	5.7	45
7	4.2	54.3	4.5	3	3.6	3.5	41.7	1.45	0.95	6.75	1.15	5.6	10.6
9	4.6	60	3.3	7	3.3	3	46.4	0.65	0.28	7.35	0.45	0.7	3.5
19	3.8	55	3.8	4	3.3	3.5	43	1.45	0.35	5.25	0.65	0.8	5.6
21	5.4	46	5.5	2	4.0	4	46	0.35	0.25	4.20	0.75	0.9	2.6

Abbreviations: As for Table 2.

Abnormal values for VPT and thermal thresholds are underlined

TABLE 5: CORRELATIONS BETWEEN TOTAL EXCHANGEABLE BODY SODIUM AND THE NEUROPHYSIOLOGICAL PARAMETERS IN 22 PATIENTS WITH ACROMEGALY

Neurophysiological Parameter	At the time of diagnosis of acromegaly		At present	
	r	P	r	P
Ankle HT	0.69	< 0.001	0.455787	0.02
Ankle CT	0.4347	< 0.05	0.428333	0.02
Tarsal VPT	0.4282	< 0.05	0.290966	NS
Median SDML	0.689	< 0.001	0.584923	0.01
Median SNAP Latency	0.4397	< 0.05	0.447054	0.02
Median SNAP amplitude	- 0.6677	< 0.001	- 0.2489	NS
Sural SNAP amplitude	- 0.679	< 0.001	- 0.424078	0.05
Sural SMAP latency	0.609	< 0.01	0.317485	NS
SDML for LPN	- 0.25	NS	- 0.157554	NS
FMNCV for LPN	- 0.4454	< 0.05	- 0.484736	0.02

Abbreviations: As in Table 2.

APPENDIX 3

MYOTONIC DYSTROPHY

A reassessment by conventional and more recently introduced neurophysiological techniques

by

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SUMMARY

A series of complementary neurophysiological investigations were carried out on 24 patients with myotonic dystrophy to determine the extent of nervous system involvement. Conventional electromyography and nerve conduction studies, computerised motor unit number estimation and motor unit potential analysis, vibration threshold studies and our recently introduced technique for heat and cold threshold estimations were undertaken in all the patients.

The results provide unequivocal evidence of widespread nervous system dysfunction. In many patients there is significant involvement of peripheral large diameter motor and sensory fibres and involvement of small diameter sensory fibres either peripherally and/or centrally.

In the light of these results and others reviewed in the literature, the concept of myotonic dystrophy as a pure myopathy can no longer be sustained.

INTRODUCTION

Myotonic dystrophy is an autosomal dominant multisystem disorder with variable penetrance (Harper 1979) in which dystrophic changes have been observed in the central nervous system (CNS). In the spinal cord, there are normal numbers of anterior horn cells but an increase in glial cells (Walton et al 1977). Diffuse electroencephalographic abnormalities in the form of theta or delta activity are noted in 50-60% of patients (Barwick et al 1965; Lundervold et al 1969; Beijersbergen et al 1980) and in over 50% of patients there is an elevation of the spinal fluid proteins (Refsum et al 1967; Pilz et al 1974). Progressive cerebral ventricular enlargement is found in all patients within five years of diagnosis, indicating a progressive atrophic process (Refsum et al 1967). Mental retardation with reduction in brain weight and microscopic changes in the cellular architecture of the cerebral cortex have been demonstrated (Rosman and Kakulas 1966) and eosinophilic inclusion bodies have been found in the thalamus (Culebras et al 1973; Wisniewski et al 1975).

The muscular wasting has been regarded as myopathic in aetiology on the evidence of both electrophysiological (Simpson 1973; Buchthal 1977) and pathological (Dubowitz and Brooke 1973) studies. The hypothesis that myotonic dystrophy is a pure myopathic disorder has been increasingly challenged. An additional neuropathic component has been postulated (McComas et al 1971a; Panayiotopoulos and Scarpalezos 1975,1976b; Ballantyne and Hansen 1975). An occasional association between myotonic dystrophy and neuropathy has been reported (Maas 1938; Caccia et al 1972a; Wendland 1974; Pilz et al 1974). Charcot-Marie Tooth syndrome (Ziegler and Rogoff 1956; Wald et al 1962; Lukas and Forster 1962), Friedreich's ataxia (Chaco and Taustein 1969) and hypertrophied peripheral nerves (Borenstein et al 1977) have been noted in individual patients.

A number of other observations lend support to the presence of a neuropathic influence. The deep tendon reflexes are lost early in the

disorder (Messina et al 1976; Olson et al 1978). Messina and his co-workers (1976) also demonstrated absent spinal monosynaptic reflexes on both electrical and mechanical stimulation and the frequent absence of the jaw reflex and the R1 component of the blink reflex. Myopathic involvement of intrafusal muscle fibres, as the explanation for the reduced or absent tendon reflexes (Daniel and Strich 1964; Swash 1972), is now regarded as unlikely (Messina et al 1976; Panayiotopoulos and Scarpalezos 1977). Prolongation of the shortest distal motor latency (SDML) and reduction of the fastest motor nerve conduction velocity (FMNCV) have been reported in this disease. (McComas et al 1971a; Caccia et al 1972a,b; Lieberman and O'Brien 1972; Kito et al 1973; Kalyanaraman et al 1973; Ballantyne and Hansen 1974c,1975; Rowinska-Marcinska 1975; Panayiotopoulos and Scarpalezos 1975,1976a,b; Panayiotopoulos 1978; Moniga and Lundervold 1975; Roohi et al 1976,1981; Olson et al 1978; Mechler et al 1982). Rossi et al (1983) have shown reduction of velocity in both rapidly and slowly conducting motor fibres. The prolongation of the duration of the supramaximally evoked muscle action potential (Caccia et al 1972b; Paramesh et al 1975; Ballantyne and Hansen 1975; Panayiotopoulos and Scarpalezos 1975,1976a,b), the significant increase in the temporal dispersion of single fibre muscle action potentials from the same motor unit (Stalberg and Trontelj 1979) and the large areas of the individual motor unit potentials (MUPs) (Ballantyne and Hansen 1975) are compatible with a reinnervation process. A significant reduction in the number of functioning motor untis has been demonstrated (McComas et al 1971a; Ballantyne and Hansen 1975). In EMG, fibrillation-like potentials (Simpson 1973; Paramesh et al 1975; Moniga and Lundervold 1975) and reduced recruitment patterns (Simpson 1973; Panayiotopoulos and Scarpalezos 1977), atypical of primary myopathy (Buchthal 1977; Barwick 1981; Lenman and Ritchie 1983), have been noted. Increased jitter and fibre density values and frequent occurrence of 'paired blocking' and 'double discharges', interpreted to be of neurogenic aetiology,

have been reported using single fibre EMG (Stalberg and Trontelj 1979).

These electrophysiological observations are supported by pathological studies of myotonic dystrophy. Anatomical abnormalities of the intramuscular nerve fibres and motor end plates have been shown (McDermot 1961; Engel and Brooke 1966; Allen et al 1969; Caccia et al 1972a; Paramesh et al 1975). Axonal degeneration, demyelination and lipid inclusion in Schwann cells (Kito et al 1973), and increased terminal branching (McDermot 1961; Woolf and Coers 1981) are further indications of reinnervation.

Minor sensory loss has been reported in patients with myotonic dystrophy (Maas 1938; Kalyanaraman et al 1973; Pilz et al 1974; Borenstein et al 1977; Olson et al 1978; Harper 1979). Slowing of conduction in both peripheral and central large fibre afferent pathways has also been reported (Caccia et al 1972a; Lieberman and O'Brien 1972; Hideo et al 1973; Moniga and Lundervold 1975; Borenstein et al 1977; Thomson et al 1983; Bartel et al 1984), while histological studies have shown both normal (Pollock and Dyck 1976) and reduced (Kito et al 1973; Borenstein et al 1977) numbers of sensory axons in sural nerve biopsies.

This study was designed to further investigate the presence or otherwise of a neuropathic disturbance in this disorder. To this end we have used our recently introduced technique for the study of thermal thresholds (Jamal et al, 1985a), our computerised technique for motor unit number estimation and motor unit potential parameters measurement (Ballantyne and Hansen 1974a,b) and conventional peripheral electrophysiological investigations. Vibration perception thresholds using the technique of Goldberg and Lindblom (1979) were also measured. The results of the application of these techniques in 24 patients with myotonic dystrophy are presented.

METHODS

Electromyography and Nerve Conduction studies:

The electromyography (EMG) and nerve conduction (NC) studies were performed using a Medelec MS6 electromyograph. The fastest motor nerve conduction velocity (FMNCV) and the shortest distal motor latency (SDML) for the right (R) lateral popliteal nerve (LPN) were recorded from surface electrodes over the extensor digitorum brevis (EDB) muscle by conventional techniques (Lenman and Ritchie 1983). The sensory nerve action potentials (SNAPs) were elicited orthodromically in the R median, ulnar and sural nerves. For each SNAP measurement, 64 evoked potentials were averaged. Sensory latencies were measured from the onset of the stimulus artefact to the peak of the negative deflection. Amplitudes were measured from peak to peak. For median and ulnar nerve sensory potential studies, the method of Gilliatt and Sears (1958) was followed. The sural nerve was stimulated at the lateral aspect of the foot immediately inferior and anterior to the lateral malleolus and the potential recorded by surface electrodes 12-14 cm proximal to the malleolus and lateral to the tendoachillis. The distance between the recording and the reference electrodes was 4 cm. Electromyographic studies were performed with concentric needle electrodes in the abductor pollicis brevis, the extensor digitorum brevis, the first dorsal interosseous, the biceps and the deltoid muscles. The presence or absence of spontaneous activity at rest and of the characteristic high frequency discharge on needle insertion or mechanical stimulation of the muscle were noted and the density of the recruitment pattern on maximal volition was assessed subjectivly. The duration, amplitude, shape and numbers of phases of single motor unit potentials (MUPs) evoked by minimal voluntary effort, were measured. The EMG and NC studies were performed by two investigators (GAJ and AIW). The ambient room temperature was kept at 22 ± 2°C. Skin temperature of the limb was maintained at 34 ± 1°C using a thermostatically controlled heating lamp.

Motor unit numbers and motor unit parameters measurement:

The composition and placement of the surface electrodes over the extensor digitorum brevis (EDB) muscle, the properties of the stimulating electrodes over the anterior tibial nerve at the ankle, and the details of the rate and strength of stimulation used to evoke motor unit potentials have been described (Ballantyne and Hansen 1974a). The amplification and display systems, the computer handling of data for the estimation of motor unit numbers in the EDB muscle, and the computer derivation of the parameters of the electrically evoked motor unit potentials have also been reported (Ballantyne and Hansen 1974 a,b).

Briefly, motor unit potentials (MUPs), recorded from surface electrodes over the EDB muscle, are evoked sequentially by finely graded incremental stimulation of the anterior tibial nerve at the ankle. Recruitment of up to 15 motor units can be recognised by a combination of visual and computer analysis of the muscle action potential increments displayed on the oscilloscope screen. The first MUP is displayed in isolation on the oscilloscope, the potential of the second is incorporated in a compound muscle action potential containing MUPs 1 and 2. As each new potential is added to the preceding one, the compound muscle action potential so constituted is stored in a computer memory (template). Template 1 contains MUP 1, template 2 contains the sum of MUPs 1 and 2, template 3 contains the sum of MUPs 1,2 and 3, and so on. Up to 15 templates can be stored. The number of motor units (MUN) in the EDB muscle is calculated from the formula:

$$MUN = \frac{A\ (M)}{A\ (N)} \times N$$

where A (M) = the area of the supramaximally evoked muscle action potential and A (N) = the area of the compound muscle action potential containing N MUPs.

By a process of template subtraction, the computer also displays the first and sequentially recruited MUPs in isolation. For example, subtraction of

template 1 from template 2 will leave MUP2 in isolation, subtraction of template 2 from 3 will leave MUP3 in isolation, and so on. The latencies, durations, amplitudes and areas of individual MUPs are then measured. Amplitudes and areas are provided by the computer while latencies and durations are measured manually from a computer printout (Ballantyne and Hansen 1974b). All potential recordings are from surface electrodes over the EDB muscle.

Thermal thresholds measurement:

Heat threshold (HT) and cold threshold (CT) values were determined for the volar aspect of the R wrist just proximal to the distal wrist crease and for the medial aspect of the R ankle behind the medial malleolus. These were expressed in temperature change from the basic skin temperature (before application of the stimulus) using a microcomputer controlled system and the two-alternative forced-choice method of psychophysical analysis. The method has been described in detail in a previous paper (Jamal et al 1985a). The components of the system are shown in Figure 1 and the following is a summary of the technique. The microprocessor system controls the stimulating probe (the thermode) and performs the forced-choice trials. The thermode is constructed from an array of semiconductor thermo-electric elements with a stimulating surface area of 12.5 cm^2 and operates on the Peltier principle. On the background of a constant skin temperature (34-35^oC), the thermode applies a quantified thermal (heat or cold) stimulus to the skin tested. The subject is placed in a comfortable position and the thermode is applied to the area of the skin tested with a standard pressure. A number of trials are performed. In each trial, the subject is presented with two periods during which a null stimulus and an actual thermal stimulus are applied and the periods are indicated to him by two lights illuminated in sequence. The order of assignment of the actual and the null stimuli to the period is randomised

by the microcomputer and is unknown to the subject and the examiner. At the end of each trial the subject must choose that period during which he/she felt or thought he/she felt the stimulus. Depending on the response, the computer will alter the stimulus strength applied during the next trial according to the up-and-down transform rule (UDTR) (Wetherhill et al 1966). The stimulus power is kept constant such that the rate of change of temperature at the skin surface is $1^{o}C/s$. The strength of the thermal stimulus is altered by changing its duration of application. The threshold is calculated as the mean of at least 12 separate trial values in accordance with the UDTR. The investigation is carried out in a quiet room temperature of $22 \pm 2^{o}C$. HT is determined first followed by CT. The time required to determine both HT and CT for one site is usually 15-20 minutes. All investigations were carried out by the same person (GAJ).

Vibration threshold measurement:

Vibration perception thresholds (VPT) were measured in all subjects on the dorso-medial aspect of the middle of the R first metatarsal bone where the overlying subcutaneous tissue is thin. The technique, its physiological basis and normal values have been described (Goldberg and Lindblom 1979). Briefly the vibration stimulus intensity is assessed from the displacement of the skin in micrometers and not from the voltage applied to the vibrameter as in earlier techniques. The degree of displacement of skin is the physiological stimulus to the vibration sensitive receptors (Lindblom and Lund 1966; Goldberg and Lindblom 1979). The apparatus (SOMEDIC AB VIBRAMETER type III) consists of an electromagnetic vibrator with a 13 mm diameter probe which vibrates at right angles to the skin. The amplitude of the skin displacement (the vibration amplitude) is measured indirectly by an accelerometer with continuous digital display. The vibrator was held against the skin with a force of of 500 ± 100 g by reference to a force indicator on the Vibrameter. The subject is placed in a comfortable position, the R leg is supported by

pillows to prevent stimulus spread and a suprathreshold test stimulus is applied to familiarise him/her with the sensation produced. The apparatus can deliver two standardised rates of increase in stimulus intensity, slow or fast. The amplitude of vibration is increased using one of these alternatives and the subject is instructed to indicate when he/she feels the stimulus. The vibration amplitude at this time is recorded. The procedure is repeated at the alternative rate of increase of stimulus intensity. The average of three trials is the VPT. In cases where there is more than 10% variation between the values, further trials are performed until 3 consecutive readings are within the 10% limit.

Vibration amplitudes in the range of 0-399.9 micrometers at 100 Hz can be produced by the apparatus. The VPT determinations are made in a quiet room with a constant ambient temperature (22 $\pm$ 2^{o}C). Skin temperature was kept at 34 $\pm$ 1^{o}C with a thermostatically controlled heat source. On the average less than 5 minutes was required for each VPT determination. All investigations were carried out by the same person (GAJ).

PATIENTS AND CONTROL SUBJECTS

The normal values for various tests come from different control groups. Healthy control subjects were drawn from among the staff and their relatives of the Institute of Neurological Sciences, Southern General Hospital, Glasgow. There were 106 control subjects for the thermal thresholds aged 6 to 73 (mean 33, SD = 17) years. A comprehensive description and selection of this control group and their normal HT and CT values have been described elsewhere (Jamal et al, 1985a). The control group for the EMG, NC studies, the motor unit number estimation and MUP parameters measurement contained 21 healthy subjects aged 23 to 69 (mean = 46 SD = 12) years. The control group for the vibration threshold measurement consisted of 27 subjects aged 17 to 64 (mean = 46.2, SD = 11.5) years.

Patients

Twenty-four patients, 12 male and 12 female with myotonic dystrophy were studied. Their ages ranged from 15 to 63 (mean = 45.7, SD = 11.8) years. The duration of clinical symptoms varied from 0.2 to 22 (mean = 8.4, SD = 6.5) years. All patients were attending the Institute of Neurological Sciences, Southern General Hospital, Glasgow. The diagnoses of myotonic dystrophy had been made by the referring neurologist, confirmed electrophysiologically by two of us (GAJ and AIW) and further supported in five cases by muscle biopsy. The illness varied in severity from patient to patient. None of the patients had been on any drug with possible effects on peripheral nerves. Impaired glucose tolerance was excluded in all cases. In some there was minimal clinical evidence of myotonic dystrophy but confirming electrophysiology, in others there was moderately severe muscle weakness and wasting leading to a degree of functional impairment. No attempt was made to grade the clinical severity of the disease. All patients were ambulant and none had such severe paresis of any limb as to render it immobile. In moderately or severely wasted limbs, the presence of entrapment neuropathy was excluded

neurophysiologically.

A family history was obtained of either proven myotonic dystrophy or of a neuromuscular disorder in 15 (62.5%) patients. In 13 of these patients, a first degree relative (parent or sibling) was affected. In 4 of the remaining 9 patients, with a negative family history early cataract and/or frontal baldness was present in at least one of their first degree relatives.

Muscle wasting was present in 19 (79%) patients, but in 16 it was mild. Twenty-three patients had distal muscle weakness. Seven patients had proximal weakness in addition to the more severe distal weakness. Deep tendon reflexes were absent or reduced in 21 (87%) patients. The distal tendon reflexes eg the ankle (87%) and the supinator (83%) were more frequently affected. No patient with abnormal knee jerk (42%) had a normal ankle jerk. Similarly no patient with an abnormal biceps and/or triceps jerks (75%) had a normal brachioradialis jerk.

Subjective sensory symptoms in the form of paraesthesiae, numbness, feelings of coldness or heat were present in the extremities in 13 (54%) patients. Five patients volunteered these symptoms and 8 agreed their presence on direct questioning (Table 1). One patient alone of the 13 (4%) had hypoalgesia to pinprick, touch and vibration in a stocking distribution.

All but two patients had clinically demonstrable myotonia of the grip (92%). Eight patients (33%) had myotonia of eyelids. The two patients without clinical evidence of myotonia were found to have such on EMG. Ten patients (42%) had bilateral ptosis. An electrocardiogram (ECG) was recorded in all the patients; 13 patients (54%) showed an abnormality; either cardiomyopathy (29%) and/or cardiac conduction defects (42%). Muscle biopsy was performed in 5 patients. In one patient, both neuropathic and myopathic changes were found. In the remaining 4, the appearances were reported as "characteristic" of myotonic dystrophy. All the patients were fully informed of the nature and the purpose of the investigations undertaken. The clinical data of the 24 patients with myotonic dystrophy are summarised in Table 1.

RESULTS

The statistical significances of the results were evaluated using the student's 't' test. The results of the neurophysiological assessments of the control subjects and the myotonic dystrophy patients are summarised in Table 2. The distribution and the relative frequencies of the abnormalities for some of the neurophysiological tests are shown in Figure 2. Values in excess of the 99th percentile were considered abnormal for all the tests.

Sural sensory nerve action potential (SNAP) amplitude and/or latency were abnormal in 17% of the patients. No abnormality of median and ulnar SNAPs was noted. The shortest distal motor latency for the LPN was significantly increased in 17% and the FMNCV for the LPN was significantly reduced in 25% of the patients. One patient (4%) had abnormal MUN in the EDB muscle (Table 3).

Thermal thresholds at one or both sites were abnormal in 20 of the 24 patients studied (83%). Thermal threshold abnormalities were generally more marked and more frequent at the ankle (79%) than at the wrist (50%). HT was more frequently abnormal than CT. Abnormal vibration threshold at the first metatarsal bone was present in 21% of patients (Table 3).

Most of the neurophysiological tests were significantly abnormal in the myotonic dystrophy patients. Thermal and vibration thresholds, latencies of the sural SNAPs and the SDML for the LPN were all significantly higher than control values; the sural SNAP amplitude, the FMNCV for the LPN and the MUN in the EDB muscles were all significantly lower in the myotonic dystrophy patients compared to the control groups (Table 2).

No correlation was found between age or duration of symptoms and the neurophysiological parameters studied in the myotonic dystrophy patients. The duration of symptoms in these patients is notoriously difficult to estimate and may account in whole or part for the lack of correlation.

DISCUSSION

Our results indicate the presence of a significant neuropathic abnormality in myotonic dystrophy involving both the motor and sensory systems. The significantly reduced FMNCVs and prolonged SDMLs seen in our patients compared to normal subjects (Table 2) are in agreement with reports in the literature (see Introduction). Deep tendon reflexes were diminished or absent, particularly distally in 87% of our patients (Table 1) similar to the pattern of involvement in peripheral neuropathy, again in agreement with reports in the literature (Messina et al 1976; Panayiotopoulos and Scarpalezos 1977; Olson et al 1978).

The significant reduction in the number of functioning motor units in the EDB in myotonic dystrophy patients (Table 2) is similar to the findings of McComas et al (1971a) and Ballantyne and Hansen (1974c). The EDB muscle is particularly suited to the technique of MUN estimation because it is easily accessible, relatively isolated from other muscles on the dorsum of the foot, has a compact and linear end plate zone (McComas et al 1971b) and is thin enough that a surface electrode can record from all the units therein. It has been claimed that this muscle is unsuitable for electrophysiological studies as it shows evidence of denervation in life in normal subjects (Flack and Alaranta 1983; Gatens and Saeed 1976). This objection is of no consequence since the variability thereby introduced is expressed within the standard deviation of the control mean. There is no published evidence that this denervation is greater in pathological conditions studied to date.

A significant increase in the mean MUP duration was seen in the myotonic dystrophy patients compared with normal subjects (Table 2). The MUP duration, when recorded from a relatively large surface area, is determined by the lengths of the muscle fibres, the propagation velocities of the action potentials in these muscle fibres, the degree of dispersion of the endplate zone of the unit and the differences in conduction time through the intramuscular nerve network of the motor unit (Ballantyne and Hansen 1975).

It is unlikely that prolongation of the duration of the MUP is due to a reduction in the propagation velocity of the action potential in individual muscle fibres as conduction velocities in dystrophic muscle fibres are reported to be normal despite the known variation in muscle fibre diameter (Buchthal et al 1960; Buchthal and Rosenfalck 1963; Stalberg and Trontelj 1979). In normal subjects the differences in conduction time through the intramuscular nerve twigs of the motor unit make a relatively small contribution, in the order of 0.5 ms, to the duration of the MUP (Buchthal et al 1957). The MUP duration may, however, be significantly prolonged when there is pathological slowing of conduction in the intramuscular nerve network (Ballantyne and Hansen 1975,1978; Martinez-Figueroa et al 1977). This slowing of conduction in the intramuscular nerve fibres accentuates the differences in their conduction times and reduces the temporal synchronisation of the muscle fibre action potentials of the motor unit. The significant negative correlation of the mean MUP duration with MUN and FMNCV and positive correlation with SDML (Table 4) lends support to this hypothesis.

The MUP latency is the time taken for a nerve impulse generated at the point of stimulation of the axon its point of branching inside the EDB muscle, plus the conduction time over the shortest intramuscular twigs and the delay at the neuromuscular junction. The mean latency of the MUPs was significantly increased in the myotonic dystrophy patients (Table 2) and correlated positively with the SDML and negatively with the FMNCV and MUN (Table 4). That the prolongation of the MUP latency is at least in part due to the presence of immature collateral sprouts from reinnervation is supported by reports of histological abnormalities (Allen et al 1969; Kito et al 1973) and of abnormal impulse conduction (Stalberg and Trontelj 1979) in the intramuscular nerve fibres in myotonic dystrophy. Reduced conduction velocity has been reported to occur in immature collateral sprouts in reinnervating conditions (Desmedt and Borenstein 1976). A disproportionate loss of the

faster conducting motor axons with their shorter SDMLs is another possible contributing factor. The latency would also be prolonged if there were a disturbance of neuromuscular transmission. A decrementing muscle action potential to repetitive stimulation is known to occur in this disorder (McComas et al 1971a; Messina et al 1976), but is probably due to blocking of transmission in the intramuscular nerve fibres (Stalberg and Thiele 1972). Furthermore the histological abnormalities of the motor end plates in myotonic dystrophy were thought to be a consequence of denervation (McDermot 1961; Schroder 1970).

The MUP area, an index of increase in the muscle fibre mass in the motor unit (Ballantyne and Hansen 1975), was significantly increased in the myotonic dystrophy patients (Table 2) and had a significant negative correlation with the MUN (Table 4). This is further evidence for the acquisition, by collateral reinnervation, of muscle fibres from denervated motor units (Wohlfart 1958).

In myotonic dystrophy, the MUP parameters in the EDB muscle indicate that the action potentials from surviving motor units are of greater area, longer duration and increased latency compared to those of control subjects and that there is a progressive increase in these parameters as the number of the motor units fall ie, a reduction in MUN is accompanied by an increase in the amount of collateral reinnervation by the surviving motor units.

The long duration, high amplitude MUPs in myotonic dystrophy patients obtained by the surface recording technique contrasts with the findings of conventional needle EMG which show a preponderance of short duration, low amplitude and often polyphasic MUPs (Simpson 1973; Buchthal 1977). The reduction in duration of the motor unit potentials on needle EMG is a consequence of the reduced muscle fibre density in the motor units whereby the early and late positive components are lost (Buchthal et al 1960). In the normal individual these components are produced by volume conduction to the relatively small recording surface of the concentric needle electrode of

action potentials of distant muscle fibres (Buchthal et al 1960) and these are reduced in numbers in myotonic muscular dystrophy. The potential recorded with the much larger surface electrode is more indicative of the number of muscle fibres in the motor unit than their spatial distribution (Kaeser 1970). These circumstances leading to the shortening of the MUPs found in needle studies do not occur with surface electrodes.

The abnormalities of the sural SNAP occurred in 17% of the patients. This change indicates peripheral large fibre afferent pathway dysfunction (Buchthal et al 1984). Abnormal VPTs in the foot were found in 37% of patients. This indicates involvement of the peripheral and/or central large fibre afferent pathway (Goldberg and Lindblom 1979). The VPTs showed a significant negative correlation with the sural SNAP amplitude and a significant positive correlation with the sural SNAP latency. These correlations suggest that the reduction in vibration sensitivity is at least partly of peripheral origin. There is also evidence of a defect in the central large fibre afferent pathway in this disorder on the basis of SSEP studies (Moniga and Lundervold 1975; Thomson et al 1983; Bartel et al 1984).

HT and/or CT for ankle and/or wrist were abnormal in 20 patients (83%) with myotonic dystrophy. The technique examines the small fibre thermal afferent pathways as a whole and cannot distinguish between peripheral and central involvement (Jamal et al 1985b). However, the greater frequency of abnormalities of thermal thresholds at the ankle (83%) compared to the wrist (42%)is similar to the pattern of somatic sensory abnormalities found in patients with peripheral neuropathy. Our studies of SNAP parameters, thermal and vibration thresholds lend further support to earlier claims of sensory abnormalities in myotonic dystrophy patients (see Introduction).

CONCLUSION

The results of the application of a number of independent neurophysiological techniques show clearly that in addition to the previously described myopathy, patients with myotonic dystrophy have significant dysfunction of peripheral motor and large and small sensory fibre pathways. In the light of these results and those of other workers, the concept of myotonic dystrophy as a pure myopathy can no longer be sustained.

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TABLE 1: Summary of clinical data of 24 patients with myotonic dystrophy

	Number		Percentage
Family History (FH)			
positive FH (total)		15	62.5%
In parents or siblings	13		
In aunts or uncles	2		
negative FH (total)		9	37.5%
negative FH of myotonic dystrophy but positive FH of cataract and/or frontal baldness	4		
Muscle weakness and/or wasting (total)		23	96%
mild muscle wasting	16		
moderate-severe muscle wasting	3		
distal muscle weakness	23		
distal and proximal muscle weakness	7		
Absent or diminished reflexes (total)		21	87%
absent or diminished ankle jerk	21		
" " brachioradialis jerk	20		
" " biceps/triceps jerk	18		
" " knee jerk	10		
Myotonia on clinical examination (total)		22	92%
myotonia of grip	22		
myotonia of eyelids	8		
Myotonia on EMG examination (total)		24	100%

TABLE 1 (cont.)

Subjective sensory symptoms (total)		13	54%
paraesthesiae	10		
numbness	9		
abnormal heat or cold sensation	2		
Objective sensory signs (total)		1	3.7%
pinprick	1		
touch-pressure	1		
vibration	1		
Ptosis (total)		10	42%
bilateral ptosis	10		
Abnormal ECG (total)		13	54%
cardiomyopathy (total)	7		
cardiomyopathy alone	3		
conduction defect (total)	10		
conduction defect alone	6		
cardiomyopathy and conduction defects	4		

EMG = electromyography

ECG = electrocardiography

TABLE 2: Comparison of neurophysiological parameters between normal control groups and patients with myotonic dystrophy

Parameter		Group	N	Mean	SD	P
Ankle HT	[°C]	Normal	106	1.35	0.73	< 0.0001
		MYD	24	5.1	1.63	
Ankle CT	[°C]	Normal	106	0.17	0.06	< 0.002
		MYD	24	0.49	0.41	
Wrist HT	[°C]	Normal	106	0.23	0.06	< 0.005
		MYD	24	0.47	0.37	
Wrist CT	[°C]	Normal	106	0.15	0.05	< 0.0001
		MYD	24	0.26	0.10	
Sural SNAP amplitude	[/uV]	Normal	21	6.8	2	< 0.0001
		MYD	24	3.5	2.2	
Sural SNAP latency	[ms]	Normal	21	3.62	0.44	< 0.0002
		MYD	24	4.3	0.64	
Median SNAP amplitude	[/uV]	Normal	21	17.8	7	< 0.03
		MYD	24	13.9	6.8	
Median SNAP latency	[ms]	Normal	21	2.92	0.26	NS
		MYD	24	3.0	0.3	
Ulnar SNAP amplitude	[/uV]	Normal	21	12	5.5	< 0.02
		MYD	24	8.7	4	
Ulnar SNAP latency	[ms]	Normal	21	2.87	0.25	NS
		MYD	24	2.82	0.5	
Vibration threshold (foot)	[/um]	Normal	27	1.63	0.45	< 0.05
		MYD	24	2.43	1.73	

Parameter		Group	N	Mean	SD	P
SDML (LPN)	[ms]	Normal	21	3.59	0.44	< 0.0005
		MYD	24	4.42	0.77	
FMNCV (LPN)	[m/s]	Normal	21	50.5	4.6	< 0.0001
		MYD	24	42.2	6.2	
MUN (EDB muscle)		Normal	21	200	54	< 0.0001
		MYD	24	106	41	
Mean MUP latency	[ms]	Normal	21	4.62	0.66	< 0.002
		MYD	24	5.56	1.12	
Mean MUP amplitude	[/uV]	Normal	21	60.5	12.7	NS
		MYD	24	74.7	44.9	
Mean MUP duration	[ms]	Normal	21	9.4	1.2	< 0.0002
		MYD	24	12.6	3	
Mean MUP area		Normal	21	17.0	4.0	< 0.01
		MYD	24	23.3	10.4	

HT = heat threshold
CT = cold threshold
MYD = myotonic dystrophy
SNAP = sensory nerve action potential
SDML = shortest distal motor latency
FMNCV = fastest motor nerve conduction velocity
LPN = lateral popliteal nerve
EDB = extensor digitorum brevis
MUP = motor unit potential
MUN = motor unit number

TABLE 3: Frequency of abnormality* of neurophysiological parameters in 24 patients with myotonic dystrophy

Neurophysiological parameter(s)	No. of patients with abnormal values	% of patients with abnormal values
Ankle HT	19	79
Ankle CT	18	75
Wrist HT	10	42
Wrist CT	7	29
Vibration threshold	5	21
Sural SNAP amplitude	1	4
Sural SNAP latency	4	17
FMNCV (LPN)	6	25
SDML (LPN)	4	17
MUN (EDB muscle)	1	4
HT and/or CT at wrist and/or ankle	20	83
HT and/or CT at ankle	19	79
HT and/or CT at wrist	12	50
Sural SNAP amplitude and/or latency	4	17
FMNCV and/or SDML of LPN	8	33

*Values in excess of the 99th percentile were considered abnormal for all the tests.

HT = heat threshold
CT = cold threshold
MYD = myotonic dystrophy
SNAP = sensory nerve action potential
SDML = shortest distal motor latency
FMNCV = fastest motor nerve conduction velocity
LPN = lateral popliteal nerve
EDB = extensor digitorum brevis
MUP = motor unit potential
MUN = motor unit number

TABLE 4: Correlations referred to in text

Correlation between			r	P
Ankle HT	-	Sural SNAP amplitude	-0.671	< 0.01
Ankle HT	-	MUN (EDB muscle)	-0.604	< 0.01
Ankle HT	-	Vibration threshold	-0.433	< 0.05
Ankle CT	-	Sural SNAP amplitude	-0.429	< 0.05
Ankle CT	-	MUN (EDB muscle)	-0.422	< 0.05
Ankle CT	-	Vibration threshold	-0.546	< 0.01
Vibration threshold	-	Sural SNAP amplitude	-0.410	< 0.05
Vibration threshold	-	Sural SNAP latency	0.433	< 0.05
MUN (EDB muscle)	-	Mean MUP latency	-0.668	< 0.01
MUN (EDB muscle)	-	Mean MUP amplitude	-0.496	< 0.02
MUN (EDB muscle)	-	Mean MUP duration	-0.467	< 0.05
MUN (EDB muscle)	-	Mean MUP area	-0.563	< 0.01
FMNCV (LPN)	-	SDML (LPN)	-0.788	< 0.01
FMNCV (LPN)	-	Mean MUP area	-0.449	< 0.05
FMNCV (LPN)	-	Mean MUP latency	-0.805	< 0.01
FMNCV (LPN)	-	Mean MUP duration	-0.605	< 0.01
SDML (LPN)	-	Mean MUP latency	0.887	< 0.01
SDML (LPN)	-	Mean MUP duration	0.769	< 0.01

HT = heat threshold
CT = cold threshold
SNAP = sensory nerve action potential
SDML = shortest distal motor latency
FMNCV = fastest motor nerve conduction velocity
LPN = lateral popliteal nerve
EDB = extensor digitorum brevis
MUP = motor unit potential
MUN = motor unit number

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An improved automated method for the measurement of thermal thresholds. 1. normal subjects

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An improved automated method for the measurement of thermal thresholds. 1. normal subjects

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SUMMARY Clinical tests of thermal sensation are poorly quantified and not strictly modality specific. Previous automated thermal testing systems have had limited usefulness with high intra- and inter-individual variability. This paper describes an automated thermal system (Glasgow system) which is an extensive modification of previous techniques to answer these criticisms. It comprises a microprocessor-driven Peltier element and utilises the forced choice method of psychophysical analysis to determine the thresholds to thermal stimulation. In a control group of 106 healthy subjects the mean heat threshold for the wrist was found to be 0·23°C (SD = 0·06°C) and the mean cold threshold 0·15°C (SD = 0·05°C). Repeated determinations showed a maximum of 5% intra-individual variation in comparison to previously reported values of up to 150%.

Clinical disorders of sensation are common in neurological practice and are assessed routinely at the bedside clinical examination. However, lack of sensitivity and quantitation limits the usefulness of these techniques. Early modifications of the clinical techniques of measurement of thermal sensation were inaccurate and insufficiently reproducible.[1,2] Kenshalo introduced a thermo-electric method employing the Peltier principle,[3,4] where the direction of current flowing in a metal thermode caused either heating or cooling. The amount of current passed gave an accurate measure of the amplitude of the stimulus. In addition, the skin temperature beneath the stimulator could be maintained at a constant predetermined value ± 0·2°C. The technique was the first to apply the stimulus without tactile cues, countering the objection that tactile stimulation of slowly adapting mechanoreceptors could be the basis for appreciation of a cold stimulus.[5] Later modifications included continuous water circulation through the element to maintain background skin temperature, allowing the heat pumping capacity of the thermode to be reserved exclusively for the test studies.[6]

Simple measurements of thresholds were superseded by the "Marstock method" where the temperature interval between the perceptual thresholds for warm and cold stimuli was defined as the most sensitive index of neural abnormality.[7–9] In this interval, the "warm-cold difference limen", no thermal sensation is appreciated. These short-term studies were repeated over periods of minutes but longer term studies repeated over days showed an unsatisfactory intra-individual variation of up to 150% between estimations.[10] This variability was attributed to central processing mechanisms although variation due to patient bias and reaction time had not been excluded.

The most recent studies have used automated control systems to operate the Peltier element and the "forced-choice" method of psychophysical analysis to exclude patient bias.[11,12] However, no reports of intraindividual variation were included.[12]

This study was designed to modify the current techniques to improve sensitivity and reduce intra-individual variability to allow meaningful longitudinal studies of disorders of sensation.

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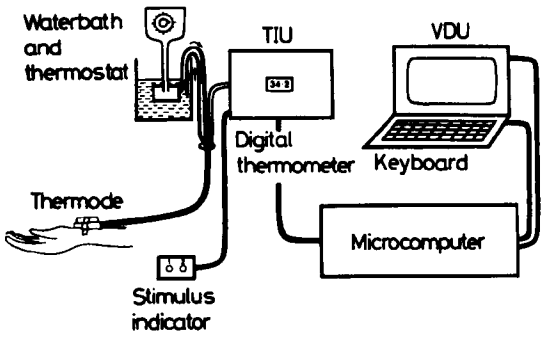

Fig 1 *The Glasgow Automated Thermal System. TIU = Thermode Interface Unit; VDU = Visual Display Unit.*

Design

The Glasgow thermal system is made up of the following components: a thermode, a thermode interface unit (TIU) with a digital thermometer; a stimulus indicator, a microcomputer assembly, a waterbath with a thermostat, a visual display unit (VDU) with keyboard for communication with the computer (see simplified diagram, fig 1).

The stimulating thermode, with a surface area of 12·5 cm^2, is constructed from arrays of semiconducting thermo-electric elements operating by the Peltier principle. An aluminium block is mounted on the top of the thermode and is continuously perfused with circulating water at a constant temperature (34·0 ± 0·1°C) from the waterbath. The thermode surface, in contact with the skin, is heated or cooled according to the direction of the current. A thermocouple, bonded to the centre of the thermode, measures the temperature of the skin in contact with the thermode continuously. This is displayed by the digital thermometer on the TIU. The TIU contains a thermocouple amplifier with analogue to digital converter and a digital to analogue converter. The former measures and displays the skin temperature while the latter provides input to a power amplifier which drives the thermode.

The thermal stimulus output from the thermode is determined by three terms in the heat flow equation (1) The pumped Peltier heat [proportional to the current input (I)]. (2) The joule heat generated by the flow of the current through the thermode (proportional to I^2). (3) The heat leak back due to the difference in temperature between the junctions.

In order to maintain a specified constant power output level, it is necessary to calculate the thermode current continuously from the heat flow equation. This task is performed by the microcomputer once every 100 ms. During the sampling interval the current is constant (equal to zero if no stimulus is applied). At the end of this interval the error in the power output, due to change in temperature difference between junctions, is less than 1%. The duration of the stimulus is in multiples of the sampling intervals. A stimulus always starts and ends at the computer sampling times. The stimulus is graded by altering its duration while the power and thus the rate of change of temperature, is constant (see below).

The stimulus indicator is a small box with two light emitting diodes numbered 1 and 2 (fig 1). It is handed to the subject to watch during testing. In the testing procedure, each light is illuminated in sequence to indicate two separate time periods. During one of the periods there is a null stimulus while during the other a real stimulus is presented to the subject. The order of stimulus application is assigned randomly by the computer and is unknown to both the subject and the operator (it may be made known to the operator if desired). At the end of the trial, the subject must choose the period during which he felt the stimulus (that is forced-choice method[13]). The answer is entered into the computer which then scores a success (S) or a failure (F). This triggers the computer to give the next stimulus which is of the same, longer or shorter duration according to the up-and-down transform rule (UDTR).[12 14] The UDTR is modified in our technique so that initially, the stimulus duration, starting at 6 seconds, is reduced in steps of 1 second for each S until the first F which changes the direction upwards. It is after this first change in direction that the standard UDTR begins and the steps of change in stimulus duration are then of 100 ms. For the standard UDTR, programming is such that F, SF or SSFF causes a 100 ms change to a higher value while SSS or SSFS causes a 100 ms change to a lower value. After six changes in direction (excluding the first one following the initial large steps) the threshold is calculated as the mean of the points of change in direction. The threshold value is given as the change from the basic skin temperature and

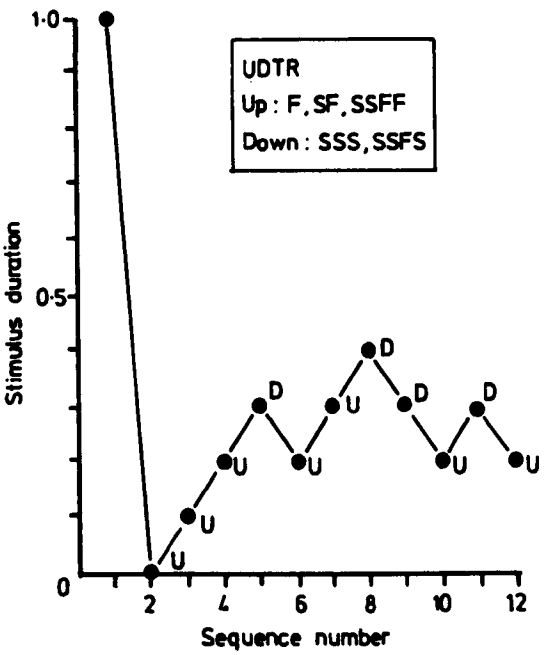

Fig 2 *The graphical representation of stimulus duration (in seconds) and sequences used in the determination of each thermal threshold. UDTR = Up-and-Down Transform Rule, F = failure, S = success.*

displayed on the VDU. Figure 2 shows a typical series of trials. The avarage number of trials needed to determine one threshold for one site was 15 (that is lasting about nine minutes). The UDTR could be started from one to nine seconds stimulus duration. In all of the normal subjects the test was started from one second stimulus duration. These modifications have two important advantages. First they allow a fast approach to the threshold level and reduce the test time considerably and secondly, they provide up to 90 levels of stimulus duration. This makes the technique very precise in determining the threshold value. In another automated method using UDTR re 21 levels of stimulus intensity are available, ma , normal people fall outside the available range.[11,12] The microcomputer system not only controls the thermode current but also runs the forced-choice trials and the modified UDTR.

There are certain critical aspects of the apparatus design that require further descriptions. These are as follows:

1 *Thermode size.* The Peltier based thermode stimulating area of 12·5 cm² (25 mm × 50 mm) was selected as the most suitable for the skin sites examined. The variability of thermal thresholds increases with small sized probes[15] and complete contact with the skin is difficult with larger probes.

2 *Thermode application.* The thermode pressure on underlying skin was standardised at all sites in all subjects by adding a fixed weight to the thermode. The total mass of the thermode and the additional weight was 350 g. The alteration of the cutaneous circulation caused by the application of the thermode was thought to be negligible (fig 1).

3 *Initial skin temperature.* The initial skin temperature under the probe was always kept between 34–35°C. In a few cases this was only achieved by changing the temperature of the circulating water. This is important as variation in the initial skin temperature causes variability in the thermal thresholds.[1,15,17] At this chosen range (34–35°C) the influence on thermal thresholds is minimal and complete and quick adaptation to temperature sensation occurs.[1,16,17]

4 *Rate of change of temperature.* The rate of change of temperature was kept constant throughout in all the sites and all the subjects. Thermal thresholds, the peak discharge frequency and the cumulative number of impulses in warm nerve fibre units from human skin vary considerably with variations of rate of temperature change.[1,7,10,16–24] The effect of this rate change is variable in different people.[1] The variation in thermal thresholds and impulse discharge frequency are at their lowest between 0·5–1·5°C/s and greatest at rates below 0·1°C/s.[1,21,25] A rate of change of 1°C/s which is the middle of the preferred range, was selected as most suitable for human skin areas[7] and could be maintained fairly constant over a wide range of skin temperatures with the thermode used.

The selected rate approaches conditions of daily experience with thermal sensation.[22] With a rate of 1°C/s, the numerical value of change of skin temperature in °C is equal to the duration of stimulus application in seconds.

5 *Calibration of the thermode.* The thermode is calibrated on each application in all the subjects. The exact power (and hence the current) needed to obtain a rate of 1°C/s is calculated. Heat transfer and exchange in the skin depend not only on the power applied but also on the physical properties of the skin (see below). The power needed to give the same rate (1°C/s) of temperature change ranged between 2800–4200 mW being higher for the ankle and lower for the wrist and forearm.

6 *Stimulus sites.* Four different sites for thermal stimulation on the right side were used: (a) The volar aspect of the wrist just proximal to the distal wrist crease, (b) The medial aspect of the ankle where the lower edge of the probe lies posterior to the medial malleolus, (c) The volar aspect of the mid-forearm, (d) The anterior aspect of the thigh midway between the anterior superior iliac spine and the tip of the patella. In order to study contralateral variations, the homologous site on the left forearm was also tested.

Thermal properties of the skin show marked variations between sites leading to differences in the thermal sensitivity of the skin of these sites.[25–31] These regional variations are greatest at threshold levels.[30] The amount of energy transferred to the receptor zone determines thermal sensation[1] which in turn depends on skin thermal conductivity.[27,30] This varies with its physical architecture, chemical and fluid composition, homogeneity of various skin layers, initial skin temperature and most important of all, the epidermal thickness.[27,31] The thicker the epidermis, which acts as an insulating layer, the greater is the resistance against heat transfer to the receptor zone.[27,31] Epidermal thickness varies considerably between sites and from individual to individual.[31] At the volar aspect of the wrist and forearm (sites (a) and (c)) the epidermis is relatively thin with only negligible interindividual variation.[31]

Subjects and methods

One hundred and six healthy control subjects, aged between 6–73 (mean = 33, SD = 17) years, all free of neurological illness and none taking drugs or excessive quantities of alcohol were examined. Of these 45 were male and 61 female. None of them had previous experience of sensory testing. The tests were carried out in a quiet room at a constant temperature of 22 ± 2°C. Five sites as described were studied in each patient. The subject was placed in a comfortable position so that the thermode and the weight, taped in place, acted perpendicularly on the site tested. Each subject was placed such that he/she could not see the VDU screen or the digital thermometer on the TIU. All measurements were carried out by the same person (GAJ). The subject was then handed the stimulus indicator and instructed that the two lights would illuminate in sequence at intervals of 30 seconds. With one of the lights a hot (or cold) stimulus would be applied, immediately following which the subject was forced to choose in which time period the stimulus occurred. Whenever felt necessary, a short demonstration of the test was carried out. Heat Threshold (HT) was determined first followed by Cold Threshold (CT). Some subjects were tested for all sites in the morning (n = 39), others in the afternoon (n = 35) while a third group was tested during

Table 1 *Thermal threshold values for 106 normal subjects*

Site	*Type of threshold*	*Mean °C*	*Standard deviation °C*	*Upper limit of normal (99% CL) °C*
Wrist	HT	0·23	0·06	0·40
	CT	0·15	0·05	0·27
Forearm	HT	0·24	0·06	0·41
	CT	0·15	0·05	0·29
Thigh	HT	0·23	0·06	0·40
	CT	0·15	0·05	0·27
Ankle	HT	1·35	0·73	3·28
	CT	0·17	0·06	0·32

HT = heat threshold CT = cold threshold
These threshold values represent the change from the basic skin temperature.

both periods (n = 32). Both HT and CT determinations were repeated in the right forearm three times at intervals of 24 hours (between the first and the second) and more than two weeks (between the first and the third). In some cases the second interval was up to two months. These intervals were chosen to assess the short and long term reproducibility of the threshold measurement.

Results

Table 1 summarises the results of thermal threshold values given as the deviation from basic skin temperature with mean, standard deviation (SD) and 99% upper confidence limit for the various sites tested. The normal mean HT for the wrist was 0·23°C (SD = 0·06°C). The CT was 0·15°C (SD = 0·05°C).

(1) There was no significant difference in the thermal thresholds between males and females. (2) Both the mean HT and CT and respective SD showed a trend to increase with age at the ankle (fig 3A, B). Many older subjects, however, were as sensitive as younger subjects. There was also a significant linear increase of these thresholds with age for the wrist CT ($r = 0{\cdot}321$; $p < 0{\cdot}001$) but not in the case of wrist HT ($r = 0{\cdot}017$; NS). In 80 subjects above the age of 20 years, the leg length measured from the anterior superior iliac spine to the tip of the medial malleolus did not correlate with HT ($r = 0{\cdot}0225$) or CT ($r = 0{\cdot}195$). As expected, there was also no correlation between age and leg length ($r = 0{\cdot}0249$). Subjects above age 20 were selected for this correlation because of the epiphyseal closure after which minimal growth of the leg length occurs. (3) The results of repeated determinations performed on the right forearm are summarised in table 2. The largest deviation from the initial determinations was 5%. Analysis of variance of heat threshold determination showed significant difference only between the first and the third test two or more weeks later ($p < 0{\cdot}01$). However, the difference between the first and the third test for HT was approximately one third of the smallest available step in stimulus intensity (see Design). This small change is of no practical significance in the implementation of the technique. No significant difference was noticed between the first and second testings for heat threshold and between first, second and third tests for cold thresholds (table 2). There was a weak trend towards lower values with consecutive determinations of both HT and CT values. (4) After the initial three determinations were done, a further 17 were undertaken daily on two subjects. The range of variation in threshold values was 0 to 0·03 °C corresponding to a coefficient of variation of 0 to 6%. This is also much less than the smallest available step in stimulus duration. (5) There was no significant correlation between age and the intraindividual variation in the right forearm HT expressed as the difference between first and third determinations ($r = 0{\cdot}189$). (6) There was no significant difference between thermal threshold measured at different times of the day

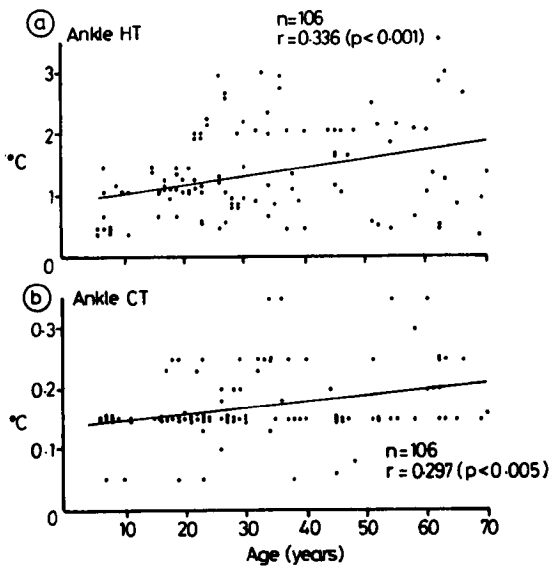

Fig 3 *(A) Ankle cold threshold (CT) changes with age. (B) Ankle heat threshold (HT) changes with age.*

Table 2 *Consecutive thermal thresholds comparing repeated ipsilateral and contralateral investigations in 106 normal subjects*

Site and type of the thermal threshold	*Mean °C*	*Standard deviation °C*	*Change in Mean*
HT—R Forearm 1st	0·243	0·063	
2nd (24–48h)	0·236	0·061	−2·9% } from 1st investigation
3rd (2 wk)	0·230	0·059	−5·3% } from 1st investigation
L Forearm	0·229	0·059	−0·4% from R side
CT—R Forearm 1st	0·152	0·052	
2nd (24–48 h)	0·151	0·050	−0·6% } from 1st investigation
3rd (2 wk)	0·148	0·051	−2·6% } from 1st investigation
L Forearm	0·142	0·046	−4% from R side

HT = heat threshold CT = cold threshold
For a discussion of the statistical significance see text

(morning or afternoon) either for HT (t = 0·0524) or for CT (t = 0·0114).

Discussion

The consistently lower values for thermal thresholds obtained by our technique contrasts with the higher values obtained by the Marstock method using an identical probe.[7] In the latter method the subject was required to switch off the heating (or cooling) one the sensation was appreciated. This introduces a considerable error as once the perception threshold was reached, thermal stimulation continued for a period of time equal to the delay in the afferent pathway (delay of perception) and the subject's reaction time. The measured threshold was therefore greater than the real threshold by the heat produced over that time interval. In our method, where the time of application of heat is predetermined by the computer, this problem does not arise.

We have found that thermal thresholds varied only slightly between wrist, forearm and thigh (table 2). The SDs were almost half the smallest step in the stimulus intensity. Ankle HT and to a lesser extent CT were higher than elsewhere. The reasons for this increase are not known. We have already shown that leg length does not contribute in this context. Thermal thresholds are known to vary in different sites.[1 11 15 26 27 29–31] The skin of the calf has been found to be the least sensitive especially at threshold levels.[27 30 31] This may be due to differences in the thermal properties of the skin.[27 31] A considerable variation in the density of thermal receptors from one region of the skin to another has been reported.[11 30 32] The density of the heat receptors is absolutely less but their variability is greater than that of the cold receptor.[33] If these thermal receptors are present in a lower density distally, such might explain the higher thresholds at ankle. It also remains possible that central processing influences temperature appreciation at different sites.

The inter-individual variation by our technique remains small (table 1), even at the ankle where variability is greatest, compared with the variation in the Marstock method.[7 10] In their automated method Dyck *et al*[11 12] have not produced figures for this variability, but examination of their results suggests that it is indeed large. We have extracted data from their graph of normal thermal-cooling thresholds at foot where the range of values at the ages between 10–20 years are from 0·2 to 4°C and at the ages between 60–70 years from 0·3 to 8°C.[11] The ankle CT range of values for the corresponding age groups with our technique are 0·05–0·25°C and 0·15–0·37°C respectively.

The increase of thermal thresholds with age (figure 3A, B) is expected and has been reported in other studies.[1 7 11 12] This may be due to a progressive reduction in the number of nerve fibres with age,[11 12] and/or a decrease in the number of receptors per nerve fibre.[32] Alternatively, changes in the functional properties of these fibres and/or end organs in the absence of structural changes may be of importance.[11] The increase in thermal thresholds with age was greatest at the ankle.

Intra-individual variation for CT was negligible (table 2). A slight but statistically significant variation of HT between the first and third test, done two or more weeks later, was noted ($p < 0·01$) but not between the first and second or the second and third. However, the greatest change observed was less than 5%, much less than those reported in other studies where differences of up to 150% were found.[10] This small intra-individual variation in our technique, which was less than 15% of the SD and smaller than the smallest step in stimulus intensity, is unlikely to influence the usefulness of the technique for longitudinal follow up of patients. The changes were always towards lower values, perhaps suggesting that a learning process is operative. Intra-

individual variability in the technique most closely related to ours[11 12] is not reported.

The main advantages of the Glasgow method over others in the literature are as follows:
(1) the intensity of the thermal stimulus is varied by altering the stimulus duration. The rate of change of temperature is constant throughout at 1°C/s, (2) The thermode is calibrated at each site in each subject to measure the exact amount of power required to obtain a rate of temperature change of 1°C/s.This reduces errors due to differences in the thermal properties of the skin at different sites, (3) The thermode pressure on the underlying skin is standardised at all sites, (4) The larger probe reduces the variability of the response,[15] (5) The skin sites chosen are those with the smallest variability in thermal properties, (6) The initial skin temperature under the probe is always in the range of 34–35°C. This significantly reduces variability in thermal thresholds,[11 15–17] (7) Threshold determinations take a short time (15–20 minutes for both HT and CT determinations at one site).

We anticipate that this technique will have a wide application in the assessment of function in the thermal pathways and in the study of clinical and subclinical abnormalities of thermal sensation. It will also be valuable in the serial follow up of patients to monitor the progress or the response of an illness to a treatment regimen.

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SUMMARY Thermal thresholds were determined by a new technique, at wrists and ankles in 143 patients with peripheral neuropathies of diverse aetiologies. Ninety-nine percent of patients (141/143) had abnormalities of one or both thresholds. In only two patients with mild/early Friedreich's ataxia were thermal thresholds normal. Electromyography was performed and fastest motor nerve conduction velocities and sensory nerve action potential parameters were measured in all the patients using conventional techniques in ulnar, median and sural nerves. Eighty-nine percent of patients (127/143) had one or more abnormalities on these electrophysiological studies. However, 39 of 40 patients with completely normal sensory nerve studies had an abnormality of one or more thermal thresholds. Eighty-six percent of 48 patients with normal sural nerve studies had abnormal thermal thresholds at the ankle. Sixty percent of 70 patients with normal sensory median and ulnar nerve studies had abnormal wrist thermal thresholds. This improved technique for the determination of thermal thresholds reveals that disturbances of thermal sensibility are present in the majority of peripheral neuropathies irrespective of aetiology. In some patients disturbances of thermal thresholds antedate the appearance of abnormalities on conventional electrophysiological investigation. The findings suggest that this technique has considerable usefulness in the detection of small nerve fibre dysfunction in the context of generalised neuropathy.

Thermal sensation depends on impulses reaching the central nervous system by adequate stimulation of thermal receptors. These impulses are carried exclusively in the non-myelinated (C) and the thinly myelinated (Aδ) fibres.[1] Activity in these fibres is not adequately tested by conventional electrophysiological methods.

The literature on the measurement of the perception threshold of heat and cold sensations has been reviewed in a previous paper.[2] We have shown that by modification of some of the available methods, reliable quantitative and reproducible indices of the functional integrity of these endorgans and fibre populations, can be obtained.[2] We believe that this method may be useful for the detection of dysfunction in the small fibre population of peripheral nerves as an early manifestation of peripheral neuropathy and to detect small fibre damage in ongoing generalised neuropathy.

The present paper describes the result of application of this new technique for thermal threshold measurement in a large group of patients with neuropathy from different causes. The primary aim was threefold: (1) to illustrate the clinical usefulness of the technique, (2) to evaluate the frequency of involvement of the small unmyelinated and thinly myelinated fibres in neuropathy in general, (3) to compare the sensitivity of this technique with electromyography and nerve conduction studies in the early diagnosis and the ongoing assessment of peripheral neuropathy.

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Methods

Electromyography and nerve conduction (EMG and NC) studies

These were undertaken on a Medelec MS6 electromyograph. The fastest motor conduction velocity (FMCV) and the shortest distal motor latency (SDML) for the right (R) common peroneal and median nerves were obtained recording from surface electrodes over the target muscle by conventional techniques.[3] The amplitude and duration of the compound muscle action potential, so evoked, were also measured. Sensory action potentials (SAP) were elicited orthodromically in the R median, ulnar and sural nerves. For each SAP measurement, 64 evoked potentials were averaged. Sensory latencies were measured from the onset of the stimulus artefact to the peak of negative deflection. Amplitudes were measured from peak to peak. For median and ulnar nerve sensory potentials, the method used by Gilliatt and Sears[4] was followed. The sural nerve was stimulated at the lateral aspect of the foot immediately inferior and anterior to the lateral malleolus and the potential recorded by surface electrodes 12–14 cm proximal to the malleoli lateral to the tendo Achillis. The distance between the recording and the reference electrodes was 4 cm. Electromyographic studies were performed with concentric bipolar needle electrodes in one or more of the following muscles: the R extensor digitorum brevis, the R tibialis anterior and the first dorsal interosseous muscles. The ambient room temperature was kept at 22 ± 2°C. Skin temperature of the limb was maintained at 34 ± 1°C using a thermostatically controlled heating lamp.

Thermal thresholds measurement

Heat thresholds (HT) and cold thresholds (CT) were determined using a microcomputer controlled automated system incorporating the two alternative forced-choice method of psychophysical analysis.[2] Two distal sites, relevant for examination of polyneuropathy, were selected. These were the volar aspect of the R wrist just proximal to the distal crease and the medial aspect of the R ankle behind the medial malleolus, two sites identical to those examined in the control group. The ambient temperature of the room was kept constant at 22 ± 2°C. Thermal threshold determinations for controls[2] and patients were carried out by the same person (GAJ).

Patients and control subjects

The control subjects for the thermal thresholds consisted of 106 healthy volunteers aged between 6–73 (mean = 33; SD = 17) years. Full description of selection of these subjects and their HT and CT values are described separately.[2] The control group for the EMG and NC studies were 42 healthy subjects aged between 18–59 (mean = 35; SD = 10) years. There were 143 patients with polyneuropathy of varied severity and aetiology. Most were ambulant and in good general health. All were cooperative and informed. Their age ranged between 9–77 (mean = 49; SD = 16) years. The mean duration of neuropathy was 48 months with a range of 2 days–40 years. The causes of the neuropathy are summarised in table 1.

Full general and neurological examination was performed on all the patients and any abnormalities of touch, pinprick and vibration were noted. Full laboratory examination was undertaken to determine the aetiology of the neuropathy.[5,6] The diagnosis in the suspected cases of hereditary aetiology was established by the clinical examination and laboratory investigation of the patients and relatives.

The aetiology of the polyneuropathy was determined in 70% of the patients. In 47% an acquired cause (toxic, metabolic-endocrine, autoimmune, paramalignant or allergic) was responsible whle hereditary factors were operative in 23%. In the remaining 30%, no cause was discovered (table 1).

Table 1 *Classification of the 143 neuropathy cases by aetiology*

Aetiology	*Number and percentage*
Acquired known cause (total)	67 (46·8%)
Diabetes mellitus	30
Hypothyroidism	3
Alcoholic neuropathy	10
Blood disorders (folate, Vit B12 deficiency)	3
Rheumatoid arthritis	2
Porphyric neuropathy	1
Carcinoma associated	2
Guillaine Barré Syndrome	4
Heavy metals (for example, mercury, lead)	5
Drugs (for example, phenytoin, aminodarone, thalidomide, isoniazid)	7
Hereditary neuropathies (total)	33 (23·1%)
HMSN type I	13
HMSN type II	9
HMSN type IV (Refsum's syndrome)	1
HSN type II	1
Friedreich's ataxia	5
Hereditary spastic paraplegia and neuropathy	3
Retinitis pigmentosa and neuropathy	3
Idiopathic (total)	43 (30·1%)

HMSN = hereditary motor sensory neuropathy
HSN = hereditary sensory neuropathy

Table 2 *Clinical, conventional electrophysiological and thermal threshold assessment of 143 patients with neuropathy*

Evidence for neuropathy	*Number and percentage*
One or more symptoms of neuropathy (total)	109 (76%)
pain	53
paraesthesia	86
numbness	63
weakness and/or fasciculation	81
autonomic	42
altered thermal feeling	69
One or more signs of neuropathy (total)	114 (79·7%)
abnormal touch	77
abnormal vibration	76
abnormal pinprick	94
weakness, wasting and/or fasciculation	80
Abnormal EMG and/or NC studies (total)	127 (88·8%)
abnormal one or more SAP	103
abnormal sural SAP	95
abnormal ulnar and/or median SAP	73
Abnormal one or more thermal threshold (total)	141 (98·6%)
Abnormal ankle: HT	125
CT	127
HT & CT	114
CT or HT	141
Abnormal wrist: HT	88
CT	70
HT & CT	56
HT or CT	102
Abnormal ankle HT & CT and wrist HT & CT	55

EMG & NC: electromyography and nerve conduction
SAP: sensory action potential
HT: heat threshold
CT: cold threshold

Results

Table 2 summarises the clinical, electrophysiological and thermal studies on these patients. Abnormality of thermal thresholds was considered to be present if values exceeded the 99th percentile. Abnormality of conduction was considered to be present if values exceeded the 95 percentile of the corresponding normal mean. Normal values for the thermal thresholds are described in detail elsewhere.[2] Normal values for nerve conductions are summarised in Table 3. One hundred and nine of the 143 patients studied (76%) had one or more symptoms known to be associated with neuropathy[7] while 114 (79·7%) showed some abnormality of sensation on clinical examination for one or more of the modalities tested. EMG and/or NC studies were abnormal in 127 (88·8%) patients, of whom 103 (72%) had an abnormality of the amplitude, duration and/or latency of one or more of the SAPs determined. In 40 patients (28%) all of these parameters (amplitude, duration and latency) of the ulnar, median and sural SAPs were within the normal range. Sixty-eight of the 143 (47·5%) showed abnor-

Table 3 *Normal nerve conduction values for 42 healthy subjects at skin temperature of 34 ± 1°C*

I Normal SAP values						
	Latency		*Amplitude*		*Duration*	
Nerve	*Mean ms*	*SD ms*	*Mean μV*	*SD μV*	*Mean ms*	*SD ms*
Median	2·92	0·26	17·8	7·4	1·26	0·16
Ulnar	2·87	0·25	12·0	5·5	1·16	0·17
Sural	3·62	0·44	6·8	2·0	2·17	0·42
II Normal FMCV and SDML values						
	SDML		*FMCV*			
Nerve	*Mean ms*	*SD ms*	*Mean m/s*	*SD m/s*		
Common peroneal	3·6	0·5	50·5	4·6		
Median	3·5	0·3	58·6	4·8		

SAP: sensory action potential (orthodromic, surface recording)
FMCV: fastest motor conduction velocity
SDML: shortest distal motor latency
SD: standard deviation

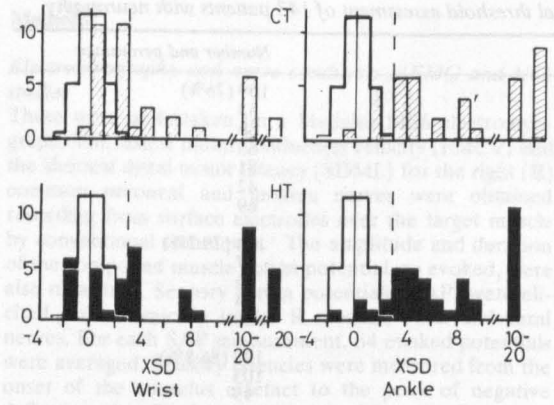

Fig 1 *Ankle and wrist thermal thresholds in 40 patients with normal sensory median, ulnar and sural nerve studies on conventional electrophysiology; vertical axis = number of patients; horizontal axis = multiples of standard deviation (×SD) from normal control mean; open histogram = normal control values distribution; solid vertical line = mean value for normal controls; dashed vertical line = 3 × SD above normal control mean; HT = heat threshold; CT = cold threshold.*

malities in the ulnar and/or median SAP. Ninety-five of the 143 (66%) showed abnormalities in the sural nerve SAP. One or more of the thermal thresholds determined were abnormal (outside the 99th percentile) in 141 patients (98·6%). Only one patient, a recently diagnosed case of Friedreich's ataxia, with abnormal sural SAP had normal thermal thresholds.

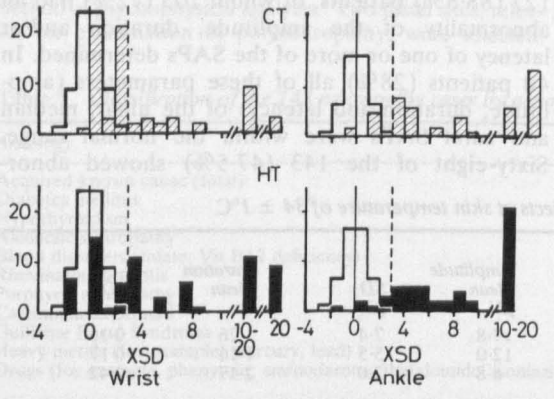

Fig 2 Fig 3

Fig 2 *Wrist thermal thresholds in 70 patients with normal sensory ulnar and median nerve studies on conventional electrophysiology. (symbols as in fig 1)*

Fig 3 *Ankle thermal thresholds in 48 patients with normal sensory sural potential on conventional electrophysiology. (symbols as in fig 1)*

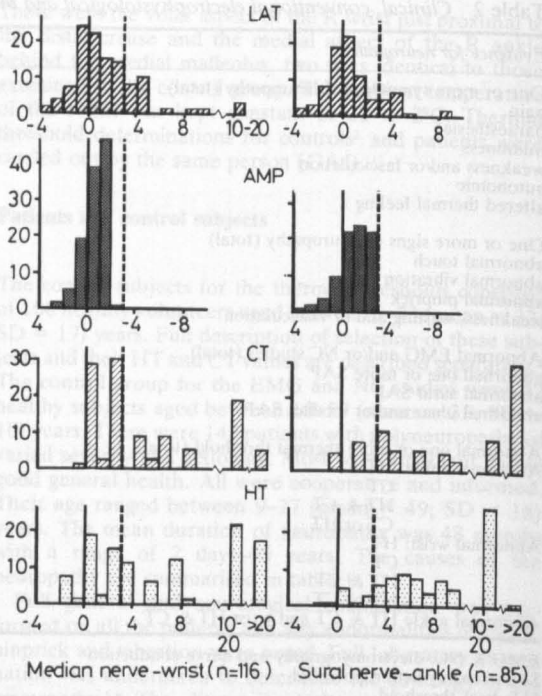

Fig 4 *Comparison of conventional sensory electrophysiological studies and thermal thresholds in patients with neuropathy†. vertical axis = number of patients; horizontal axis = multiples of standard deviation (×SD) outwith the normal control mean*; solid vertical lines = mean value for normal controls; dashed vertical lines = 3 × SD above normal control mean; LAT = latency of the sensory action potential (SAP); AMP = amplitude of the SAP; CT = cold threshold; HT = heat threshold; †patients with absent median SAP (when compared with wrist thermal thresholds) and those with absent sural SAP (when compared with ankle thermal thresholds) are excluded. *negative values are on the right side of zero in the AMP histogram as these represent abnormalities of amplitude.*

The other patient, a female aged 17 years also with a recently diagnosed Friedreich's ataxia, had both the thermal threshold values and the sural SAP studies within normal limits. Abnormalities of thermal thresholds were generally more marked at the ankle (98·6%) than the wrist (71·3%). It is noteworthy that in nine asymptomatic patients with minor abnormalities in EMG, known to have disease predisposing to neuropathy, there was no abnormality on NC studies. These nine patients were found to have significant abnormalities of one or more of the thermal thresholds.

Discussion

The results of the application of the Glasgow

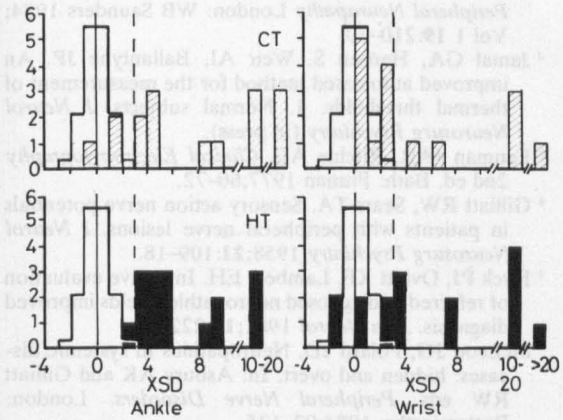

Fig 5 *Ankle and wrist thermal thresholds in 16 patients with clinical evidence of neuropathy but normal conventional electrophysiological (EMG and NC) studies. (symbols as in fig 1)*

method to patients with peripheral neuropathy underlines its usefulness in these disorders. Abnormalities of thermal sensation were detected in 141 patients (98·6%) compared to 79·7% on clinical examination of the sensory system and 72% on sensory conduction studies (table 2). While significant alterations of thermal thresholds were most often observed in patients with concomitant abnormalities on clinical and electrical test, they also occurred in isolation. Similar observations have been reported by other workers using different methods.[8] Among 40 patients with normal SAP studies in the median, ulnar and sural nerves (fig 1), 34 (85%) had ankle HT and CT outside the 99th percentile while 20 (50%) had abnormal wrist HT and CT values. One of more thermal thresholds were abnormal in 39 (97·5%) of the 40 patients. Figure 2, from 70 patients with normal ulnar and median SAPs, shows wrist HT and CT values expressed in multiples of the standard deviation (×SD) for the control group outside the normal mean. In 42 (60%) of these, one or both wrist thermal threshold values were abnormal. Figure 3, from 48 patients who had normal sural SAP, shows ankle HT and CT values. These thermal threshold values were abnormal in 86% of the patients.

Although abnormality within the central nervous system cannot be entirely excluded in patients with neuropathy, with certain exceptions (for example, hereditary neuropathies) one can assume that the abnormal thermal threshold values were mostly due to dysfunction of the peripheral fibre population subserving thermal sensation and/or their end organs. The observation that fewer patients had abnormal values from wrist compared to ankle, is compatible with the increasing severity of dysfunction distally in peripheral neuropathy.

The SAP parameters, indices of the functional integrity of the large diameter afferent fibres, and the thermal thresholds, indices of the functional integrity of the small diameter afferent fibres, were compared. Patients with absent SAP, all of whom had abnormal thermal threshold values, were excluded. Latencies and amplitudes of the R median and sural nerves were compared with HT and CT of the wrist and the ankle respectively. To facilitate this comparison, each value was expressed as a figure representing the ×SD outside the corresponding normal mean and the histograms plotted in fig 4. Again the standard deviation used is that of the corresponding control parameter. None of the SAP amplitude values was more than 3 × SD outside the normal mean and few had their SAP latency values outside this value. The majority of patients had their thermal threshold values in excess of 3 × SD above the normal mean. This emphasises the sensitivity of our technique in assessing small fibre function compared to available conventional methods.

The thermal thresholds for wrist and ankle were also correlated with the corresponding SAP parameters. Patients with absent SAP were again excluded. The most consistently significant correlation was with the SAP amplitude, a measure of loss of large afferent fibres in neuropathy.[9] A reduction in the median (or ulnar) SAP amplitude was accompanied by an elevation of the wrist HT ($p < 0{\cdot}05$) and CT ($p < 0{\cdot}05$). The same correlation was obtained between the sural SAP amplitude and ankle HT ($p < 0{\cdot}02$) and CT ($p < 0{\cdot}001$) values. These findings suggest that in most neuropathies a more or less parallel drop occurs in both fibre population groups but not necessarily to the same extent in each type of neuropathy. This appears to be true of the neuropathies in general.[10 11]

In 16 patients, no abnormality of EMG and NC studies was found. All, except one with recently diagnosed Friedreich's ataxia, had symptoms and signs of peripheral nerve dysfunction. Another patient with paraesthesiae in the feet, had taken phenytoin for several years. The remaining 14 of the 16 had clinical features to suggest involvement of small fibres, for example spontaneous pain in the extremities, diminished pain and temperature sensation and autonomic features, for example orthostatic hypotension, disturbances of sweating, disturbances of genito-urinary function (intermitted stream, post micturition dribbling, retention with overflow incontinence and failure of erection and ejaculation), disturbances of bowel function and nocturnal diarrhoea.[7 11 12] Muscle strength, tendon reflexes and other sensory modalities (touch-

pressure, vibration and joint position) were preserved in these patients. Diabetes mellitus was the underlying cause in eight but no obvious cause was discovered in the remaining six patients. Figure 5 gives a summary of the thermal threshold values for these 16 patients. All the 14 patients with small fibre dysfunction and the patient on phenytoin had abnormal thermal thresholds. In the patient with Friedreich's ataxia, all the threshold values were normal. Normal thermal threshold values have been observed before in patients with Friedreich's ataxia, in which the large afferent fibres are more severely affected.[12] This technique, therefore, is specifically useful in cases of neuropathy where small fibre dysfunction may be the earliest or the only abnormality and also in assessing a concomitant small fibre dysfunction in somatic neuropathies.

In conclusion, the data presented in this study clearly show the superiority of our technique over clinical testing in detecting small fibre involvement in peripheral neuropathy even in the absence of clinical or other electrophysiological evidence of dysfunction. In combination with other electrophysiological techniques testing large afferent fibre function, it gives a good idea about the pattern of involvement of various fibre populations in peripheral neuropathies.

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Sensory involvement in motor neuron disease: further evidence from automated thermal threshold determination

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Sensory involvement in motor neuron disease: further evidence from automated thermal threshold determination

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SUMMARY Thermal thresholds were determined in 40 patients with motor neuron disease and in 40 age- and sex-matched healthy subjects. The thermal thresholds were estimated on the skin of wrist and ankle using an automated microprocessor controlled system and the "two alternative forced-choice method" of psycholphysical analysis. Abnormalities of thermal thresholds (≥99th percentile) were seen in 80% of the motor neuron disease patients. The results are in agreement with reports of sensory pathway involvement in the literature. Thermal threshold abnormalities are common in motor neuron disease and indicate the involvement of the small fibre afferent pathways.

Most authorities consider motor neuron disease to affect exclusively the motor system. Subjective sensory symptoms are however not uncommonly reported and variously described as paraesthesiae, coldness, prickling, numbness, aches and pains.[1–5] Objective sensory abnormalities in contrast are rare[3–5] but nevertheless occasional reports of objective dysfunction have appeared implicating all modalities including pain and temperature sensation.[6–9]

At necropsy, degeneration of posterior columns[1 2 7 10–14] and anterior and lateral columns of the spinal cord outwith the cortico-spinal tract,[6 12–15] loss of neurons in the posterior horns,[1 2 11 13 16] abnormalities in the parietal lobe,[1] degeneration in the thalamus[14] and abnormalities in the posterior root ganglia and dorsal roots[2 16] have been described. Pathological abnormalities in peripheral sensory pathways have also been found[2] and Dayan *et al* 1969 have demonstrated primary Schwann cell damage in sensory nerves.[17] Shahani *et al* 1971,[18] found evidence of abnormal resistence of peripheral sensory nerves to ischaemia in most patients with motor neuron disease. The literature therefore supports the possibility of both peripheral and central sensory abnormalities in these patients, albeit mild when compared with those of the motor system. They are as a rule of insufficient severity to produce clinically detectable changes of sensation[3–5] or significant abnormalities using conventional electrophysiological techniques.[19 20] In a single study, however, one of 13 patient with motor neuron disease, had an absent median sensory nerve action potential as an isolated finding and minimal impairment of vibration sense and two point discrimination.[21]

More sophisticated quantitative techniques have demonstrated abnormalities of touch-pressure, vibration and thermal cooling sensations in a small number of patients.[2 22] In a recent study,[23] two-thirds of motor neuron disease patients had abnormalities of somatosensory evoked potentials and in one-third of these, the abnormalities were thought to arise in the peripheral sensory pathways.

The above observations suggest that more sophisticated techniques for the quantification of sensation might provide further confirmation and a higher incidence of dysfunction in the sensory pathways in patients with motor neuron disease. The purpose of this study was to use such a technique (The Glasgow thermal system[24]) to define thermal thresholds in motor neuron disease as an index of sensory dysfunction and to quantify the severity of this dysfunction.

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Table 1 *Summary of clinical data of 40 motor neuron disease patients*

	Number		*Percentage*	
Type amyotrophic lateral sclerosis		*37*		
Progressive muscular atrophy		*3*		
Cramps (total)		*34*		*85%*
lower & upper limbs	27		67·5%	
lower limbs (LL) alone	7		17·5%	
upper limbs (UL) alone	0			
Muscle wasting (total)		*33*		*82·5%*
UL > LL	18		45%	
LL > UL	6		15%	
both nearly equal	9		22·5%	
Bulbar weakness (total)		*10*		*25%*
mild	6		15%	
moderate-severe	4		10%	
Fasciculations (clinically overt) (total)		*31*		*77·5%*
tongue alone	1		2·5%	
tongue (total)	16		40%	
generalised	8		20%	
Sensory symptoms (total)		*19*		*47·5%*
ache	15		37·5%	
paraesthesia	10		25%	
coldness of extremities	9		22·5%	
abnormal heat	4		10%	
numbness	7		17·5%	

While some patients spontaneously volunteered the occurrence of cramps and sensory symptoms, most did not but did confirm their presence on direct questioning. Sensory symptoms were recurrent and each bout lasted for about 15 minutes.

Patients, controls and methods

Forty patients with motor neuron disease were included in this study. Their age ranged between 36 and 73 (mean = 56·7, SD 11·2) years. There were 25 male and 15 female patients. This sex ratio of 1·6:1 is in agreement with most other published series.[1 22 25] The duration of the symptoms varied between 2–72 (mean = 17·1, SD = 16·8) months. In all the patients the diagnosis of motor neuron disease had been made on clinical grounds by the referring neurologist and was confirmed electrophysiologically (EMG and nerve conduction studies) by ourselves using established criteria.[26] In particular, no patient, with objective sensory abnormality or abnormality of sensory action potential was included. Any cases which did not fully satisfy our clinical and electrophysiological criteria were excluded from the study. All the patients were ambulant, well nourished and none of them had severe paresis of any limb. In wasted limbs, the possibility of entrapment neuropathy was excluded electrophysiologically. None had a family history of neuromuscular disease. All the patients were fully informed of the nature and the purpose of the investigation undertaken. The clinical data of the 40 motor neuron disease patients is summarised in table 1.

The control group consisted of 40 healthy age- and sex-matched subjects. The age and sex distribution of the control and the motor neuron disease group is presented in table 2.

Heat threshold (HT) and cold threshold (CT) values were determined for the volar aspect of the right (R) wrist just proximal to the distal wrist crease and for the medial aspect of the right ankle behind the medial malleolus. These were expressed in °C from the basic skin temperature (before application of the stimulus) using a microprocessor controlled system and the two-alternative forced-choice method of psychological analysis.[27] The method has been described in detail in a previous paper,[24] but the following is a précis of the technique. The microprocessor system controls the stimulating probe (the thermode) and performs the forced-choice trials. The thermode is constructed from an array of semiconductor thermo-electric elements with a stimulating surface area of 12·5 cm^2 and operates on the Peltier principle. On the background of a constant skin temperature (34–35°C), the thermode applies a quantified thermal (heat or cold) stimulus to the skin tested. The subject is placed in a comfortable position so that the thermode is applied with a standard pressure. A number of trials are performed. In each trial, the subject is presented with two periods during which a null stimulus and an actual thermal stimulus is applied and the periods are indicated to him by two lights in sequence. The order of assignment of the actual and the null stimuli to the periods is randomised by the microcomputer and is unknown to the subject and the examiner. At the end of each trial the subject must choose that period during which he/she felt or thought he/she felt the stimulus. Depending on the response, the computer will alter the stimulus strength applied during the next trial according to the up-and-down transform rule (UDTR).[28] The stimulus power is kept constant such that the rate of change of temperature at the skin surface is 1°C/s. The strength of the

Table 2 *Age and sex distribution of motor neuron disease patients and control subjects*

		Motor neuron disease	*Control*
Total No.		40	40
Age range (yr)		36–73	36–73
Age groups	36–49 (yr)	12	13
	50–59 (yr)	8	9
	60–73 (yr)	20	18
Mean Age (yr)		56·7	55·9
SD		11·2	10·9
Sex distribution	Male	25 (62·5%)	25 (62·5%)
	Female	15 (37·5%)	15 (37·5%)

Table 3 *Thermal threshold values for the motor neuron disease patients and the normal control subjects*

Thermal threshold		*Normal subjects (40)*		*Motor neuron disease patients (40)*		*Test of significance*	
		mean	*SD (°C)*	*mean*	*SD (°C)*	*t*	*p*
wrist	HT	0·23	0·06	0·51	0·34	5·13	<0·0001
wrist	CT	0·17	0·05	0·26	0·14	3·83	<0·0001
ankle	HT	1·53	0·68	4·81	2·05	9·61	<0·0001
ankle	CT	0·18	0·06	0·67	1·03	3·00	<0·005

HT = heat threshold. CT = cold threshold

thermal stimuli is altered by changing its duration of application. The threshold is calculated as the mean of at least 12 separate trial values in accordance with the UDTR. The investigation is carried out in a quiet room at a temperature of 22 ± 2°C. HT is determined first followed by CT. The time required to measure both HT and CT for one site is usually 15–20 minutes. All investigations were carried out by the same person (GAJ).

Results

The mean and SD of HT and CT for the 40 healthy control subjects and the 40 motor neuron disease patients are presented in table 3. Since the control group of this study is of significantly greater mean age, the mean values for thermal thresholds are slightly higher than those in our previously published control group.[24] All the thermal thresholds, both HT and CT, were significantly increased in patients with motor neuron disease (table 3).

Abnormality of thermal thresholds was considered to be present when the value in motor neuron disease patients exceeded the 99th percentile. Table 4 provides a summary of the thermal thresholds testing in the 40 motor neuron disease patients. Thirty two of the 40 patients (80%) had an abnormality of one or more thermal thresholds. All patients with abnormal wrist HT and CT had abnormal ankle thresholds. Abnormalities of thermal thresholds were more frequent at ankle (80%) than at wrist (55%) (see table 4).

The figures shows HT and CT values in motor neuron disease patients for wrist and ankle expressed in multiples of the standard deviation (×SD) from control mean values. Ankle HT values were more than 3 × SD above the normal mean in 60% of the patients and ankle CT values were more than 3 × SD above the normal mean in 55% of the motor neuron disease patients. At the wrist, 45% had HT values more than 3 × SD above the normal mean while 12·5% had CT values 3 × SD above the normal mean.

Discussion

Several pathological studies in the literature have demonstrated the presence of degeneration in both central and peripheral sensory pathways in motor neuron disease.[1,2,6,7,10–17] In general these abnormalities are not associated with clinical sensory loss during life but Brownwell *et al*[14] reported one such case in their series where loss of pain and thermal sensation was noted clinically, and at necropsy evidence of anterior and lateral column degeneration, extending outwith the pyramidal tract, was seen. The same authors found degeneration of the central nuclear complex of the thalamus in 53% of their cases while 56% without sensory symptoms had evidence of anterior and lateral column degeneration. Other motor neuron disease patients with abnormality of thermal and pain sensation have been described.[6,9,29] Posterior column degeneration has been much more widely reported,[1,2,7,10–14] as a rule unaccompanied by clinical symptomatology.

Histological abnormalities of large efferent fibres of peripheral nerves was noted by Kawamura *et al*,[16] and Dyck *et al*[2] reported defects of myelination in the afferent fibres in the superficial peroneal and sural nerves. Primary segmental demyelination in the sural nerve was observed by Dayan *et al*[17] in eight of 10 patients.

Our results indicate that dysfunction in the small fibre thermal pathways is a frequent occurrence in motor neuron disease. Of the 19 patients with sensory symptoms, 18 (95%) had abnormal thermal thresholds while 14 of 21 without sensory symptoms showed qualitively similar abnormalities. Since our technique tests the integrity of both peripheral and

Table 4 *Summary of thermal thresholds testing results in 40 patients with motor neuron disease*

	number	*percentage*
One or more TT abnormal	32	80%
Ankle HT and/or CT abnormal	32	80%
Wrist HT and/or CT abnormal	22	55%
Ankle HT abnormal	24	60%
Ankle CT abnormal	22	55%
Wrist HT abnormal	18	45%
Wrist CT abnormal	5	12·5%

TT = Thermal thresholds
HT = Heat threshold
CT = Cold threshold

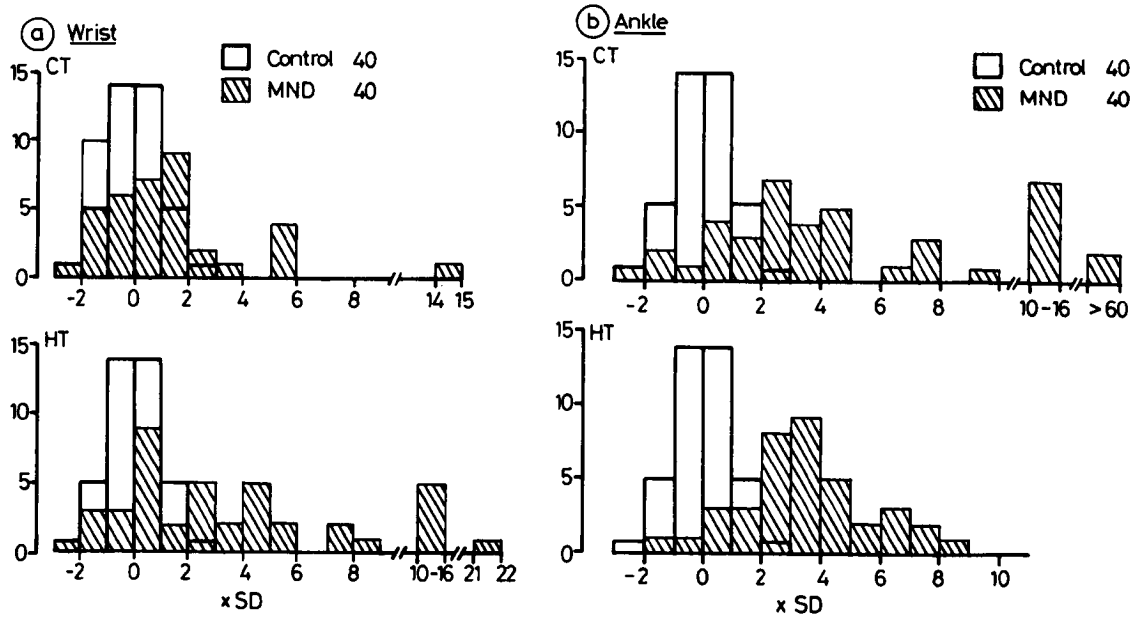

Fig *Thermal thresholds in 40 control subjects and 40 patients with motor neuron disease. (A) Heat threshold (HT) and cold threshold (CT) values for the wrist, (B) HT and CT values for the ankle. Each thermal threshold value is expressed as a figure representing the number of standard deviations (×SD) from the mean control value. Vertical axis = number of patients or controls. Horizontal axis = number of SDs greater or less than the normal control mean.*

central thermal pathways the site of dysfunction can not be determined.

It is unlikely that thermal thresholds are influenced by the degree of muscle wasting in these patients as wasting in general was not severe, the sites of thermal testing did not overlie sites of marked muscle wasting and wasting was more severe in the upper limbs in which abnormalities of the thermal thresholds were least marked. In a separate study of four patients (two with spinal muscular atrophy and two with old poliomyelitis), where there was severe muscle wasting, thermal thresholds were normal. Finally, we found no correlation between the age of the patient, the duration of clinical symptoms and the severity of abnormality of thermal thresholds.

It is concluded that whether arising centrally of peripherally, abnormalities of thermal thresholds are common and are indicative of involvement of small fibre afferent pathways in patients with motor neuron disease.

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