PAIN MECHANISMS — A REVIEW
I. Characteristics of the peripheral receptors*

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This paper is the first in a series summarizing recent developments in our understanding of pain mechanisms. While neural mechanisms must exist for the two components (perception and aversion) of pain experience, the prime role of pain systems is still unclear. The major difficulties encountered in experimentally evaluating pain are considered briefly, as it is essential that these be appreciated by workers in this field. General sensory mechanisms are briefly summarized, including factors determining whether conscious awareness of a stimulus occurs and the acuity of stimulus site localization. Nociceptors ("pain" receptors) are considered in terms of their structural characteristics and fibre groups. Although it is still unclear precisely how nociceptors are activated, their known functional characteristics probably provide the basis for distinguishing stabbing from burning pain, and for the sensations associated with primary hyperalgesia.

Role of the pain system

With few exceptions, pain is experienced by all people. However, although pain is responsible for a great deal of human suffering, it still proves difficult to define pain precisely. The following has perhaps proved the most comprehensive in recent years: pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'(IASP Subcommittee on Taxonomy 1979). This definition suggests that a pain experience has two essential components. The first, the perception of the actual, threatened or imagined tissue damage, requires the presence of an appropriate sensory mechanism. This sensory mechanism, in addition to detecting appropriate signals, must be able to code for these stimuli in terms of their intensity and location as well as their physical and temporal properties. The second component of pain is that of aversion or unpleasantness. This requires the presence of a neural mechanism which, subsequent to such interpretation, will motivate appropriate physiological and psychological changes such as various somatic, autonomic or emotional responses. Even although the responses that usually accompany a pain sensation will often help to maintain homeostatic conditions, this need not be the case, and sometimes the responses may in fact prove most disadvantageous (see Bonica 1979).

Recently it was suggested that pain should be considered as an awareness of a need state, rather like hunger and thirst, instead of being viewed as a sensation (Wall 1979). This raises the interesting, and as yet infrequently examined consideration that the purpose of pain is primarily to promote healing rather than to avoid further injury. Regardless of what is the prime role of the pain system, there is no doubt that the absence of pain-signalling mechanisms, such as occurs, for example, in patients suffering from congenital insensitivity to pain, may lead to severe problems, including ulceration and other severe infections, degenerative arthritis, and even premature death.

Experimental evaluation of pain

As the experience of pain is always subjective it cannot be observed or measured directly either in experimental or clinical studies, and must be inferred from various behavioural responses. In human studies the different experimental procedures employed usually require that the pain experience is translated into particular words or signs, although more recently the use of cerebral-evoked potentials has been introduced. The usual criteria used in animal experiments are either some form of muscular activity (for example tail flick, limping, writhing, withdrawal) or vocalization.

Any attempts to measure the extent of pain are faced with many difficulties. For example, not only do different emotional reactions and cognitive interpretations complicate behavioural responses, but there are also inherent difficulties in attempting to independently evaluate both the physiological and emotional aspects of pain (see Melzack 1975,

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Rollman 1977, Craig 1980, Wolff 1980, Price et al 1980). In addition, doubts have been expressed about the validity of comparing experimentally induced pain with naturally occurring pain, or acute pain with chronic pain (Procacci et al 1979, Bonica 1979). Furthermore, there are many problems associated with the choice of the experimental noxious stimulus employed to elicit the sensation of pain (Procacci et al 1979).

Even after the selection of a noxious stimulus, the problem is further complicated by differences in pain perception, not only between individuals, but also within the same individual. For example, daily and monthly rhythms of pain threshold exist (Procacci et al 1974), which may, in fact, represent changes in endogenous (naturally occurring) opioid systems (Frederickson et al 1977, Wesche and Frederickson 1979). Finally, there are, of course, ethical problems and considerations when undertaking experiments on humans and other animals aimed at elucidating pain mechanisms. While a detailed consideration of the above and of other difficulties is beyond the scope of this paper, many notable advances have been made in these areas, both in terms of outlining the problems and providing worthwhile alternative or additional methods (see the above references, and Lloyd and Appel 1976, Jones 1979, Grossberg and Grant 1978, Reading 1980)

In recent years there have been considerable advances in clarifying the neuroanatomical basis of pain, and in attempting to characterize the physiological and pharmacological properties of pain systems. Furthermore, attention has focused on endogenous pain control mechanisms that monitor and modulate the activity of the pain transmitting systems. It is the aim of this paper to review the advances in our understanding of peripheral pain mechanisms. In two subsequent papers, afferent pain pathways and endogenous pain modulation mechanisms will be considered (Watson 1981 a,b). Many detailed reports and reviews have appeared in recent years on different aspects of pain mechanisms. The reader is referred to these for additional information and references (for example Kerr 1975, Mayer and Price 1976, Casey 1978, Fields and Basbaum 1978, Snyder and Childers 1979, Beers and Bassett 1979, Kosterlitz and Terenius 1980). In a series of later papers this knowledge of pain systems and natural mechanisms of pain modulation will be related to the rationale for various electrophysical treatments employed for the relief or reduction of clinical pain by physiotherapists (Watson, in preparation).

General principles of sensory mechanisms

Receptors associated with primary afferent fibres must be able to detect some form of stimulus energy applied to the receptive field of that fibre, and respond to that stimulus in such a way that electrical currents are caused to flow. If a stimulus is of sufficient intensity that it reaches threshold for that fibre, action potentials (APs) or nerve impulses are generated, which then propagate along the primary afferent fibre to the central nervous system (CNS). An increased intensity of stimulation is associated with an increase in the frequency of APs generated, until some maximum frequency is achieved. Increasing stimulus strength also leads to recruitment of additional afferent fibres as their threshold values are reached.

The electrical activity generated as a result of the peripheral stimulus may or may not reach conscious awareness, depending on the nature and extent of various modulatory mechanisms at the receptors and at the synaptic junctions along the sensory pathway. At the receptor level, the frequency of APs generated is reduced if receptor adaptation occurs, whereas in the case of sensitization there is an increase in responsiveness and therefore in AP generation. This is considered in more detail later in this paper. Within the CNS, generation of action potentials in any one neuron depends on the net activity of all the converging input neurons, some of which are inhibitory and others of which are excitatory. An increase in the level of activity of excitatory input neurons or a decreased amount of converging inhibition would have a facilitatory effect, aiding AP generation in the output neuron. Conversely, reduced excitatory input or additional inhibitory input would suppress or reduce AP firing in the output neuron. From this brief consideration, it is evident that there exist mechanisms that may modify AP frequency and therefore influence the intensity of the resultant sensation if any. Of course, there may also be no conscious appreciation of a stimulus because it is sub-threshold for the activation of the particular receptor(s) in question. The above general features of sensory mechanisms are summarized in Figure 1.

It is worth noting that due to branching of the primary afferent fibres in the periphery, any one primary afferent will usually transmit sensory information that was collected from more than one receptor. This is shown diagramatically in Figure 2a. A single primary afferent fibre plus all its associated receptors is called a sensory unit, with the total collecting area for that sensory unit being called its receptive field. While some primary afferents may only be associated with a single receptive terminal or sensory cell, the majority (including those conveying information about actual or potential tissue damage) branch or diverge to varying extents. One consequence of such divergence and increased receptive field size is that it is more difficult for the sensory system to precisely code for a single point in or on the body. At a perceptual level, then, increased peripheral divergence will be associated with a decreased ability to precisely localize the site of a stimulus.

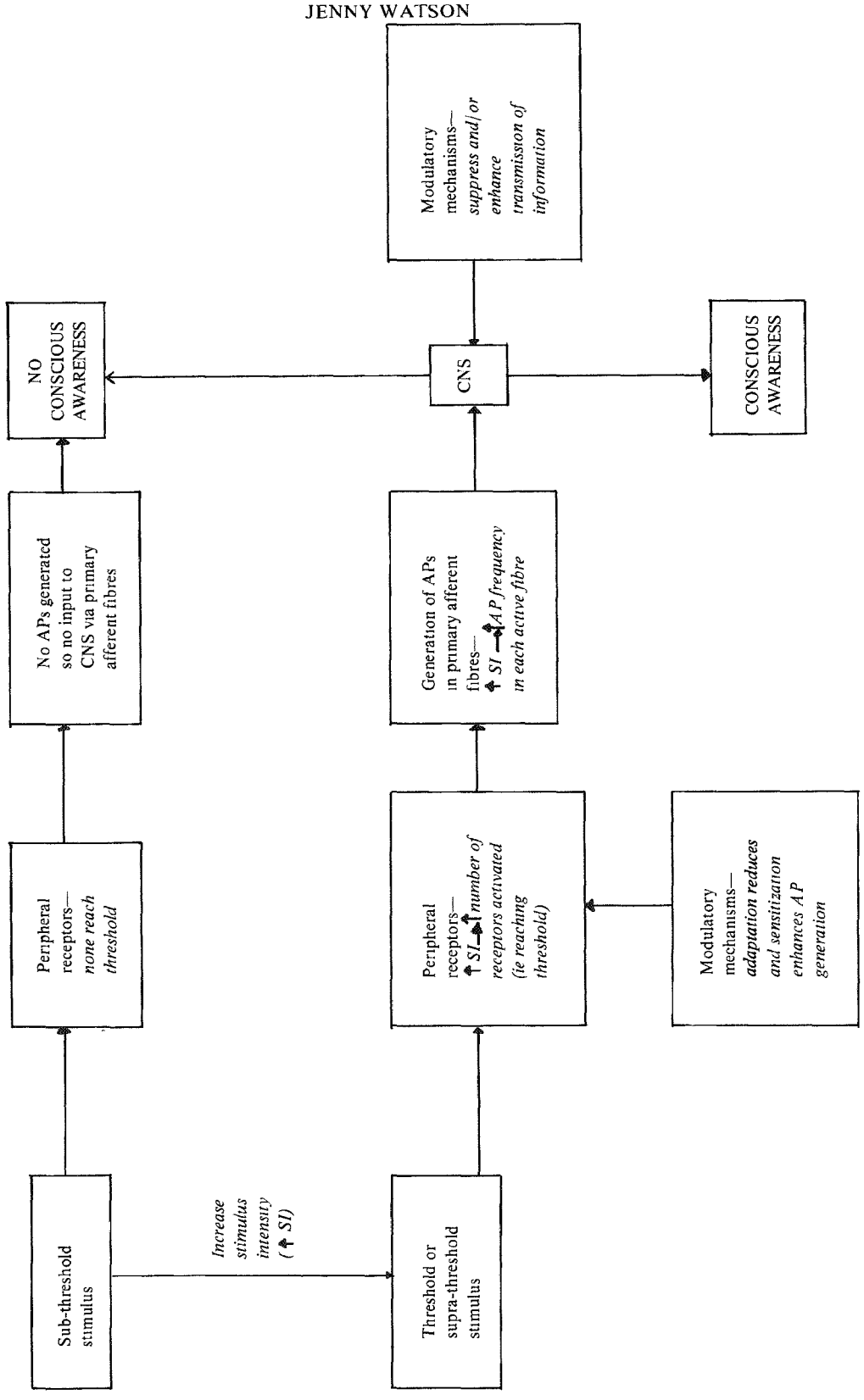
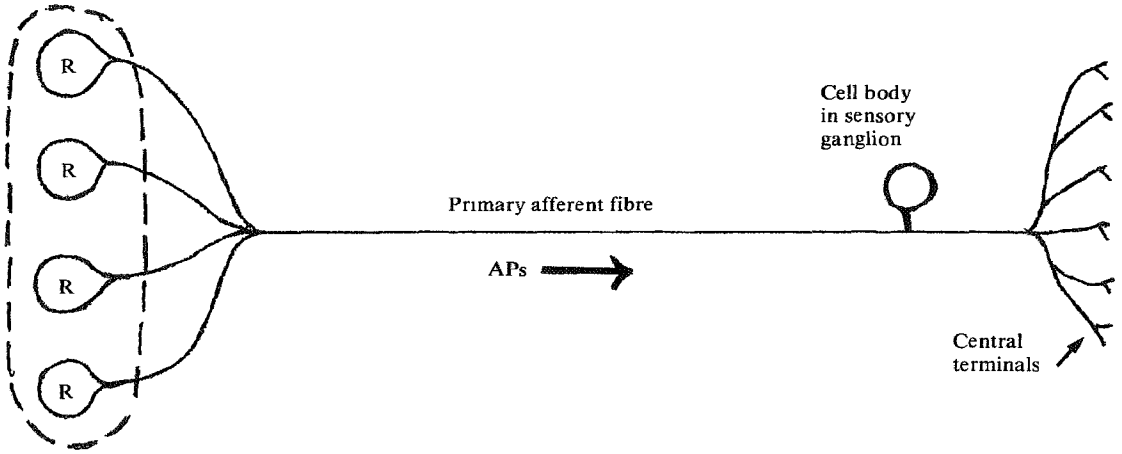


Figure 1: Schematic representation of the events occurring in a generalized sensory system

(a) A sensory unit, consisting of a primary afferent fibre plus all its associated receptors (R) and central branches



(b) Overlap of adjacent receptive fields (RF) and central terminals

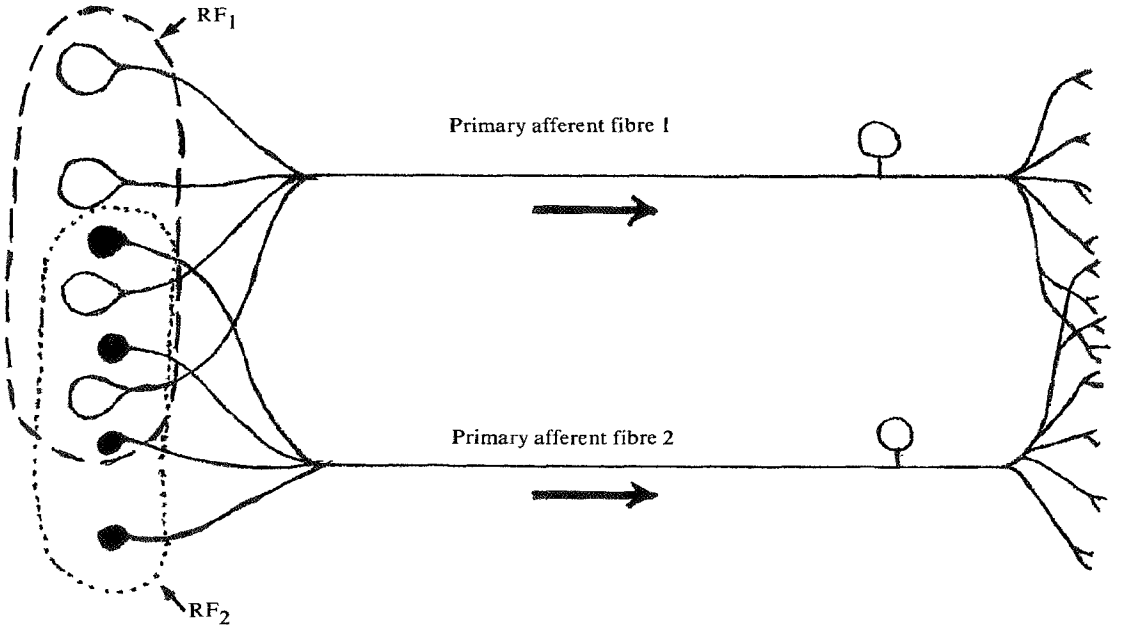


Figure 2: Diagram illustrating features of the peripheral sensory apparatus

Ability to precisely localize the site of stimulation is also influenced by the density of receptors in a given area (that is, the number of receptors per unit area), with an increased receptor density being associated with increased stimulus site acuity. Increased localization acuity also results from a decreased amount of overlap of adjacent receptive fields associated with a particular type of stimulus (see Figure 2b). Thus, if one compares sensitive areas of the body (such as the finger tips and lips) with less sensitive areas (such as the back of the trunk or the viscera), it is found that in the former the sensory units have lesser amounts of divergence while the receptive fields are smaller and overlap less. In addition, the total sensory innervation of the finger tips and lips is greater—that is, receptor density is higher.

Finally, the presence or absence of appropriate receptors in a particular area is also of relevance. Thus, for example, we have no photoreceptors other than those in the retina, and thus no light stimulus can be detected, much less precisely localized, if the eyes are closed. Of course, if the light source also generates heat, then thermoreceptors in the skin might allow some detection and localization to occur—but this would now be related to thermal input and not to the light stimulus itself.

Peripheral somatosensory fibres may be divided into groups as follows.

- large, rapidly conducting, myelinated fibres (groups A-alpha, beta and gamma), which are non-noxious, being involved with tactile and proprioceptive sensibility;
- small, slowly conducting, myelinated fibres (A-delta), some of which are associated with nociceptors ("pain" receptors);
- small, very slowly conducting, unmyelinated fibres (group C), about 90 per cent of which are noxious.

Thus, the somatic pain afferents belong to both the A-delta (A-δ) and C fibre groups (Van Hees and Gybels 1972, Torebjork and Hallin 1973, Perl 1980). Noxious information of visceral origin is carried by group C visceral afferents.

Structural considerations of nociceptors

It is generally agreed that specialized nerve endings exist which are responsive to different forms of somatic stimulation, yet little is known about the structure of nociceptors. They are usually described as being unspecialized, free nerve endings, although there have only been limited observations to support this view (Kruger et al 1979). As nociceptive afferents are considered to be very extensively branched, each primary afferent would have a large receptive field. This would contribute to the much poorer ability to precisely localize a noxious stimulus compared with, say, precise tactile acuity.

Nociceptors are found in different densities in different tissues of the body. While some tissues have high densities (for example skin, mucous membranes, arterial walls), most tissues are less densely innervated. However, there are some tissues that lack nociceptors—these include articular cartilage, articular fat pads, synovial membranes, periosteum, neural tissue within the CNS, most of the lungs, visceral pleura and visceral pericardium. Thus different tissues may be either more or less sensitive or insensitive to noxious stimulation, depending on the presence or absence of nociceptive innervation, and on the density of such innervation.

Functional characteristics of nociceptors

Not only do different tissues have different excitabilities, but nociceptors themselves have different sensitivities. They have been classified according to their responses to mechanical, thermal and chemical stimulation, and according to the conduction velocity of their afferent nerve fibre. While it is the A-δ and C fibres that convey nociceptive information to the central nervous system, this does not exclude the possibility that information carried by other fibre groups may also contribute to pain perception, nor does it imply that A-δ and C fibres are exclusively involved with the mediation of pain. As nociceptive afferents innervating the skin have been most extensively studied, it is these that will be considered below. For a detailed review of somatosensory activity in human peripheral nerves, see Vallbo et al (1979).

A-δ pain fibres are of two types. Some have a high threshold, responding only to intense mechanical stimulation, and these seem well adapted to transmit information related to the localized pricking or stabbing pain produced by mechanical stimulation. The second type of A-δ afferent, in addition to responding to intense mechanical stimuli, also responds to heat at both non-noxious and noxious skin temperatures. To date, only occasional recordings have been made from nociceptors supplied by A-δ fibres in humans (Van Hees 1976 a, Torebjork and Hallin 1973), although they are well documented for the skin of cats and monkeys (Perl 1968, Beck et al 1974, Campbell et al 1979).

The group C nociceptive afferents are polymodal, responding to noxious mechanical, noxious thermal and irritant chemical stimuli, and sometimes to intense cold. These fibres, which probably account for the burning type of second pain, have been identified in human skin (Torebjork 1974, Van Hees and Gybels 1972) as well as in the skin of cats and monkeys (Bessou and Perl 1969, Burgess and Perl 1973, Beitel and Dubner 1976 a-c, Duclaux et al 1980). Table 1 summarizes some of the important characteristics of nociceptors.

There are other important characteristics of the group C polymodal nociceptors, including an absence of spontaneous activity in normal skin at

Table 1: Summary of nociceptor classifications

Fibre group	*Fibre diameter (μm)*	*Structure*	*Conduction velocity (m/s)*	*Functional classification*	*Effective stimuli*	*Areas of innervation*	*Resultant sensation*
A-δ	*1-4*	Myelinated	5-15	Unimodal	Intense mechanical stimulation	Somatic structures	Pricking or stabbing
				Bimodal or polymodal	Intense mechanical and thermal stimuli, and non-noxious thermal stimuli		
C	< 1	Unmyelinated	0.2-2	Polymodal	Variety of noxious stimuli	Somatic structures	Burning
						Visceral	Aching

normal temperatures (Torebjork 1974). Furthermore, repeated application of low intensity noxious stimuli may lead to nociceptor sensitization. This is characterized by several signs, including a decrease in the stimulus intensity needed to reach threshold, an increased frequency of discharge elicited by a supra-threshold stimulus, a decreased latency to the first action potential, the presence of afterdischarge (that is, continued discharge after cessation of the stimulus), and the development of spontaneous activity (Beck et al 1974, Beitel and Dubner 1976 b and c, Perl 1976). Such enhanced sensitivity and afterdischarge may well contribute to the sensations associated with primary hyperalgesia—a decrease in burning pain threshold, enhanced thermal and mechanical sensitivity, and the onset of spontaneous burning pain.

Other C polymodal nociceptors may show fatigue and adaptation or suppression (Beitel and Dubner 1976 a and c, Price et al 1977), suggesting that thes neurons serve a functional role different from that of neurons that exhibit sensitization. As fatigue and adaptation may occur after repetitive or maintained stimulation respecitively, it is evident that some C nociceptors have little ability to maintain a given level of activity for long periods of time. In this regard, it is interesting to note that in human volunteers the C afferent activity is reported to be of low frequency, rarely exceeding 2 impulses per second, even when the stimuli are described as strongly painful (Van Hees 1976 b). It would therefore appear that increased fibre recruitment must also play a large part in signalling pain intensity.

The mechanisms involved in the activation of nociceptors by noxious stimulation are still unclear. However, there is evidence that noxious stimuli that lead to tissue damage are associated with the release of chemical substances that can lower pain threshold or directly produce pain (Bilisoly et al 1954, Chapman et al 1961, Chahl 1979). As yet it is not clear which is the critical substance (or substances) but of the many naturally occurring pain promoting substances (Keele 1970, Arcangeli and Galletti 1974, Chahl and Kirk 1975) four seem the most likely potential candidates. These are 5-hydroxytryptamine (5-HT) or serotonin (a naturally occurring amine), substance P (SP, a polypeptide consisting of 11 amino acids), a bradykinin-like substance (bradykinin is also a polypeptide), and one or more of the prostaglandins (naturally occurring lipids). Perhaps in any situation of tissue damage it is the release of an appropriate chemical substance (or of more than one such substance) that in fact activates the pain receptors and therefore leads to the generation of action potentials.

In many cases these chemicals would be released from damaged neighbouring non-neural elements. For example, 5-HT is found in highest concentrations in cells of the gastrointestinal tract and in blood platelets (as well as in certain areas of the CNS), bradykinin is produced in blood plasma as a result of tissue damage, and the various prostaglandins are present in different tissues and are released in response to a wide range of insults including mechanical, thermal and chemical damage. 5-HT, bradykinin and the prostaglandins all affect vascular smooth muscle and therefore local blood flow and vascular permeability, and they are all implicated in some way in various aspects of the inflammatory reactions that occur after tissue damage. In addition, they all affect neural excitability, causing pain, or sensitizing nociceptors to the effects of other stimuli.

SP, on the other hand, is not only present in non-neural elements (such as certain cells of the gastrointestinal tract) but is also located within nerves in the central and peripheral nervous system. The presence of SP in the peripheral processes of small diameter afferents, and its release as a result of electrical activity in the nerves (see, for example, Hokfelt et al 1976, Cuello et al 1978, Jessell et al 1979) supports the idea that it may be involved in peripheral nociceptive mechanisms. Perhaps it is the release of SP from these peripheral terminals that actually activates the nociceptors. Moreover, during repeated stimulation of a nociceptor, the resultant maintained AP discharge might produce SP release from the peripheral terminals, leading to nociceptor sensitization and the associated characteristic changes considered earlier.

Conclusions

During the past decade, and particularly in the past 5 years, there have been many advances in our understanding of peripheral mechanisms associated with nociception. Thus it is clear that the afferent fibres responding to noxious stimulation are of small diameter, belonging either to the smallest myelinated fibre group (A-δ) or to the even smaller diameter, slower conducting group of unmyelinated C fibres. The receptors themselves have been found to be complex functionally, responding to different forms of noxious stimulation and exhibiting changes in response patterns following prolonged or repeated stimulation.

However, there are still many aspects of nociceptor structure and function about which little is known. Our knowledge of nociceptor structure is very limited, and it is not evident what provides the basis for the different functional categories of nociceptors or for the changes in response characteristics that may occur during stimulation of long duration. In fact, the precise mechanism of nociceptor activation remains unclear, as does the role of the pain-promoting chemicals in pain perception. It is to be hoped that significant advances will be made in these areas in the next few years so that our knowledge of peripheral pain mechanisms will be extended further.

References

Arcangeli P and Galletti R (1974), 'Endogenous pain producing substances', in J J Bonica, P Procacci and C A Pagni (eds), *Recent Advances on Pain (Pathophysiology and Clinical Aspects),* Charles C Thomas, Springfield, Illinois, pp 82-104.

Beck P W, Handwerker H O and Zimmermann M (1974), 'Nervous outflow from the cat's foot during noxious radiant heat stimulation', *Brain Research,* **67,** 373-86.

Beers R F and Bassett E G (eds) (1979), *Mechanisms of Pain and Analgesic Compounds,* Raven Press New York.

Beitel R E and Dubner R (1976 a), 'Fatigue and adaptation in unmyelinated (C) polymodal nociceptors to mechanical and thermal stimuli applied to the monkey's face', *Brain Research,* **112,** 402-6.

Beitel R E and Dubner R (1976 b), 'Response of unmyelinated (C) polymodal nociceptors to thermal stimuli applied to monkey's face', *Journal of Neurophysiology,* **39,** 1160-75.

Beitel R E and Dubner R (1976 c), 'Sensitization and depression of C-polymodal nociceptors by noxious heat applied to the monkey's face', in J J Bonica and D Albe-Fessard (eds), *Advances in Pain Research and Therapy, Volume 1,* Raven Press, New York, pp 149-53.

Bessou P and Perl E R (1969), 'Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli', *Journal of Neurophysiology,* **32,** 1025-43.

Bilisoly F N, Goodell H and Wolff H G (1954), 'Vasodilatation, lowered pain threshold, and increased tissue vulnerability', *AMA Archives of Internal Medicine,* **94,** 759-73.

Bonica J J (1979), 'Important clinical aspects of acute and chronic pain', in R F Beers and E G Bassett (eds), *Mechanisms of Pain and Analgesic Compounds,* Raven Press, New York, pp 15-29.

Burgess P R and Perl E R (1973), 'Cutaneous mechanoreceptors and nociceptors', in A Iggo (ed), *Handbook of Sensory Physiology, Somatosensory System, Volume 2,* Springer, Heidelberg, pp 29-78.

Campbell J N, Meyer R A and LaMotte R H (1979), 'Sensitization of myelinated nociceptive afferents that innervate monkey hand', *Journal of Neurophysiology,* **42,** 1669-79.

Casey K L (1978), 'Neural mechanisms of pain', in E C Carterette and M P Friedman (eds), *Handbook of Perception, Volume VIB, Feeling and Hurting,* Academic Press, New York, pp 183-230.

Chahl L A (1979), 'Pain induced by inflammatory mediators', in R F Beers and E G Bassett (eds), *Mechanisms of Pain and Analgesic Compounds,* Raven Press, New York, pp 273-84.

Chahl L A and Kirk E J (1975), 'Toxins which produce pain', *Pain,* **1,** 3-49.

Chapman L F, Ramos A O, Goodell H and Wolff H G (1961), 'Neurohumoral features of afferent fibers in man: Their role in vasodilatation, inflammation, and pain', *Archives of Neurology,* **4,** 617-50.

Craig K D (1980), 'Ontogenetic and cultural influences on the expression of pain in man', in H W Kosterlitz and L Y Terenius (eds), *Pain and Society,* Verlag Chemie, Weinheim, pp 37-52.

Cuello A C, Del Fiacco M and Paxinos G (1978), 'The central and peripheral ends of the substance P-containing sensory neurones in the rat trigeminal system', *Brain Research,* **152,** 499-509.

Duclaux R, Schafer K and Hensel H (1980), 'Response of cold receptors to low skin temperatures in nose of the cat', *Journal of Neurophysiology,* **43,** 1571-77.

Fields H L and Basbaum A I (1978), 'Brainstem control of spinal pain-transmission neurons', *Annual Review of Physiology,* **40,** 217-48.

Frederickson R C A, Burgis V and Edwards J D (1977), 'Hyperalgesia induced by naloxone follows diurnal rhythm in responsivity to painful stimuli', *Science,* **198,**756-58.

Grossberg J M and Grant B F (1978), 'Clinical psychophysics: Applications of ratio scaling and signal detection methods to research on pain, fear, drugs, and medical decision making', *Psychological Bulletin,* **85,** 1154-76.

Hokfelt T, Elde R. Johansson O, Luft R, Nilsson G and Arimura A (1976), 'Immunohistochemical evidence for separate populations of somatostatin-containing and substance P-containing primary afferent neurons in the rat', *Neurosciences,1,* 131-36.

IASP Subcommittee on Taxonomy (1979), 'Pain terms: A list with definitions and notes on usage', *Pain,* **6,** 249-52.

Jessell T, Tsunoo A, Kanazawa I and Otsuka M (1979), 'Substance P: Depletion in the dorsal horn of rat spinal cord after section of the peripheral processes of primary sensory neurons', *Brain Research,* **168,** 247-59.

Jones B (1979), 'Signal detection theory and pain research', *Pain,* **7,** 305-12.

Keele C A (1970), 'Chemical causes of pain and itch', *Annual Review of Medicine,* **21,** 67-74.

Kerr F W (1975), 'Neuroanatomical substrates of nociception in the spinal cord', *Pain,* **1,** 325-56.

Kosterlitz H W and Terenius L Y (eds) (1980), *Pain and Society,* Verlag Chemie, Weinheim.

Kruger L. Perl E R and Sedivec M J (1979), 'Electron microscopic study of mechanical nociceptor endings in cat skin', *Anatomical Record,* **193,** 593-4.

Lloyd M A and Appel J B (1976), 'Signal detection theory and the psychophysics of pain: An introduction and review', *Psychosomatic Medicine,* **38,** 79-94.

Mayer D J and Price D D (1976), 'Central nervous system mechanisms of analgesia', *Pain,* **2,** 379-404.

Melzack R (1975), 'The McGill Pain Questionnaire: Major properties and scoring methods', *Pain,* **1,** 277-99.

Perl E R (1968), 'Myelinated afferent fibres innervating the primate skin and their response to noxious stimuli', *Journal of Physiology,* **197,** 593-615.

Perl E R (1976), 'Sensitization of nociceptors and its relation to sensation', in J J Bonica and D Albe-Fessard (eds), *Advances in Pain Research and Therapy, Volume 1,* Raven Press, New York, 17-28.

Perl E R (1980), Afferent basis of nociception and pain: Evidence from the characteristics of sensory receptors and their projections to the spinal dorsal horn', in J J Bonica (ed), *Pain,* Raven Press, New York, pp 19-45.

Price D D, Barrell J J and Gracely R H (1980), 'A psychophysical analysis of experiential factors that selectively influence the affective dimension of pain',*Pain,* **8,** 137-49.

Price D D, Hu J W, Dubner R and Gracely R H (1977), 'Peripheral suppression of first pain and central summation of second pain evoked by noxious heat pulses', *Pain,* **3,** 57-68.

Procacci P, Della Corte M, Zoppi M, Romano S, Maresca M and Voegelin M R (1974), 'Pain threshold measurements in man', in J J Bonica, P Procacci and C A Pagni (eds), *Recent Adances on Pain,* Charles C Thomas, Springfield, Illinois, pp 105-47.

Procacci P, Zoppi M and Maresca M (1979), 'Experimental pain in man', *Pain,* **6,** 123-40.

Reading A E (1980), 'A comparison of pain rating scale', *Journal of Psychosomatic Research,* **24,** 119-24.

Rollman G B (1977), 'Signal detection theory measurement of pain: A review and critique', *Pain,* **3,** 187-211.

Snyder S H and Childers S R (1979), 'Opiate receptors and opioid peptides', *Annual Review of Neurosciences,* **2,** 35-64.

Torebjork H E (1974), 'Afferent C units responding to mechanical, thermal and chemical stimuli in human non-glabrous skin', *Acta Physiologica Scandinavica,* **92,** 374-90.

Torebjork H E and Hallin R G (1973), 'Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. *Experimental Brain Research,* **16,** 321-32.

Vallbo A B, Hagbarth K E, Torebjork H E and Wallin B G (1979)''Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves', *Physiological Reviews,* **59,** 919-57.

Van Hees J (1976 a), 'Human C-fiber input during painful and nonpainful skin stimulation with radiant heat', in J J Bonica and D Albe-Fessard (eds), *Advances in Pain Research and Therapy, Volume 1,* Raven Press, New York, pp 35-40.

Van Hees J (1976 b), 'Single afferent C fiber activity in the human nerve during painful and nonpainful skin stimulation with radiant heat', in Y Zotterman (ed), *Sensory Function of the Skin in Primates,* Pergamon, Oxford, pp 503-5.

Van Hees J and Gybels J M (1972), 'Pain related to single afferent C fibers from human skin', *Brain Research,* **48,** 397-400.

Wall P D (1979), 'On the relation of injury to pain. The John J Bonica Lecture' *Pain,* **6,** 253-64.

Watson J (1981 a), 'Pain mechanisms — a review. II. Afferent pain pathways', *The Australian Journal of Physiotherapy,* in press.

Watson J (1981 b), 'Pain mechanisms — a review. III. Endogenous pain control mechanisms, manuscript in preparation.

Wesche D L and Frederickson R C A (1979), 'Diurnal differences in opioid peptide levels correlated with nociceptive sensitivity', *Life Sciences,* **24,** 1861-67.

Wolff BB (1980), 'Perceptions of pain. What is it? How can it be measured?', *The Sciences,* **20,** 10-29.