HANDBOOK OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EDITOR-IN-CHIEF A. RÉMOND

VOLUME 9

Somatic Sensation

EDITOR: W.A. COBB

The National Hospital, London (Great Britain)

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Editor-in-Chief: **Antoine Rémond**
Centre National de la Recherche Scientifique, Paris (France)

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International Federation of Societies for EEG and Clinical Neurophysiology

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A great need has long been felt for a Handbook giving a complete picture of the present-day knowledge on the electrical activity of the nervous system.

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The Handbook begins with an appraisal of 40 years of achievements by pioneers in these fields and an evaluation of the current use and future perspectives of EEG and EMG. The work subsequently progresses through a wide variety of topics—for example, an analysis of the basic principles of the electrogenesis of the nervous system; a critical review of techniques and methods, including data processing; a description of the normal EEG from birth to death, with special consideration of the effect of physiological and metabolic variables and of the changes relative to brain function and the individual's behaviour in his environment. Finally, a large clinical section covering the electrical abnormalities in various diseases is introduced by a study of electrographic semeiology and of the rules of diagnostic interpretation.

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Preface

Volume 9 constitutes an expanded version of the Second Common Session of the VIIth International Congress of Electroencephalography and Clinical Neurophysiology (San Diego, September 14th, 1969) and, as such, differs from the other Handbook volumes. The Congress and the Handbook were planned together from the start and those who contributed to the various sessions of the Congress are, to a large extent, those who form the teams responsible for the same topics of the Handbook. In general, however, their presentations to the Congress were necessarily too specialized and too fragmentary to form more than a skeleton, or embellishments, for the larger work of the Handbook; since the Congress the groups of authors have expanded their topics to give full integrated coverage of each one. In this volume, as at the Congress, each author has covered a defined part of the subject, from receptor to cortex, and each contribution paves the way for the next in a logical manner, while at the same time being complete in itself.

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Somatosensory Mechanisms

CHAIRMAN'S INTRODUCTION

PATRICK D. WALL

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The six papers presented here cover many of the major points of emphasis in the past 40 years of research into somatosensory mechanisms. That research has tremendously expanded our factual knowledge but most of those facts have been fitted into a conceptual framework as old as the hills of introspection, as described by Aristotle and Descartes. Forty years ago Adrian and Erlanger and Gasser had set the scene with their remarkable power and precision which was to affect the following play. Since then it has been physiologists with a number of new techniques who have been the most productive of the various disciplines. Two schools in particular have taken a major part in these contributions. Physiologists and physiology spread out from Bard's department at Johns Hopkins, from Sherrington's at Oxford and from his pupil Fulton's department at Yale, but many others have made their crucial contributions. The subject commanded the attention of many, partly because of the necessity to respond to clinical needs and partly because of the advantages of analysis of this sensory system over others. The various stages of reception, analysis and transmission are widely separated and can be approached with relative ease. Many of the investigations could proceed *pari passu* with the study of the proprioceptive system, that other great target of the Sherrington school. Many of the cells and axons were of sufficient size, and grouped together in large tracts, so that the development of various recording and analysis methods took place most easily on them. A disadvantage of the system is the relative difficulty of meaningful stimulus control. As Dawson discusses in his paper, the development of techniques for intra- and extracellular unit recording has been the new technique from which much of our new knowledge derives. The new possibility of extending those techniques to recording from single units in behaving animals is certain to play a major role in the next period of development. The use of micro-electrodes allowed probes to approach active cells sufficiently closely for the direct recording of changes of membrane potential. An alternative approach which had a dominating effect, particularly in the study of man, was the recording of extremely small potentials at a distance from groups of active structures. This was achieved by Dawson's averaging technique, which allowed small time-locked signals to be extracted from noise.

The gross anatomical plan of the somatosensory systems was known 40 years ago except for the role of fibres in dorso-lateral spinal cord. The development of silver techniques by Glees and Nauta allowed the inclusion of unmyelinated fibres and the study of the details of approach of systems to their destination cells. The ability of the

physiologists to analyse some of the details of cell–cell interaction encouraged a revival of interest in the Golgi technique, which could provide many of the needed morphological details. This same ability provided an appreciative audience for some of the electron microscopists and for those who applied the Fink–Heimer technique, with its ability to locate degeneration of terminals.

Clinicians and experimental psychologists have also played an important role, particularly with their improved and standardized testing procedures, their study of the appearance and disappearance of defects after lesions, their increased skill at making experimental or therapeutic lesions and their rigorous definition of the location of lesions. The most striking and complete failure of fundamental advance has been in the chemical field, where no understanding of the chemical basis of synaptic transmission in the somatosensory systems has been forthcoming and therefore we cannot yet see a rational pharmacology of the somatosensory systems, which is so badly needed in the area of analgesics and anaesthetics.

The first major concept around which many of the facts are organized is the idea of *specificity*. It is important to notice that many of the experiments are designed in such a way that they can only show a subdivision of the entire sensory nervous system in terms of specific modalities. Some time ago Melzack and I commented on these matters in two reviews (1962 and 1965). Since our approach is mentioned in a number of the papers, I would like to take the chairman's prerogative by commenting and bringing our views up to date. The concept of specificity originates with Muller and, in his cautious wording, it is entirely acceptable. He simply assigned special properties to five parts of the nervous system, each part to handle one of Aristotle's five senses. Muller was asserting that no amount of manipulation of the auditory system would lead to visual experience. The trouble has come from the subsequent enthusiastic elaboration of his ideas with their extension into more and more subdivisions of each sense. By the time of von Frey at the end of the last century a muddle of interlocking specificity were described; anatomical, physiological and psychological. It was touch, pressure, cold, warm and pain. For each modality, three different types of specificity were described; anatomical, physiological, and psychological. It was proposed that, if a particular anatomical structure were stimulated, impulses would result in a particular set of fibres which would trigger one and only one sensation. This equivalence from anatomy through physiology to psychology was believed to run in both directions so that any separable quality of the sensory world would be found to be associated with activity in a specific set of peripheral afferents. *Vice versa*, if a specific group of afferents were detected, they would produce their mark by generating some detectable qualitatively different form of sensory experience. Let us examine the facts. Highly specific anatomical end-organs exist but it has yet to be shown that these are required for any particular sensation. Their numbers vary too widely from one region of skin to another and from one age to another for there to be any simple correlation. Next, highly specific physiological properties link the appearance of impulses in peripheral fibres to the type of stimulus applied to their ends. Thanks particularly to the work of Perl and Iggo and their associates we now know a great deal more about these physiological specificities, particularly of smaller high thres-

hold fibres, than was known when we wrote the reviews. The question remains what is the relation between the undoubtedly specific properties of afferent axons and the specifiable subdivisions of sensory experience. Drs. Perl and Dyck present the evidence that there is a locked one-to-one relationship between these two specificities. They give two examples. The first relates to vibration sensitivity and the elegant results of Mountcastle and his associates (Talbot *et al.* 1968). The results show first that psychological tests on man demonstrate that our ability to detect vibration depends on the frequency of the vibration. Furthermore, the curve relating threshold to frequency appears to have two components. The second set of results shows that two groups of fibres exist in skin which might be candidates for signalling the presence of vibration. The performance of one type of fibre matches in shape and sensitivity the low frequency end of the human psycho-physical curve and the other matches the high end. We must emphasize the trap of drawing general conclusions from such threshold measurements. These measurements are best for discovering discontinuities in either the detection, transmission or analysis systems. One radio receiver may be found to detect one station at its lowest amplification while another radio picks up a different station. This observation tells one something of their circuits but it certainly does not prove that the sets were designed to receive from a single station or that they normally operate in that fashion. It is of interest that a very similar type of threshold experiment in vision shows the existence of rods and cones in the retina with differing spectral sensitivities, the Purkinje shift, and yet no-one suggests that rods and cones must each monopolize some special aspect of vision under normal conditions. Von Frey and many of his followers fell into the trap of threshold measurements when they demonstrated the existence of sensory spots and then generalized to propose that our sensory world is formed by a mosaic of such spots. They neglected completely the fact that the nature and distribution of the spots is completely dependent on the details of the particular stimulus used. They also failed to notice that the position of the spots meandered about on the surface of the skin from minute to minute and therefore could hardly be explained by the existence of specific structures, each triggering its specific sensation. The work of the past 40 years has beautifully confirmed and elaborated the existence of specific anatomical end-organs and of specific and rigidly fixed relations between stimulus and response in special types of afferent nerve fibres. The same period has re-emphasized that the sensory experience is only rigidly related to the stimulus in two artificial circumstances. The first is with threshold measurements in which special types of fibre suddenly become active and contribute to the afferent barrage and signal their existence to the sensorium. Sensation depends on a number of factors such as attention, distraction, expectation, immediate and past experience, significance etc. and, in addition, it depends on impulses arriving over afferent systems. Most stimuli fire off impulses in several different physiologically specific systems. Careful arrangement of stimulus parameters can produce activity in one system. Under these circumstances it is not surprising that sensation which depends in part on the arrival of afferent volleys should depend on the threshold characteristics of the particular type of fibre which responds to the stimulus. This is the significance of the Mountcastle results. They do not prove "specificity". They prove that our sensorium

depends in part on the properties of peripheral afferents. If our sensation did not depend on these properties, we should be in the mystical realm of extrasensory perception. When a stimulus such as pressure increases in intensity, more and more afferents are recruited. Since the thresholds of the afferents are not distributed evenly, the central nervous system will receive surges of impulses as each category of fibre adds to the afferent barrage. In this sense and in this sense only, our sensation is dependent on the specificity of afferents. Under ordinary circumstances, our sensation depends on the combination of all afferent signals in combination with all the other factors I have mentioned. Combinations of active peripheral afferents interact with central factors to produce conscious sensation. The second artificial circumstance is that in which trained skilled subjects are used in very stable conditions. Where such groups produce scales relating stimulus to response we find each laboratory reporting a different relationship and great difficulty in maintaining fixity for any one subject. Nowhere is the problem of relating stimulus to response more obvious than in the patient in pain.

This leads us to a consideration of the second prop of the classical conceptual framework : *specialized projection pathways.* It is clear that if von Frey were right and the peripheral end-organs detected events in the environment in the same terms as they are perceived by the sensorium then private pathways must connect periphery to sensorium. Only the dorsal column–medial lemniscus pathway fulfills this requirement and, as we shall show, its relation to sensation is now appearing as an intriguing mystery. The other pathways usually show evidence of convergence of different types of specialized input. These are the pathways formed from cells in the dorsal horn of spinal cord. We have suggested that interactions between incoming impulses, some inhibitory and some excitatory, partly decide the messages travelling up the afferent pathways toward the head. There has been considerable discussion between physiologists as to whether the location of these interactions is presynaptic, postsynaptic or both. These arguments should not be allowed to confuse the issue. Interactions exist, whatever their mechanism. Even where specialized dorsal horn cells are shown, we have still to explain the shifts of sensitivity associated with partial destruction of peripheral nerves. We suggested that some of the pains associated with peripheral nerve disease were not necessarily produced by a drop in threshold of peripheral endings which normally triggered pain. Instead we suggested that some of the afferent volley is normally inhibitory and, if this mechanism is eliminated, light stimuli trigger pain. This would be an example of convergence with various types of stimuli and of afferent nerve impulses interacting to produce the ascending message. This fits the observed physiology of most of the observed dorsal horn cells which might be candidates for signalling the existence of tissue damage. Certain large diameter cutaneous afferents seem particularly powerful in triggering inhibition. Dyck, in his paper, supports the classical position that pain is triggered by activity in small diameter fibres without interaction with other fibres. His evidence is clear but one must be particularly careful to judge his use of threshold measures and of chronic cases in his conclusion of a fixed relation between pain and activity in certain fibres. In the chronic cases, large fibres were only diminished in numbers. The disease

process may have begun even before birth and may have given time for re-establishment of inhibitory mechanisms, either by shifts of central cell excitability or by collateral sprouting of remaining fibres. Before concluding that pain or any other sensation is triggered by the simple existence of impulses in one type of afferent I suggest the attempt to explain why a normally innocuous stimulus to normal tissue sets off pain when applied to a region of skin to which pain is referred in visceral disease. Interactions of stimuli are the rule in ordinary circumstances. Conflicting stimuli are carefully eliminated in experiments by those who are convinced that interactions do not occur except in the mysterious realms of psychiatry.

The next major item of the conceptual model has been that the mechanism for the generation of *conscious sensation resides in cortex*. This had led to a particular concentration of work and search on those pathways projecting by the most direct route to cerebral cortex. The effect of lesions on sensation is usually interpreted in the classical model. Analgesia following section of the ventral quadrant of the cord is automatically attributed to section of the spino-thalamic tract, in spite of the fact that an effective lesion cuts a mass of white matter in addition to the rather puny direct spino-thalamic tract and in spite of the curious and conflicting claims for the effectiveness of destroying the end stations of this tract in the thalamus. Some of the effective regions in the thalamus are not on any of the classical ascending pathways and raise the possibility that descending controls may be affected. Others, faced with the persistence of pain after massive bilateral thalamotomies, question cortical dominance and begin to look elsewhere. Most continue to find the standard view quite satisfactory. This has been one of the reasons for particular emphasis on the dorsal column-medial lemniscus projection to thalamus and cortex. Other reasons for emphasis on this pathway are its recent evolution, large size and its discrete preservation of peripheral specificity and location. The information passing over this pathway has been believed to be the main input on which discriminative somatosensory behaviour is based. There are now ten independent studies in the literature showing that sensory discrimination such as touch threshold, two point discrimination and vibration sensitivity are unaffected by surgically complete lesions of the dorsal column (Wall 1970). To mention only the most recent example, Tapper (1970) showed that cats conditioned to respond to a threshold stimulus to a single touch corpuscle became more sensitive after dorsal column section. These results have been "explained" by the assumption that the information travelling in dorsal columns must also be present in other pathways. This redundancy argument has been checked and shown to be unacceptable because animals with all white matter sectioned except for the dorsal columns fail to show any behavioural response to peripheral stimuli, in spite of the presence of large cortical evoked potentials (Wall 1970). These results suggest, at a minimum, that impulses ascending dorsal columns have an effect only in relation to impulses arriving over other pathways. If the cortex is not simply receiving information about discrete events on the surface of the skin over the various specialized inputs then what is the function of the various parallel inputs?

This leads to the final and most fundamental parts of the model of somatosensory mechanisms. In the accepted picture, the sensing conscious individual exists within

his own brain, fed information by highly reliable afferent pathways. In his sanity or madness the individual then interprets the given "data". The model is passive where the "mind" is presented with the true facts and proceeds from them. This dualistic model was acceptable to classical thinkers up to the present time and was quite specifically described by Russell. In the past 100 years there have arisen a number of questions about this picture. It is possible to force an animal or man into this passive role in which the world is impressed on him and he is forced to interpret his world. This is the situation of most neurological and psychological tests in which a stimulus is presented and an answer demanded. "Say "yes" if I touch you", "Press the button if you see a light". In these tests the patient is forewarned of what is to happen, he is alerted and concentrating and knows the class of probable stimuli. These are the common stimuli of our investigations but the rarest stimuli of the real world. Usually we actively search the world for the existence of objects. We play an active part in obtaining stimuli rather than being passive recipients. The method by which we search our environment, both external and internal, determines the stimuli we receive. I suspect that the next 40 years of study in somatosensory mechanisms and other sensory systems will see us moving from passive to active. Given the existence of sophisticated descending controls, such as the pyramidal tract which ends on sensory as well as motor systems, we have mechanisms for questioning our own afferent systems and for questioning or exploring our external worlds. I believe we are at a transition stage from understanding how we receive passive impressed stimuli to going forward to search for how we set about exploration and the setting of our sensory pathways to receive information about expected stimuli. This would change the conceptual model from one of a passive receiver to one of an active searcher.

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Receptors

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The bases of somesthesis must remain obscure until it is possible to specify the functional organization of the peripheral receptive structures and their technique for communicating with the central nervous system. It may surprise some to learn that even after many years of investigation uncertainties still exist about this phase of the somatic sensory process. In other words, we do not know enough about the meaning of messages in receptors (the primary afferent neurons with a sensitive peripheral apparatus at one end and connections to the central nervous system at the other). Since neurons convey activity (over any distance) by an impulsive event with a definite threshold and a limited capability for repetition, certain restraints are forced upon this signalling system. In particular, a major transformation must take place so that such impulses can provide details on the broad continuum of environmental changes affecting the body. From the very beginning of electrophysiology, electrical recordings have suggested a general similarity in the conducted impulses of various nerve fibers. Thus, it is usually assumed that functional differences in the messages transmitted by various primary afferent neurons derive from: (1) the means of their activation, (2) their frequency of activity and (3) the effect of their discharges upon central neurons. The present discussion will dwell on observations relevant to the first two points. In passing, however, it should be emphasized that current thinking would give dissimilar functional values to impulses in different primary afferent fibers, either because of systematic variation in the types and locations of central neurons they contact, or in the nature of their central synaptic junctions.

The first direct observations on the transmission of signals by primary afferent neurons were reported over 40 years ago by Adrian (1926). This pioneering work emphasized the relatively stable nature of the nerve impulse and the effects of stimulus intensity and duration on the frequency of impulses. From such early investigations we learned that increased intensity of stimulation usually produces an increased frequency of discharge in an afferent nerve which consists in a higher frequency of impulses in a given nerve fiber and of impulses in an increased number of fibers. This general principle of primary afferent neural activity and Adrian and Zotterman's observations (1926) on the adaptation of discharge during a constant stimulus are still considered valid. Subsequent investigation has done much to extend and quantify the relations between discharge frequency and stimulus intensity and has confirmed the fact that there are important differences between primary receptive units. Most current investigators would agree that there are other features of the "code" inherent

in the signals of primary afferent neurons, but there the agreement might cease. In 1961, Hensel, in answer to those postulating a special pattern in the repetition of sensory impulses as an indication of the nature of the stimulus, argued that experimental evidence only supports a relation between frequency of impulses and graduations of stimulus intensity.

Certain recent work bears directly on the traditional theory that different modalities of somatic sensation stem from activation of given types of receptors. If this concept is true, the specificity of the receptive nerve terminals and any other tissue intimately associated with them becomes an important part of the detection and transmission system. Furthermore, one set of results suggests that, in at least some situations, the frequency of impulses in the primary afferent neuron can reflect a stimulus variable in addition to intensity.

Many types of experiments are only possible on animals since the procedures involved are destructive of tissue or demand approaches unacceptable when man is the subject. On the other hand, sensation, as we commonly use the term, is a phenomenon only reportable by human beings. As a consequence, there is an inherent gap between the objective measurements that can be obtained on animals and their direct relevance to the sensory experience of man. A technique of great value for bridging this gap consists in utilizing observations on man to define stimulus or other properties associated in a peculiar or restricted way with given sensations and then to perform animal experiments using equivalent conditions. Approaches of this type underlie the investigations described below.

A. *Receptors for pain*

One of the long-standing controversies in somatic sensation concerns the specificity of receptors for pain. Physiologists generally have accepted the existence of a specific receptive apparatus for pain following von Frey's dictum (von Frey 1896; see Zotterman 1959), but there have been vigorous denials (Goldscheider 1920; Nafe 1929, 1934, 1942; Sinclair 1955; Melzack and Wall 1965). The issue at present is whether pain and its associated reactions are initiated under normal circumstances by discharges from receptors activated uniquely or most effectively by intense stimuli, or whether the pain process begins with the appearance of a special pattern (distribution) of discharge in a population of receptors also responsive to innocuous stimuli.

The problem has been narrowed by some well-established psychophysical observations. It is common knowledge that pain usually follows tissue damage or those circumstances threatening to cause it. Sherrington (1906) used this fact to define a stimulus as "noxious" if it posed the threat of tissue damage and suggested that this concept might be used in animal studies of mechanisms associated with pain. In this connection, it must be kept in mind that the stimulus intensity representing a noxious level varies with the tissue and location. For example, there is a point at which mechanical stimulation causes obvious insult to the skin but this intensity differs considerably for the glabrous skin of the palm and the hairy skin of the inguinal region. Similar considerations would apply to the effects of temperature, chemicals and radiant energy.

Heinbecker *et al.* (1933) provided a psychophysical correlation of great value in helping to define the receptive mechanism of pain only a few years after the significance of the compound action potential of nerve had been discovered. Fig. 1, *A* from their study shows the complete compound potential of a human cutaneous nerve removed from a subject just before amputation of a limb for gangrene. A lesser stimulus, initiating the compound potential of Fig. 1, *B*, was associated with a report of pain by the conscious subject. The most rapidly conducting fibers in Fig. 1, *A* ("100" or A-alpha) had a lower threshold to electrical stimuli than more slowly conducting fibers ("25" or A-gamma, delta); therefore they could be activated in isolation and did not provoke a painful or unpleasant sensation in this subject. Parallel experiments on dogs supported the belief of Heinbecker *et al.* (1933) that the fibers making up the second peak (A-gamma, delta) carried the signals essential for pain. The third peak in Fig. 1, *A* ("1.5") represents impulses in the most slowly conducting fibers, the C or unmyelinated group. Later, part of the unmyelinated fiber population was shown by

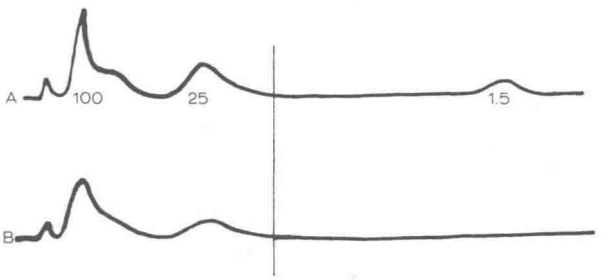

Fig. 1. Compound action potential of human cutaneous nerve. The records were obtained from an excised nerve *in vitro*. *A*, complete potential: deflections marked in meters per second; *100* produced by myelinated fibers of A-alpha beta group, *25* produced by myelinated fibers of A-gamma delta group and *1.5* produced by unmyelinated fibers. *B*, potential initiated by the intensity of the electrical shock that evoked pain when the exposed nerve was stimulated in the patient's body. From Heinbecker *et al.* (1933) by courtesy of the authors and *Archives of Neurology*.

Clark *et al.* (1935) to be at least partially sensory and to initiate reactions related to pain. The lack of pain from impulses confined to the A-alpha conduction range and its appearance with the addition of impulses in more slowly conducting fibers of the A-gamma, delta range were emphatically confirmed by Collins *et al.* (1960) in conscious man; the latter also reported that electrical shocks strong enough to recruit C fibers to the afferent volleys produced an intensely painful sensation, of somewhat different character than that associated with volleys composed solely of myelinated afferent fibers.

These observations on man demonstrated that slowly conducting afferent fibers, particularly from the skin, either transmit impulses which, by themselves, indicate the presence of noxious stimulation or modify the effect of impulses in the A-alpha group so as to initiate central pain mechanisms. The choice between the two possibilities has not been simple. There have been periodic reports of cutaneous receptors with elevated thresholds to "natural" stimulation of the skin (Zotterman 1939;

Maruhashi *et al.* 1952; Dodt 1954; Iggo 1959, 1960, 1963; Hunt and McIntyre 1960; Iriuchijima and Zotterman 1960), in particular for receptive units with unmyelinated afferent fibers. Even for these, the number of such high threshold units that have been described has been very small compared to the known number of afferent fibers and there has been no consistent set of properties attributed to them. Thus, as late as 1965 Melzack and Wall found the argument in favor of specific receptive elements for pain wanting. At this point it was apparent that a systematic examination of the type of activity initiated in different cutaneous receptive units by noxious, as opposed to innocuous, stimuli was needed.

A successful survey of this kind demanded a technique that could record the activity of single elements with a minimal bias in their selection. Recordings from high impedance micro-electrodes inserted into a peripheral nerve proved to be both efficient and adequately stable for the analysis of activity in single myelinated fibers (Burgess and Perl 1967). Confirming earlier work, the majority of myelinated afferent units were found to be excited by weak mechanical stimuli. Substantial differences appeared in

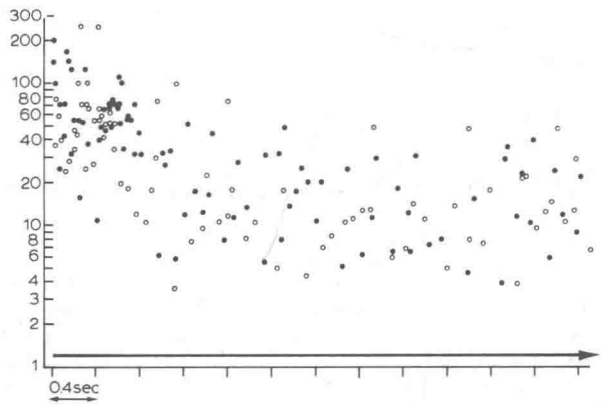

Fig. 2. Discharge of a slowly adapting receptor from monkey glabrous skin plotted as the reciprocal of the interval between impulses. A constant pressure of moderate intensity for the response indicated by the filled circles, and of clearly noxious damaging intensity for that indicated by the open circles, was applied across a fold of skin containing the receptive field. Conduction velocity of afferent fiber was 34 m/sec. From Perl (1968). This and Fig. 3 are reproduced by courtesy of the *Journal of Physiology*.

the responses of certain elements as compared to others and the general grouping of receptors into different types according to (a) adaptation rate to maintained stimuli, (b) excitation by hair movement alone, (c) demands upon a minimal rate of change by the mechanical stimulus, and (d) organization of the receptive field, largely supported previously established conclusions (Burgess *et al.* 1968; Perl 1968). It did become clear, however, that the response to noxious stimuli of low threshold mechanoreceptors could be mimicked by innocuous stimulation. Thus, there was nothing unique about the signals evoked by noxious stimuli in the low threshold receptors (Perl 1968). An example of the type of analysis leading to this view is shown in Fig. 2 for a slowly adapting receptor from the glabrous skin of a monkey. The discharges of this receptor

were plotted against time as the reciprocal of the interval between impulses ("instantaneous frequency"); the response indicated by the filled circles was initiated by moderate pressure across a fold of skin in the receptive field, while that of the open circles was evoked by a damaging level of pressure across the same skin fold. No consistent difference between the responses to these two stimuli could be found.

Most myelinated afferent fibers from hairy skin conducting at A-delta velocities, the range shown to have a special relation for pain, are associated with hair receptors and give maximal responses to gentle mechanical stimuli (Hunt and McIntyre 1960; Burgess and Perl 1967; Perl 1968). On the other hand, a significant fraction (20–30%) of receptors with slowly conducting myelinated afferent fibers were noted to have widely dispersed receptive terminals with high thresholds for mechanical stimuli. The receptive fields of such high threshold mechanoreceptors consisted of a number of points of maximal responsiveness separated by regions of little or reduced sensitivity.

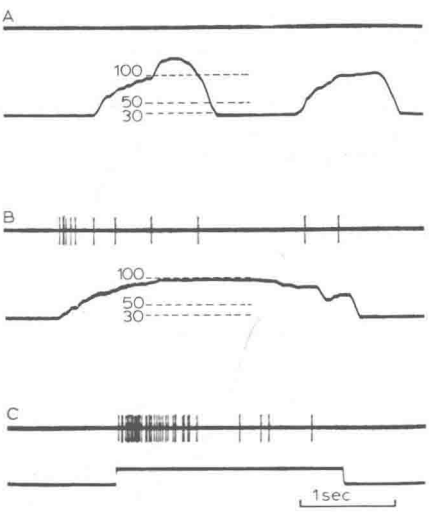

Fig. 3. Responses of a receptor with a myelinated afferent fiber innervating monkey glabrous skin (upper trace). In *A* pressure was exerted against the receptive field with a blunt, calibrated probe; in *B* the calibrated probe was fitted with a needle tip and the same skin spot stimulated (force of stimulus indicated in grams for *A*, *B*). In *C* the skin area stimulated in *A* and *B* was pinched by a forceps with sharp teeth. From Perl (1968).

Responses of this kind of element from primate glabrous skin to graded stimuli are shown in Fig. 3; only the stimuli in *B*, *C*, causing skin damage by penetration, evoked a discharge. Some receptors of this type could be excited only by the most intense stimuli, those clearly causing damage, while others discharged to moderate pressure; however, all of those that responded to an innocuous stimulus increased their frequency and number of impulses when the stimulus intensity reached the overtly damaging level. The conduction velocities of these high threshold myelinated units were scattered over the entire A-gamma, delta range (40–5 m/sec) in both cat and monkey.

Rapid heating of the skin to 50°C or above, a stimulus ordinarily causing pain,