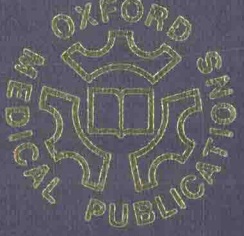

Mechanisms of Cutaneous Sensation

David Sinclair

MECHANISMS OF CUTANEOUS SENSATION

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PREFACE

IN 1978 I agreed to write a second edition of my book *Cutaneous Sensation*, which was published by the Oxford University Press in 1967. When I began work it immediately became obvious that so much information and opinion had accumulated in the interval that virtually the entire book would have to be rewritten. Developments in electrophysiology, advances in our understanding of the relationship between structure and function, new methods of investigation, and above all, the explosion of interest in the genesis and treatment of pain – all these and more have focused current interest on new research fields scarcely envisaged at the time *Cutaneous Sensation* was published. Accordingly I felt it desirable to make it clear in the title that this is a different book, although its general framework is similar and part of the original material remains, as well as some of the original illustrations.

In the preface to *Cutaneous Sensation* I apologized for making a ruthless selection of references and for concentrating on those written in English, which has for some time now been the language in which most of the relevant reports have appeared. I repeat this apology, but without contrition, for to include even a quarter of the articles which have appeared in the last thirteen years would have rendered the book unacceptably detailed. Instead, I have added as many new papers as I believed necessary to illustrate modern ideas, and have cast out approximately half of those which were previously included. There are now many excellent reviews and symposia to which those in search of detailed information on a particular topic can turn with assurance, and at the end of each chapter I have given examples.

An account such as this can make no pretension to durability; it is intended merely to afford a survey of factual information and ideas at the time of writing. Nevertheless I hope it may be found useful as an attempt to examine the wood rather than the innumerable individual trees which infest this fascinating but still mysterious branch of human biology.

I am greatly indebted to all those who so kindly permitted me to borrow their illustrations, and to Mrs Jean Clifton-James, who typed the final draft.

Nedlands, Western Australia DS
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1. BASIC IDEAS

SINCE the time of Aristotle it has been customary to speak of five human senses. Four of these – vision, hearing, taste, and smell – possess specially developed circumscribed organs which have no other function. The fifth, and oldest, sense is located in the skin, a diffuse organ which serves many other purposes. Aristotle called the fifth sense 'touch', but the diversity of cutaneous sensations made him uncertain whether it should properly be classed as one sense or several (Keele 1957). This difficulty later led to the use of the term 'general sensation', which included not only sensations aroused from the skin but also those arising from joints and other deep tissues, from the viscera, and from the semicircular canals and the static postural organs. Nowadays cutaneous sensation and some of these additional sensory groups are often considered together under the heading of 'somaesthesia', but in this book attention will be confined to sensations which can be initiated from the skin.

MODALITY AND SPECIFICITY

In order to understand current views on the nature of cutaneous sensation it is necessary to go back to the beginning of the nineteenth century. Cutaneous sensation had been studied long before this, and one need only mention the names of Locke, Berkeley, and Hume to conjure up the immense philosophical contribution to the subject of perception. But it was not until the time of Charles Bell that the scientific method began to be applied to the study of cutaneous sensation. Bell was the first to make the explicit suggestion that there was some sort of 'specificity' of the nerves subserving the various senses of Aristotle. His idea gained currency, and in 1838 the physiologist Johannes Müller set out a series of propositions relating to the 'specific energies' and 'specific irritability' of the nerves. In view of the trouble which the word 'specific' has caused, and is still causing (Wall 1978), it is worth trying to define exactly what Müller meant. Müller had to explain the known consequences of stimulating the nerves subserving Aristotle's five senses. Thus stimulating a given nerve always resulted in the same kind of sensation, irrespective of the nature of the stimulus. Secondly, the same kind of stimulus, applied to nerves subserving different senses, resulted in different sensory experiences.

Thirdly, it did not matter where in its course a given nerve was stimulated, the sensory result was always the same. To account for these findings, Müller postulated an intrinsic difference of some kind between the nervous mechanisms subserving the five senses. This idea he expressed in the unfortunate term 'specific energy', by which he merely meant a qualitative distinction between the five kinds of nerve. He did not suggest any anatomical or physiological peculiarity of the receiving or conducting apparatus, but gave the specificity an anatomical habitation in the central portion of the nerve or in its termination in the brain rather than in the periphery. His 'specific energy' could well have resided merely in the different central connections made by the nerves of the five senses, as Descartes had previously suggested.

By 'specific irritability' (a much better term) Müller meant that the peripheral terminations of the nerves belonging to the five senses were in some way specialized to react preferentially to certain stimuli. Though any given nerve could be set in action by several different stimuli applied to its sensory terminals, it was always easiest to arouse it by the stimulus appropriate to the sensation which the nerve mediated. There was, in fact, a *relative stimulus-specificity* (though Müller did not use this term) as well as the *absolute sensation-specificity* he had already postulated. He did not claim any form of specificity extending along the whole length of the nerve.

Müller made no attempt to suggest the existence of any specificity within a given sense, and his 'specific energy' related solely to the characteristic types of sensation produced by stimulating nerves mediating each of the Aristotelian senses. But it was not long before Müller's ideas were applied by Volkmann (1844), Natanson (1844), and others to the different sensations which could be aroused from the skin; Volkmann, for example, supposed that there must be separate nerve endings (borne on separate nerve fibres) subserving every subdivision of cutaneous sensory experience, and this view still has some currency (Brindley 1977).

About this time von Helmholtz introduced the term 'sensory modality' to designate 'a class of sensations connected by qualitative continua' (Boring 1942). If this criterion is applied, tone perception becomes a single modality, since in hearing there is a continuous series of tones with no qualitative gaps. Similarly, colours can be represented on the colour solid as a continuous spectrum. The cutaneous sense, however, cannot be considered to be a single modality, since it embraces several groups of cutaneous sensations, and these groups are not connected by a continuum of introspective quality.

A considerable amount of information had already accumulated about the way in which cutaneous sensations 'dissociated' from each other in diseases or injuries of the nervous system, during anaesthesia, or as a result of experimental blocks. The concept of Helmholtz thus struck root into prepared ground, and without any formal statement in the literature the four major dissociable sensory categories of touch, warm, cold, and pain were promoted to the status of modality.

Regrettably, 'modality' and 'quality' are words which are used in different senses by different people. Most commonly touch, warm, cold, and pain are called modalities, and the word 'quality' refers to the introspectively recognizable varieties of experience within these broad headings. We may say, for example, that a pain has a 'burning' quality. Some writers, however, particularly in the psychological literature, use the word 'modality' for each of the five senses, and the word 'quality' is then applied to the introspective subdivisions of cutaneous sensation – the same touch, warm, cold and pain which most people call 'modalities'. Conversely, the word 'sense' may be applied to indicate a 'modality', as in such expressions as 'the warmth sense'. Such practices are needlessly confusing, and the introduction of the term 'sub-modality' by Brindley (1977) makes matters worse.

Helmholtz's original conception of modalities of sensation depended wholly upon introspection, the ultimate court of appeal in all sensory problems, and one in which individual opinions inevitably replace scientific evidence. For some observers the sensations of pressure, touch, pricking touch, and tickle are all unique, and are united by no 'qualitative continua'; for others, equally skilled, they merge insensibly into each other. The mind is a private place, and introspection is an individual affair.

If we had had to rely on purely introspective evidence to decide whether or not a given sensation should qualify as a sensory modality, the concept would not have advanced very greatly. However, further criteria developed with the progress of research on sensory dissociation. In the next few years the ideas of Volkmann and those of Helmholtz firmly blended together, and it became generally accepted that there existed a series of 'specific nerve fibres' subserving introspectively circumscribed sensations or groups of sensations; thus, in 1867, Nothnagel used this idea to explain the distinction between the modalities of cold and warm. This, of course, was an extension of the original position of Müller, who had said nothing about 'specific fibres'.

The next step was taken when Blix (1884) discovered the existence in normal skin of a sensory mosaic of tiny 'spots', each of which reacted

preferentially to touch, cold, warm, or pain. The spots for warm and cold were clear cut and easily separable; those for touch were much more numerous, and those for pain were so closely set together that Blix later became doubtful of their individuality. It was at once suggested that the mosaic-like sensitivity of the skin was due to the varying distribution of modality-specific nerve fibres, and the fact that Blix had described four kinds of spots, one for each of the commonly accepted modalities, strengthened belief in the existence of a separate anatomical apparatus subserving each of the four modalities of touch, warm, cold, and pain.

It is true that initially there was some trouble over the postulation of separate apparatus for cold and for warm. Hering (1879) had suggested that one and the same end organ served both warm and cold, being capable of responding in different ways to warming and cooling, and Riley (1894) argued

> 'hot' and 'cold' are, in physics, only relative terms. It is not at all natural to suppose that absolutely different apparatus, distinct and separate, each occupying a local position of its own, should be required for these two sensations which are developed by the same form of energy in different quantities. . . . Heat and cold are to the temperature sense what light and darkness are to the sense of sight. Cold is the absence of heat, as darkness is the absence of light.

Nevertheless, the different anatomical distribution of warm spots and cold spots in the skin carried the day in favour of the individuality of the modalities of cold and warm.

By 1895, therefore, the idea of a modality as something with an individual anatomical substrate was already well accepted. Nor had the anatomists been backward in providing the necessary apparatus. Improvements in microscopic technique, together with the founding of the dyestuffs industry after Perkin's discovery of aniline in 1856, had enormously stimulated histology, and many morphologists had begun to take an interest in the innervation of the skin and mucous membranes. In addition to the free nerve endings universally permeating the skin and surrounding the hairs, six types of anatomically differentiated nerve endings had been described in human skin. These were: the Pacinian corpuscles (1834) (see Pacini 1840), the Meissner corpuscles (Meissner 1853), the Krause end-bulbs (Krause 1859), Merkel's discs and domes (Merkel 1875), and the Ruffini endings (Ruffini 1891).

Eventually Max von Frey (1894, 1895, 1896) suggested that under the skin of each sensory spot there lay an end organ or group of end organs specialized to respond to a particular type of stimulus. This

specialized end organ was connected to a fibre which conveyed the impulses aroused by the stimulus up to the brain, where they were appropriately interpreted. von Frey considered that the specialization of end organs would be manifest anatomically, and allotted each of the four established modalities to one of the known kinds of end organ. He gave pain to the free nerve endings, cold to the Krause end-bulbs, warm to the Ruffini endings, and touch to the basket formations of free endings around the hair follicles and, in the glabrous skin, to the Meissner corpuscles.

The allocation of a peripheral analytical function to morphologically distinguishable end organs in the skin was the final coping stone on the gradually growing concept of an all-pervading 'specificity' throughout the whole sensory nervous system. It was implicit in the theory of von Frey that each stimulus-specific end organ was connected to a modality-specific point in the brain by a kind of private telephone line which was necessarily 'specific' for the given sensation, though in an undefined sort of way. It became accepted that for each modality, and perhaps for each quality, of cutaneous sensation there existed a specific type of end organ, a specific nerve fibre, and anatomically distinct specific pathways within the nervous system. The kind of specificity meant varied according to the exigencies of the discussion.

This hardening of the word 'modality' into an anatomical mould had the effect of stimulating anatomical and physiological inquiry. There began a hunt for specific nerve endings, fibres, pathways, and 'centres', and also a slow shift of emphasis; today, for every psychologist who interests himself in the field of cutaneous sensation there are six or seven electrophysiologists, clinicians, anatomists, biochemists, and pharmacologists. There were even attempts to minimize the psychological element in the definition of a modality. Thus Bishop (1944*b*), discussing pain, wrote

> a rational and unequivocal definition of modality could be based upon physiological mechanisms, more objectively than upon psychological reactions, even though psychological experience is involved in the identification of sensory mechanisms. This to be sure amounts to cutting the Gordian knot and defining pain as the response normally obtained to the adequate stimulation of 'pain' endings.

But the theory of von Frey was not accepted unchallenged. A strong body of opinion, led by Goldscheider, criticized the inclusion of pain as a modality in the anatomical sense (Geldard 1972). The pain spots in the skin are so densely distributed that it is almost impossible to find a touch,

cold, or warm spot which is not also sensitive to pain. Again, pain is unique in that it can be produced by almost any kind of stimulus, provided it is intense enough. On this and other evidence Goldscheider (1898) maintained that pain had no separate receptors but was produced in the nervous system as a result of the summation of impulses excited by the application of pressure or of temperature to the skin. Goldscheider continued to support this claim as late as 1927, but after the paper of Achelis (1936) little was heard of the summation theory of pain until it was revived by Noordenbos (1959), Denny-Brown and Yanagisawa (1973), and Crue and his colleagues (Crue and Carregal 1975; Crue, Kenton, and Carregal 1976).

Others objected to the idea of pain as a modality on slightly different grounds. For Aristotle pain was a 'passion of the soul', the opposite of pleasure, a state of mind rather than a sensation. Those who still held the Aristotelian view and believed pain to be a 'feeling-tone' or a 'quale' rather than a sensory modality found it difficult to rebut arguments such as those by Witmer (1894): 'The symptoms of syringomyelia, the action of cocaine and other anaesthetics, the phenomena of hypnotism, all present cases of the absence of pain without an entire loss of any other form of sensation – an impossible condition on the quale hypothesis'. The idea of pain as an 'affective quality' persisted, however, and in 1923 Piéron carefully distinguished the sensation of pinprick (*'piqûre'*) from pain. He considered that 'piqûre' was a true sensory modality (i.e. based on anatomical apparatus), but that pain was, like pleasure, an 'affective category' more or less closely linked to certain types of cutaneous stimuli, including pinprick. In his book Piéron (1952) reiterated the concept of pain and pleasure as 'affective categories', and distinguished them from 'tactile sensation', in which he included sensations of temperature. He suggested that much of the confusion over the fundamental nature of pain might be due to failure to distinguish between the sensation of prick and the sensation of pain. Most people today would agree with Piéron that pain is not on quite the same footing as touch, warm, and cold, for it is separable into two definite components, the sensation itself, and the emotional reaction to the sensation (Chapman, Dingman, and Ginzberg 1965). As Leriche once put it: 'Physical pain is not a simple affair of an impulse travelling at a fixed rate along a nerve. It is the resultant of a conflict between a stimulus and the whole individual.'

Sometimes pain behaves as if the pure sensation were the dominant factor, and sometimes as if the 'affective component' were the more

important of the two, and purely psychological factors can evoke pain in the form of a somatic hallucination (Walter 1961).

The second major criticism of the von Frey theory was that it failed to account for the range of sensory experiences which can be derived from the skin. In its original form the theory limited the number of modalities to four, and gave no convincing explanation of the fine qualitative distinctions of which the skin is capable (Sinclair 1955). To meet this point attempts were made to describe sensory experiences such as roughness, hardness, greasiness, stickiness, and clamminess as 'sensory blends' resulting from stimulation of different permutations and combinations of the four basic types of end organ, along the lines of the trichromatic theory of colour vision. The best known of such attempts was that of Alrutz (1900) to explain the sensation of 'heat' as a combination of warm and cold. Work of this kind was never universally accepted (Boring 1942), and the 'idea of differentiating separate skin senses in terms of four and only four separate receptors and separate nerve supplies turns out to appear embarrassingly naïve' (Stevens and Green 1978).

But the most obvious failure of the von Frey theory lay in its attempt to match end organs with sensations. von Frey was no histologist, and his suggestions were made on the basis of evidence which it would be no exaggeration to call ludicrously inadequate (Hagen *et al.* 1953). It is perhaps because this evidence is hidden in a relatively inaccessible German journal that his original allocations were accepted for so long by English-language texts. The truth is that the anatomical details of the von Frey theory fell to the ground almost at once. Repeated attempts to establish a consistent relationship between marked sensory spots and the underlying histology proved unavailing, and the distribution of the various end organs incriminated by von Frey was found to be quite at variance with the distribution of the four modalities.

It is in fact curious, as Boring (1942) remarked, that von Frey should ever have put forward his correlations, since he ought to have known that both Goldscheider (1884) and Donaldson (1885) had already excised both cold and warm spots without finding any receptors other than free nerve endings.

Yet discrediting the association between function and receptor morphology was a long way from discrediting a possible association between function and receptor biochemistry or biophysics. It could not be proved that no 'specific' endings existed; all that was established was that, with existing methods, no morphological or biochemical differences could be

detected between the hypothetical nerve endings concerned with the four cutaneous modalities. Those who still adhered to the von Frey concept could merely assert their belief that a difference would some day be found; their opponents had to perform the most difficult of biological feats, that of proving a negative.

A less-rigid view of end organ specificity was take by Sherrington (1900) when he wrote:

> The sensorial end-organ is an apparatus by which an afferent nerve fibre is rendered distinctively amenable to some particular physical agent, and at the same time rendered less amenable to, i.e. is shielded from, other excitants. It lowers the value of the limen of one particular kind of stimulus, it heightens the value of the limen of stimuli of other kinds.

This proposition, embodying the idea of an 'adequate stimulus' which Lotze put forward in 1848 (Woodward 1975), did not rule out the possibility that an end organ could respond to two or perhaps more types of stimulation, though it would react preferentially to one of them. As regards cutaneous sensation Sherrington's statement remained without experimental backing for over 50 years, for even the larger and more organized endings could not be explored until electronic advances had made this possible. The stimulus-specificity of the Pacinian, Pinkus (Merkel '*Tastfleck*'), and Ruffini corpuscles has now been investigated, with results that support Sherrington. But the endings described by Krause and Meissner still await direct electrophysiological experiment, though the 'amenability' of the Meissner corpuscle to external 'excitants' has been indirectly (and conceivably incorrectly) deduced from other evidence (p. 201).

The ubiquitous 'free' endings in the skin, which do not acquire connective tissue capsules or other distinctive morphology, were still more difficult to examine physiologically, but it is now known that many members of this class of apparently uniform endings exhibit well-marked stimulus-specificity. On the other hand, a substantial minority, while responding preferentially to one kind of stimulation, will also transduce one or more additional forms of energy (p. 106): it is possible that intermediate types in a continuum of sensitivity may exist.

For a long time after von Frey's original formulation there was no suggestion of a morphological basis for the specificity of sensory nerve fibres. But in 1929 Gasser and Erlanger investigated the manner in which the fibres in an excised animal nerve succumbed to the influence of pressure or of local anaesthetics. They found that the fibres tended to fall out not at random but in a manner correlated roughly with their diameters, and that the sequence was different in the two types of block.