

THE GATE CONTROL THEORY OF PAIN MECHANISMS

A RE-EXAMINATION AND RE-STATEMENT

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INTRODUCTION

IN 1965, Melzack and I proposed a gate control theory and later we modified and modernized the original proposal (Melzack, 1973; Wall, 1973, 1974, 1976). Nathan (1976) has written a detailed review in which he concentrates particularly on mechanisms. Here I would like to extend his review to show where new knowledge requires a modification of our previous thinking, where the theory stands now and where gaps in our knowledge still prevent movement from speculation to reality. There were certain points in our original statement which seem to have been misunderstood and these need clarification. The diagram of mechanism we published had all the disadvantages of excessive clarity with its emphasis on the substantia gelatinosa and presynaptic mechanisms. The body of the paper mentioned other possible mechanisms but it has seemed to some that the entire theory rested on the diagrammatic mechanism which we shall see is not the case. Of course there have been many interesting discoveries since 1965 which need reviewing. Some of these new facts show that the data on which some of the theory was based was frankly misleading. Finally we shall try to show where the persistent inadequacy of technique still prevents an elucidation of mechanism.

Specificity

Nathan writes 'The theory neglected the facts known about stimulus-specificity of nerve fibres'. There are two completely different uses of the word specificity, one diagnostic and the other prognostic. The diagnostic meaning is that one can specifically diagnose the nature of the events which occur at a peripheral receptor which generates nerve impulses. All investigations of peripheral nerve fibres have shown that under defined conditions there is a fixed and specific relation between stimulus and response. Any theory which neglects these facts should indeed be dismissed. The general paper which Melzack and I wrote in 1962 and the more

detailed one in 1965 started from the fact of stimulus-response specificity in this diagnostic sense. It is true, of course, that preceding stimuli and concomitant events modify the excitability of a nerve terminal and that nerves respond to adequate changes of both mechanical, thermal and chemical perturbations of their environment but these addenda do not deny the basic specificity of the stimulus-response connection under defined conditions. However, we do take very strong issue with the use of the term specificity in its predictive prognostic sense. This version states that if a nerve impulse is detected in a particular type of nerve fibre, then one can make a specific prediction of the type of sensation which will result. The diagnostic use of the word refers to the past cause of the observed nerve impulse and we accept this as fitting the overwhelming body of facts. The predictive use of the word states what will happen in the future as a consequence of the impulses. Far from neglecting the second use of the word specificity the major point of both our papers (1962, 1965) was that we denied that the facts allowed one to move from the observations of impulses in some special fraction of peripheral fibres to a prediction that a specific sensation would inevitably result. In insisting on this differentiation, we were not being particularly revolutionary. The introduction of the word 'nocipient' by Sherrington (1903) was an example of a diagnostic word: a structure detecting the existence of a noxious event is a nociceptor. The discovery of a nociceptor does not allow a *volte face* to label the fibre a 'pain' fibre which presumes an ability to predict the consequences of excitation of nociceptors. The use of the word 'specific' in its diagnostic sense frees one to classify nerve fibres in many more ways than is possible if a classification is attempted where each category of fibre must be associated with a modality of sensation.

Pain

Our research and thinking was prompted by the problems of pain and its wild and variable relation to the stimulus which evokes it. We then tried to propose ways in which this psychological phenomenon could be related to the rigid stimulus bound response properties of peripheral nerve. It is true that in exactly defined experimental situations, the trained subject can relate perceived pain strength to stimulus intensity but even amongst trained subjects a comparison of studies shows a wide variation of the relationship reported in different laboratories (Sternbach and Tursky, 1964). In the real world outside the laboratory, the variation of the relationship between pain and injury occupies all positions between injury with no pain and pain with no injury. These variations are not to be dismissed as vagaries of the mind and they are therefore a proper study for science and neurology. Not only does the subjective statement vary but the objective signs of reflex activity and autonomic responses are equally and independently variable. Some variation follows known rules. Injury is followed by tenderness. Some tenderness, primary hyperæsthesia, is to be explained by the sensitization of previously high threshold endings by tissue breakdown of products so that light

pressure evokes impulses in fibres which previously required intense pressure for excitation. Such a change in characteristics of stimulus response requires no modification of classical theory. However, if primary hyperæsthesia persists, a secondary tenderness spreads to areas far distant from the injury. The most dramatic examples occur in referred pain where normal skin becomes tender indicating some deep and distant disorder. Here innocuous stimuli to normal tissue evoke pain. Any theory of pain must take such pain into account. Similarly the neuropathies, some painful, some painless, must be accounted for. In 1965 we attempted to consider all types of pain and their variations and to suggest a way in which the facts then known about physiology and anatomy might be brought together to produce a correct framework for pain mechanisms. We broke out of the straight-jacket of classical theory only to find ourselves still in a mad-house. To help understand the present position, I would like first to make a general re-statement of the gate control theory in a form which I think is useful and defensible and then to discuss the details in which we were clearly wrong in the light of subsequent work and the details which remain unknown.

Gate Control Theory: a General Re-statement

(1) Information about the presence of injury is transmitted to the central nervous system by peripheral nerves. Certain small diameter fibres ($A\delta$ and C) respond only to injury while others with lower thresholds increase their discharge frequency if the stimulus reaches noxious levels.

(2) Cells in the spinal cord or fifth nerve nucleus which are excited by these injury signals are also facilitated or inhibited by other peripheral nerve fibres which carry information about innocuous events.

(3) Descending control systems originating in the brain modulate the excitability of the cells which transmit information about injury.

Therefore the brain receives messages about injury by way of a gate controlled system which is influenced by (1) injury signals, (2) other types of afferent impulse and (3) descending control.

Peripheral Nerves

Normal. In 1965, the literature on mammalian nociceptors was wrong and highly misleading because it appeared that adequate investigations of all types of peripheral nerve fibres had been carried out. In the entire literature, only 20 myelinated fibres which could be called nociceptors had been described. The most complete study by Hunt and McIntyre (1960) found 7 nociceptors among 421 A fibres. This careful paper showed that their distribution of observed conduction velocities

matched the observed distribution of fibre diameters and therefore it seemed that they had adequately sampled the entire A population. Of the unmyelinated C fibres, Iggo had reported a few nociceptors (1960). It seemed possible, however, that these might have been damaged by his dissection method because Douglas and Ritchie (1957) with their non-intrusive collision technique reported that all C fibres responded to low intensity stimuli. We reasonably concluded 'These data suggest that a small number of specialized fibres may exist that respond only to intense stimulation' (Melzack and Wall, 1965). We knew of course from the extensive work from Adrian (1931) and Zotterman (1939) and Collins, Nulsen and Randt (1960) that it had been repeatedly shown that stimulation of smaller diameter A and C fibres evoked pain and we had to match this fact with the apparent rarity of pure nociceptors. The suggested solution was that an important part of the injury signal was the high frequency and massed firing of those fibres which had a wide dynamic range and responded to low level stimuli and then increased their discharge rate with more intense stimuli. These wide dynamic range fibres also cluster in the smaller diameter range. Electrical stimuli which excited such fibres would then deliver a false injury signal because of the combined spatial and temporal summation of the impulses on central cells.

The facts were wrong. The dissection and recording techniques had grossly biased the sampling in favour of larger fibres. We now know, thanks largely to the single fibre recordings in animals of Iggo, and Perl and Burgess, that substantial numbers of nociceptors exist (reviewed in Iggo, 1973). The micro-electrode technique of Vallbo and Hagbarth shows that these fibres also exist in man (Torebjork and Hallin, 1973, 1974; Van Hees and Gybels, 1972). Some of these nociceptors become sensitized by prolonged or repeated noxious stimulation so that their threshold drops and they are excited by normally innocuous stimuli (Bessou and Perl, 1969) an observation which may be related to the primary hyperalgesia. The sensitization of nociceptors does not exclude them from being useful in signalling the presence of damage since their receptors can be said to sense the continuing subliminal presence of injury which then reaches threshold when minor innocuous stimuli occur. Some terminals become less sensitive following injury and these clearly do not signal the sequelæ of injury or contribute to the pain suffered at some time after injury. The discovery of the class of nociceptive fibres is of obvious importance but as we stated (1965) 'this does not mean that they are "pain fibres" in that they must always produce pain and only pain when they are stimulated'. Nor does it mean that the high frequency discharge of low threshold fibres of wide dynamic range can now be neglected as playing no role in conveying to the CNS part of the message that injury exists.

Pathological peripheral fibres. The 1965 paper was written before the present explosion of information about the anatomical state of nerves in the peripheral neuropathies. We were highly influenced by the one detailed study available, on post-herpetic neuralgia (Noordenbos, 1959) in which Weddell had shown that

intercostal nerve biopsy specimens provided by Noordenbos had a preferential loss of large myelinated fibres and Noordenbos had generalized from this observation to propose that the pain was a consequence of a loss of inhibition normally provided by the large fibres. We now know that loss of large fibres is not necessarily followed by pain. In Friedreich's ataxia (Dyck, Lambert and Nichols, 1971) there is just such a preferential large fibre deficit without pain. I thought it might still be possible to defend the generalization for adults since Friedreich's ataxia begins at a very early age and it is possible that spinal cord compensations occur during the development of the unusual afferent pattern. This is no longer tenable, however, since Thomas (1975) showed that the polyneuropathy of renal failure in adults is not associated with complaints of pain although there is preferential destruction of large fibres. Any attempt to correlate the remaining fibre diameter spectrum with the symptomatology of neuropathies is no longer possible as is apparent in recent reviews (Dyck, Thomas and Lambert, 1974; Thomas, 1975). All combinations have been reported. For example, Fabry's disease is associated with loss of small myelinated fibres and pain (Kocen and Thomas, 1970) but one hereditary sensory neuropathy (Schoene, Asbury, Astrom and Masters, 1970) is associated with a loss of myelinated fibres, preserved C fibres and analgesia. In an attempt to make sense of this chaos, Dyck, Lambert and O'Brien (1976) introduced the dynamic factor of the presence of ongoing degeneration as well as the static existence of some particular fibre spectrum at the time of biopsy. Of their 72 patients with peripheral neuropathy, pain was present in 19 of 25 patients with acute fibre degeneration and only in 5 of 34 patients with other types of degeneration. Their conclusion is less impressive when one notices that 12 of the 19 patients with pain and acute degeneration had only 'a slight degree of pain, not a chief complaint and analgesics were not used'. However, it does seem reasonable to conclude that fibre diameter alone is not enough or is completely irrelevant to explain the origin of pain in the neuropathies. How can this be? One possible answer is that the biopsy has not sampled the relevant region of nerve. In a case of tabes dorsalis, the peripheral fibre spectrum was normal in spite of complaints of pain (Dyck, Lambert and Nichols, 1971), and one may presume that in this case the disorder was central to the dorsal root ganglion. In experimental neuromas of the sciatic nerve of the rat, the fibre spectrum of the parent sciatic nerve fibre is almost normal but the small myelinated afferents and the unmyelinated afferents conduct impulses from the neuroma (Devor and Wall, 1978). An anatomical study of the neuroma does not permit a statement of the diameter of the parent fibres which give rise to conducting fine sprouts which make up the neuroma. This leads to a further problem in interpreting a biopsy spectrum since one cannot know that an observed fine fibre is not connected to a larger fibre or what are the central connections of the observed fibre or what are the properties of its peripheral receptor. Obviously anatomy does not predict physiology. Intact fibres may be completely or partially blocked. Furthermore, as implied by Dyck *et al.* (1976), degenerating fibres may become spontaneously active or easily excited. Diamond (1959) showed

that regenerating fibres become sensitive to acetylcholine. Wall and Gutnick (1974*a, b*) showed that fibre sprouts within a neuroma are spontaneously active, sensitive to pressure, silenced by repetitive antidromic invasion and sensitive to noradrenaline. Evidently degenerating, sprouting and regenerating fibres have unusual impulse generation and conduction properties. It might be thought that recording from single fibres in patients with neuropathies would resolve these issues but this is not entirely true because, like the biopsy, only one area is observed and the central destination of an observed impulse is not known. It is evident that we are unfortunately almost as free to speculate about the cause of pain in neuropathies now as we were in 1965 because the cause is unknown.

Cord Cells Responding to Injury

Since only a partial survey of spinal cord cells had been carried out by 1965, we postulated the existence of injury detecting cells and gave them the non-committal name of T cells. Now that many more cells have been recorded, one must first ask what are the criteria by which cells will be labelled as being concerned with pain mechanisms. Those committed to specificity theory consider only cells responding to injury and to no other stimuli. I take a more conservative approach and consider all cells responding monosynaptically to nociceptive afferents. Some would require that candidate cells must send axons into the contralateral ventral white matter. This is an unrealistic requirement since peripherally evoked pain recurs some weeks or months after anterolateral cordotomies. Some would even require that the cells must project to the thalamus, an even more unrealistic requirement in view of the generally unsatisfactory results of thalamotomies for the long-term treatment of pain (White and Sweet, 1969). It is not even necessary that the cells should project into long running pathways since it has been known since Schiff that bilateral and polysynaptic pathways can mediate pain (Basbaum, 1973). It would be ideal if one could correlate the firing of cells with behaviour evoked by strong stimuli to determine the necessary if not sufficient conditions for the evocation of pain but no such experiments are available. Similarly, no chemical or surgical blockade succeeds in permanent abolition of pain unless a complete disruption of projection pathways is achieved. Therefore these manœuvres do not yet provide experimental evidence for selecting which cells or axons are crucial. A novel method introduced by Mayer, Price and Becker (1975) in which stimulus parameters needed to evoke pain and to stimulate particular types of cells are compared, offers a way of identifying cells involved in pain. What are the candidate cells?

Marginal cells, lamina 1. Cells exist in this lamina which respond only to nociceptive afferents and to no others (Christensen and Perl, 1970). Some of these project into contralateral ventral white matter and some of these even as far as the thalamus (Dilly, Wall and Webster, 1968; Trevino, Coulter and Willis, 1973; Kumazawa, Perl, Burgess and Whitehorn, 1975). One must warn that such cells have been detected by these skilled and hard workers in very small numbers; an

average of only two cells responding specifically to a nociceptive input have been recorded from each experimental animal. It would seem premature to adopt these cells as all that is necessary to explain pain mechanisms as Kerr (1975) has done. They exist in a population of cells most of which receive convergences from many types of peripheral afferent (Wall, 1968). This fact warns that one should be cautious in attributing one and only one function to a particular cell since, as we shall see, the degree of convergence is under control of other afferents and descending systems and is also dependent on the activity of segmental interneurons. Furthermore, these cells do not match a number of simple expected correlations between their firing and pain behaviour. A powerful substance such as bradykinin does not excite them and their discharge is not prolonged following injury (Christensen and Perl, 1970).

Lamina 5 cells. There are large numbers of cells in lamina 5 which respond to both myelinated and unmyelinated nociceptive afferents (Wall, 1967). They respond to injury and to algescic substances (Besson, Conseiller, Hamann and Maillard, 1972). Their response to injury is decreased in the presence of narcotics and anaesthetics (reviewed by Mayer and Price, 1976). Some have cutaneous receptive fields, while some receive high threshold afferents from muscle and others from viscera (Pomeranz, Wall and Weber, 1968). In addition to their response to nociceptive afferents, most of these cells also respond to low threshold afferents. Their receptive fields are therefore complex (Hillman and Wall, 1969). The most dramatic of these convergences of high and low threshold afferents are on those cells which respond to high threshold visceral afferents and also to low threshold afferents from skin (Pomeranz *et al.*, 1968). The existence of these low threshold excitatory convergences exclude these cells as candidates if complete specificity is required, but includes them if one wishes to explain such phenomena as hyperaesthesia where light stimuli increase pain. Some of these cells project to opposite ventral white matter and some to thalamus (Trevino *et al.*, 1973). The papers of Mayer, Price and Becker (1975) and Price and Mayer (1975) show that cells of this type are strong candidates for playing a role in pain evoked by stimulation of the ventro-lateral cord in man.

Other cells. A system of cells responding to intense peripheral stimulation and conducting slowly along the core of the spinal cord, medulla and mid-brain was described by Collins and Randt (1960); no single unit recordings have yet been made. It must be warned that recording methods still do not allow an exhaustive sampling of spinal cord cells. Therefore it may be that crucial populations of small cells remain undetected. One obvious group of small cells which have until very recently resisted recording are those in substantia gelatinosa. Heimer and Wall (1968) showed that fine afferents terminate on these cells in cat and rat. Kumazawa and Perl (1977) have shown that cells in this region in monkey respond to nociceptive C afferents. Our own unpublished work on cat shows that there are several types of cells in substantia gelatinosa, many of which respond to low threshold

afferents. The anatomy of the region shows that cells only project over very short distances (Szentagothai, 1964). Therefore they might only play a local segmental role in modulating the transmission of impulses from arriving afferents to cells which project over long distances (Wall, 1962). However, it is also possible that they play a role in pain mechanisms as a system of multiple chains of short projection cells as suggested by Noordenbos (1959). A continuous column of spinal grey matter is not essential for the perception of pain since cases of syringomyelia have been seen with complete obliteration of some segments of grey matter but preservation of white matter and of pain sensation. It is quite possible, however, that short loops of axons extend from grey to white to grey matter and thereby bypass the interrupted continuous column of grey matter in such cases.

Do Peripheral Afferents Inhibit the Cells Excited by Nociceptive Afferents?

An essential feature of our hypothesis was that cells excited by injury afferents would be inhibited by low threshold afferents. Subsequent discoveries have fully supported this aspect of the theory. Cervero, Iggo and Ogawa (1976) show that the discharge of the lamina 1 cells which are excited by noxious heating or by electrical stimulation of the A delta and C cutaneous afferents are inhibited by electrical stimulation of the large (Group 2) cutaneous myelinated afferents. An essential feature of the organization of lamina 5 cells is that they possess an inhibitory surround receptive field which is activated by low threshold afferents (Hillman and Wall, 1969). From the excitatory centre of the receptive field, low threshold afferents evoke an excitation followed by a prolonged period of inhibition. Since the low threshold large diameter myelinated afferents send collaterals rostrally in the dorsal columns, it is not surprising that dorsal column stimulation also inhibits lamina 5 cells (Hillman and Wall, 1969). Foreman, Beall, Applebaum, Coulter and Willis (1976) show that this inhibition is produced in the response of spinothalamic tract neurons in primates by stimulation of the dorsal columns. Electrical stimulation of bundles of axons is, of course, a crude often misleading manoeuvre; since it bypasses the specificity of input from different terminals, it fails to initiate the natural temporal pattern of impulses and it smears the differing effects which depend on the spatial origin of the fibres. In spite of this crudity, electrical stimulation of peripheral nerves or dorsal columns partially imitates the inhibition of lamina 5 cells which can be produced by discrete light pressure stimuli in spatially specific parts of the cells' receptive fields. All the candidate cells which respond to injury and which have been tested for their response to low threshold afferents have been shown to be inhibited.

What is the Mechanism of the Afferent Inhibition?

Melzack and I (1965) proposed as a secondary hypothesis that the gate control might be operated by a pre-synaptic mechanism but we also stated that post-

synaptic mechanisms could also operate. In the diagram we made the error, for the sake of simplicity, of showing only a pre-synaptic mechanism and a number of critics including Nathan have missed what was written in the text and have assumed that we proposed only a pre-synaptic mechanism and furthermore that the whole theory rested on this mechanism. The theory in fact rests on the presence of inhibitions and facilitations and these are undoubted. The question of whether these are pre- or post-synaptic is secondary but, of course, of considerable interest. Hongo, Jankowska and Lundberg (1968) showed that there were undoubted signs of post-synaptic inhibition and this work remains the only definite identified location of an inhibition. This does not exclude the possibility that pre-synaptic inhibition might not also operate. It is certain that there are depolarizations of the terminals of the afferent fibres. These generate the dorsal root potentials and the lowering of threshold of the afferent fibre's terminals. The mechanism by which this afferent depolarization occurs remains in doubt. The depolarization is very loosely coupled with an inhibition of transmission from afferents to interneurons. We had suggested that these pre-synaptic changes were associated with a block of transmission from the entering fibres into the terminal arborization (Howland, Wall, Lettvin, McCulloch and Pitts, 1955) and Eccles (1964) had proposed that a depolarization of terminals would result in a decrease of transmitter release. Both of these suggestions are based on circumstantial evidence and still lack proof in the mammal. Neither of these proposals excluded that there was not a concomitant and perhaps predominant post-synaptic change which explained the observed inhibition. I wish to emphasize that an undoubted pre-synaptic depolarization occurs; its origin is unknown; it roughly coincides with an inhibition; however, for the only candidate cells which have been examined, there are also post-synaptic changes. Therefore, it is still a matter of speculation to propose the origin of the observed inhibition. Unlike some invertebrate synapses, the mammalian dorsal horn still contains synaptic interconnections too small and too intricately interwoven to allow definite causal mechanisms to be demonstrated which explain observed input-output functions.

It was proposed that the cells of substantia gelatinosa played a role in the modulation of transmission. Their anatomical location with short running axons interposed in the junction region of afferents and dendrites made them suitable for this role. Further details of this anatomy (Kerr, 1975) emphasize this possibility but do not help in the pre- or post-synaptic controversy. A positive physiological reason for their inclusion was the observation that the Lissauer tract which interconnects the cells of substantia gelatinosa was capable of spreading the primary afferent terminal depolarization from one segment to another (Wall, 1962). Since that time Denny-Brown, Kirk and Yanagisawa (1973) have given more substantial reasons for involving the Lissauer tract and therefore the substantia gelatinosa in the regulation of the effectiveness of afferent impulses. They showed that the dermatome subserved by an isolated dorsal root, as tested by behavioural reaction to cutaneous stimulation, was greatly expanded if the Lissauer tract, entering the

innervated segment, was sectioned. Exciting and important as this observation is, it must be pointed out that it cannot tell how the substantia gelatinosa cells are involved in the pathway from the dorsal root to the observed motor responses. It is clear that techniques will have to be developed to modify independently the action of substantia gelatinosa cells and to record from them before proceeding to test how they are involved in the excitability of reflex areas or sensory transmission. All the work since 1965 shows that cord cells responding to injury are subject to inhibitions of peripheral origin but the mechanism remains obscure.

Facilitations

There has been remarkably little progress on the subject of facilitation as distinct from excitation. The reason is a technical one. The cells under discussion are excited by small diameter afferents which conduct slowly and the action potentials in the fibres are difficult to record. In certain favourable situations, cells may respond only to a particular group of small afferents as in the case of lamina 5 cells responding to the splanchnic nerve (Pomeranz *et al.*, 1968) or the lamina 1 cells (Christensen and Perl, 1970). This allows a satisfactory timing of the first discharge of the cell and a proof that it is responding, probably monosynaptically, to the leading edge of the arriving slow volley; but many of these cells then respond repetitively and it is not easy to prove if these subsequent responses of the cell are due to excitation by trailing slowly conducted impulses in the afferent volley or are produced by some reverberation within the cell or by the action of some nearby cells. We proposed in 1965 that a source of long lasting facilitation was a hyperpolarization of the terminals of afferent fibres produced by the arrival of volleys in small diameter afferents. There was, for a time, a controversy as to whether this primary afferent hyperpolarization existed at all but it now seems generally agreed that hyperpolarizations exist but are not necessarily associated with the arrival of afferent volleys in small nociceptive afferents (reviewed by Wall, 1973). In earlier work (Wall, 1959) I gave reasons to suggest that the prolonged repetitive firing of dorsal horn interneurons was neither a property of the afferent volley nor of the responding transmitting cells and therefore must be attributed to some other mechanism. For the reasons stated, this problem has not been a major target of investigation although it will be important in understanding pain mechanisms particularly in those situations of hypæsthesia where slowly repeated stimuli result in a slow wind up of sensation reminiscent of the wind up of cell response (Mendell, 1966). These gradually increasing pains are evoked by such slowly repeated stimuli that each stimulus must leave behind it a period of facilitation which exaggerates the effect of the subsequent stimulus (Noordenbos, 1959) and cannot be explained by a dispersion of the arrival time of the afferent volley.

Are the Injury Detecting Cord Cells Subject to Descending Control?

An essential feature of the gate control hypothesis was that the cord cells which received nociceptive afferents would be under descending control and this has proved to be the case in all cells so far examined. In the decerebrate animal, a powerful tonically active inhibitory system within the pons and medulla projects into the dorsal horn. This system inhibits the effects of cutaneous and visceral afferents on dorsal horn neurons. This was first noticed by Sherrington and Sowton (1915) in comparing reflex activity in spinal and decerebrate animals. Wall (1967) showed that it was possible to follow the activity of single cells before, during and after the cold block of a segment of spinal cord which blocked the descending inhibition in cerebrate animals. Cervero *et al.* (1976) located 46 cells in the marginal layer, lamina 1, 35 of which responded only to nociceptive afferents and 11 responded to sensitive mechanoreceptors as well as to nociceptors. When the spinal cord was cold blocked, both types of cell became more excitable. The lamina 5 cells have been studied in more detail by Wall (1967) and Hillman and Wall (1969). In the decerebrate state, their receptive fields are smaller, the ongoing activity is less, the inhibitory areas are more effective and the response to injury is smaller than in the spinal state. Small lesions and micro-electrode stimulation show that this inhibitory pathway descends in the dorsolateral white matter. Other descending systems such as the pyramidal tract (Fetz, 1968) and vestibulospinal system (Erulkar, Sprague, Whitsel, Dogan and Janetta, 1966) also control dorsal horn interneurons. One of these systems descends indirectly from the periaqueductal grey matter of the mid-brain, PAG. Stimulation of this area produces a profound analgesia in animals and man (Reynolds, 1969; Mayer and Liebeskind, 1974; Adams, 1976). The same stimulation inhibits the response of lamina 5 cells to noxious stimuli (Oliveras, Radjemi, Guilbaud and Liebeskind, 1974). The behavioural analgesia must be produced by a descending inhibitory system since unilateral section of the dorsolateral white matter in rat thoracic cord abolishes the analgesia in the ipsilateral hind leg while leaving the other three limbs analgesic (Basbaum, Clanton and Fields, 1976; Basbaum, Marley and O'Keefe, 1976). The descending pathway seems to relay in the cells of the nucleus raphe magnus (Fields, Basbaum, Clanton and Anderson, 1977; Basbaum, Clanton and Fields, 1976) and to be dependent on monoaminergic transmitters (Engberg, Lundberg and Ryall, 1968; Akil and Liebeskind, 1975).

The Effect of the Success of Transcutaneous Nerve Stimulation on the Gate Control Theory

The most obvious prediction of the gate control theory was that stimulation of large diameter peripheral nerve fibres should raise the threshold for detecting injury in the region served by the stimulated nerve. Wall and Sweet (1967) immediately proceeded to test this with considerable trepidation since we did not know if the predicted threshold rise would be significant or, worse, if the excitatory

effects in man would overwhelm the inhibitory ones. We were well aware of the fact that electrical stimulation of peripheral nerve produces an abnormal concatenation of spatial and temporal convergences of peripheral afferents on to central cells. However, we hoped that the artificial barrage produced by low level peripheral nerve stimulation would have an overall inhibitory effect on human cord cells as it does in the cat. The predicted rise of threshold was shown to occur in normal subjects (Higgins, Tursky and Schwartz, 1971; Satron and Goldstein, 1973; Campbell and Taub, 1973). In certain patients with chronic intractable pain, the effect of transcutaneous electrical stimulation is sufficiently powerful for therapeutic use. In a series of 336 cases with peripheral disease reported by Long and Hagfors (1975), 129 gained full relief of pain from counterstimulation while of 60 cases with central disorders only 2 responded. In a survey of over 3000 patients at various centres, 25 to 30 per cent of patients previously completely incapacitated by chronic pain were more or less completely relieved of pain (Long and Hagfors, 1975). Eleven of 30 chronic severe cases of post-herpetic neuralgia responded satisfactorily over long periods of time to transcutaneous stimulation (Nathan and Wall, 1974).

The theory proposed that stimulation of large diameter afferents would, on average, raise the threshold of central cells by increasing inhibition. In spite of the apparent support given to this proposal by the clinical results, I was from the beginning cautious about this conclusion for two reasons. One was the observation that certain types of pathological pain would completely disappear while leaving the area normally sensitive to pin prick and pinch (Lindblom and Meyerson, 1975). This suggested that there was something special about these pains whose control did not necessarily interact with 'normal' pain. The second reason was that some patients experience relief for hours after minutes of stimulation while the inhibitions which we observed in animals only outlasted the stimulus for seconds.

Campbell and Taub (1973) proposed that the electrical stimulation was so intense that the peripheral nerves themselves were blocked. Using pulse widths ten times those normally used and voltages five times higher, they presented possible evidence that peripheral nerves were blocked. Ignelzi and Nyquist (1976) also show peripheral nerve block in animals but they appear to have applied the full current across the sural nerve which is normally distributed across an entire leg. It has been known since the first man recovered from a bolt of lightning that intense electrical stimulation will block a nerve but can this be the explanation for the clinical results? The answer is no because if it were so the treated area should be anaesthetic, which it is not, and dorsal column stimulation should never work, although it does. Furthermore, in order to block a nerve with the intense currents used by Campbell and Taub, it is necessary to stimulate both large and small fibres before they block and even when part of the nerve is blocked the stimulation continues on the edge of the block. If only peripheral block were to occur the subject would be in intense pain during the onset of the block and while it was maintained. Since he is not, one must propose that some central inhibitory

mechanism has been set off by the initial low stimulus intensities used and that this inhibition is sufficient to allow the subject to tolerate the subsequent barrage generated by the higher currents.

Worried by the discrepancy between the clinical results and our predictions in which the clinical relief over-fulfilled the prediction, Wall and Gutnick (1974*a, b*) turned to examine the physiology of abnormal peripheral nerve. In rats, the sciatic nerve was cut and the end was placed in a tube so that the neuroma developed within the tube. Impulses were recorded in single dorsal root fibres whose ends lay within the neuroma. The intact parent fibres which sprout to form the neuroma include many small diameter fibres (Devor and Wall, 1978). Many of these fibre terminals give rise to ongoing activity. We placed stimulating electrodes on the proximal intact nerve and, in imitation of therapeutic counter-stimulation, a 100 Hz 0.1 ms square wave stimulation was applied. To our surprise, the antidromic invasion of the sensory terminals in the neuroma by the high frequency train of impulses was followed by long periods of silence of the previous ongoing activity and by long periods of insensitivity to electrical or mechanical stimuli. After a few seconds of tetanus, these neuroma terminals took minutes or hours to recover their previous sensitivity. If normal intact terminals are invaded by such volleys they recover their excitability within seconds. It is evident that either the nerve impulse generator mechanism or the transmission properties of axons in a neuroma have abnormal properties which fail to recover after high frequency driving. If these abnormal properties exist in the membrane of human pathological peripheral axons, it may then be that part of the explanation for the effectiveness of electrical stimulation lies in the periphery rather than in the cord. One must stress, however, that it is still necessary to postulate central inhibition as well as a possible peripheral mechanism since otherwise it would be impossible to reach the required voltages of stimulation without inflicting intolerable pain. If the stimulating current is gradually raised during the application of surface stimulation with 100 Hz 0.1 ms square waves, a voltage is reached at which the subject feels a strong buzzing tingling sensation. If a short burst of stimuli at this voltage is applied without preconditioning, the result is intense pain. The reason for this difference is that the preceding low level stimuli have produced central inhibition. The striking and long lasting abolition of pain from damaged nerve by counter-stimulation may therefore be due to a combination of central inhibition and peripheral inactivation, but it remains possible that such nerves generate unusual central patterns of response which are particularly easily inhibited by afferents.

SUMMARY AND CONCLUSIONS

In 1965, we proposed that the transmission of information about injury from the periphery to the first central cells was under control. The setting of this control or gate was influenced by peripheral afferents, other than those which signalled injury. The gate was also influenced by impulses descending from the brain.

Subsequent work has fully supported and enlarged this view. All the cells so far discovered which transmit information from nociceptors are inhibited by low threshold afferents and by descending controls. The mechanism by which this control is achieved remains completely unknown. Pre-synaptic inhibition as a phenomenon isolated from post-synaptic inhibition is in doubt. Whether the inhibitions and facilitations are pre-synaptic or post-synaptic or both is unknown. The role of the substantia gelatinosa in any function is unknown. That a gate control exists is no longer open to doubt but its functional role and its detailed mechanism remain open for speculation and for experiment.

REFERENCES

- ADAMS, J. E. (1976) Naloxone reversal of analgesia produced by brain stimulation in man. *Pain*, **2**, 161-166.
- ADRIAN, E. D. (1931) The messages in sensory nerve fibres and their interpretation. *Proceedings of the Royal Society, B*, **109**, 1-18.
- AKIL, H. and LIEBESKIND, J. C. (1975) Monoaminergic mechanisms of stimulation produced analgesia. *Brain Research, Amsterdam*, **94**, 279-296.
- BASBAUM, A. I. (1973) Conduction of the effects of noxious stimulation by short-fibre multisynaptic system in the spinal cord of the rat. *Experimental Neurology*, **40**, 699-716.
- CLANTON, C. H. and FIELDS, H. L. (1976) Opiate and stimulus-produced analgesia: functional anatomy of a medullo-spinal pathway. *Proceedings of the National Academy of Sciences*, **73**, 4685-4688.
- MARLEY, N. and O'KEEFE, J. (1976) Effects of spinal cord lesions on the analgesic properties of electrical brain stimulation. In: *Advances in Pain Research and Therapy*. Edited by J. J. Bonica. New York: Raven Press, vol. 1.
- BESSON, J. M., CONSEILLER, C., HAMANN, K. F. and MAILLARD, M. C. (1972) Modifications of dorsal horn cell activities in the spinal cord after intra-arterial injection of bradykinin. *Journal of Physiology*, **221**, 189-205.
- BESSOU, P. and PERL, E. R. (1969) Response of cutaneous sensory units with unmyelinated fibres to noxious stimuli. *Journal of Neurophysiology*, **32**, 1025-1043.
- CAMPBELL, J. N. and TAUB, A. (1973) Local analgesia from percutaneous electrical stimulation. *Archives of Neurology, Chicago*, **28**, 347-350.
- CERVERO, F., IGGO, A. and OGAWA, H. (1976) Nociceptor driven dorsal horn neurones in the lumbar spinal cord of the cat. *Pain*, **2**, 5-24.
- CHRISTENSEN, B. N. and PERL, E. R. (1970) Spinal neurons specifically excited by noxious or thermal stimuli. *Journal of Neurophysiology*, **33**, 293-307.
- COLLINS, W. F. Jr., NULSEN, F. E. and RANDT, C. T. (1960) Relation of peripheral nerve size and sensation in man. *Archives of Neurology, Chicago*, **3**, 381-385.
- and RANDT, C. T. (1960) Midbrain evoked responses relating to peripheral unmyelinated C fibres in cat. *Journal of Neurophysiology*, **23**, 47-53.

- DENNY-BROWN, D., KIRK, E. J. and YANAGISAWA, N. (1973) The tract of Lissauer in relation to sensory transmission in the dorsal horn of spinal cord in the macaque. *Journal of Comparative Neurology*, **151**, 175-200.
- DEVOR, M. and WALL, P. D. (1978) The physiology of sensation after peripheral nerve injury, regeneration and neuroma formation. In: *The Physiology and Pathobiology of Axons*. Edited by S. G. Waxman. New York: Raven Press.
- DIAMOND, J. (1959) The effects of injecting acetylcholine into normal and regenerating nerves. *Journal of Physiology*, **145**, 611-629.
- DILLY, P. N., WALL, P. D. and WEBSTER, L. E. (1968) Cells of origin of the spinothalamic tract in the cat and rat. *Experimental Neurology*, **21**, 550-562.
- DOUGLAS, W. W. and RITCHIE, J. M. (1957) Non-medullated fibres in the saphenous nerve which signal touch. *Journal of Physiology*, **139**, 385-399.
- DYCK, P. J., LAMBERT, E. H. and NICHOLS, P. (1971) Sensation related to compound action potentials and number and sizes of myelinated and unmyelinated fibres of sural nerve in health Friedrich's ataxia, hereditary sensory neuropathy, and tabes dorsalis. In: *Handbook of EEG and Clinical Neurophysiology*. Edited by A. Bemond. Amsterdam: Elsevier, vol. 9, pp. 83-118.
- and O'BRIEN, P. C. (1976) Pain in peripheral neuropathy related to rate and kind of fibre degeneration. *Neurology, Minneapolis*, **22**, 466-471.
- THOMAS, P. K. and LAMBERT, E. H., Editors (1974) *Peripheral Neuropathy*, Philadelphia: Saunders.
- ECCLES, J. C. (1964) Presynaptic inhibition in the spinal cord. In: *Progress in Brain Research. Vol. 12, Physiology of Spinal Neurons*. Edited by J. C. Eccles and J. P. Schädé, Amsterdam: Elsevier.
- ENGBERG, I., LUNDBERG, A. and RYALL, R. W. (1968) Is the tonic decerebrate inhibition of reflex paths mediated by monoaminergic pathways. *Acta Physiologica Scandinavica*, **72**, 123-133.
- ERULKAR, S. D., SPRAGUE, J. M., WHITSEL, B. L., DOGAN, S. and JANETTA, P. J. (1966) Organisation of the vestibular projection to the spinal cord of cat. *Journal of Neurophysiology*, **29**, 626-664.
- FETZ, E. (1968) Pyramidal tract effects on interneurons in cat spinal cord. *Journal of Neurophysiology*, **31**, 69-80.
- FIELDS, H. L., BASBAUM, A. I., CLANTON, C. H. and ANDERSON, S. D. (1977) Nucleus raphe magnus inhibition of spinal cord dorsal horn neurons. *Proceedings of the National Academy of Sciences*. In press.
- FOREMAN, R. D., BEALL, J. E., APPLEBAUM, A. E., COULTER, J. D. and WILLIS, W. D. (1976) Effects of dorsal column stimulation on primate spinothalamic tract neurons. *Journal of Neurophysiology*, **39**, 534-546.
- HEIMER, L. and WALL, P. D. (1968) The dorsal root distribution of the substantia gelatinosa of the rat with a note on the distribution in the cat. *Experimental Brain Research*, **6**, 89-99.
- HIGGINS, J. D., TURSKY, B. and SCHWARTZ, G. E. (1971) Shock elicited pain and its reduction by concurrent tactile stimulation. *Science*, **72**, 866-867.
- HILLMAN, P. and WALL, P. D. (1969) Inhibitory and excitatory factors controlling lamina 5 cells. *Experimental Brain Research*, **9**, 284-306.
- HONGO, T., JANKOWSKA, E. and LUNDBERG, A. (1968) Post-synaptic excitation and inhibition from primary afferents in neurons of the spinocervical tract. *Journal of Physiology*, **199**, 569-592.

- HOWLAND, B., WALL, P. D., LETTVIN, J. Y., MCCULLOCH, W. C. and PITTS, W. (1955) Reflex inhibition by dorsal root interaction. *Journal of Neurophysiology*, **18**, 1-17.
- HUNT, C. C. and MCINTYRE, A. K. (1960) An analysis of fibre diameter and receptor characteristics of myelinated cutaneous afferents in cat. *Journal of Physiology*, **153**, 99-112.
- IGGO, A. (1960) Cutaneous mechanoreceptors with afferent C fibres. *Journal of Physiology*, **152**, 337-353.
- (1973) *Somatosensory System*, Berlin: Springer-Verlag, pp. 29-78.
- IGNELZI, R. J. and NYQUIST, J. K. (1976) Direct effect of electrical stimulation on peripheral nerve evoked activity. *Journal of Neurosurgery*, **45**, 159-165.
- KERR, F. W. L. (1975) Neuroanatomical substrates of nociception in the spinal cord. *Pain*, **1**, 325-356.
- KOCEN, R. S. and THOMAS, P. K. (1970) Peripheral nerve involvement in Fabry's disease. *Archives of Neurology, Chicago*, **22**, 81-89.
- KUMAZAWA, T. and PERL, E. R. (1978) Primate cutaneous receptors with unmyelinated fibres and their projections to the substantia gelatinosa. *Journal de Physiologie, Paris*. In press.
- ——— BURGESS, P. R. and WHITEHORN, D. (1975) Ascending projections from marginal zone neurons. *Journal of Comparative Neurology*, **162**, 1-12.
- LINDBLOM, U. and MEYERSON, B. A. (1975) Influence on touch, vibration and cutaneous pain of dorsal column stimulation in man. *Pain*, **1**, 257-270.
- LONG, D. M. and HAGFORS, N. (1975) Electrical stimulation in the nervous system: the current status of electrical stimulation of the nervous system for the relief of pain. *Pain*, **1**, 109-124.
- MAYER, D. J. and LIEBESKIND, J. C. (1974) Pain reduction by focal electrical stimulation of the brain. *Brain Research, Amsterdam*, **68**, 73-93.
- and PRICE, D. D. (1976) Central nervous system mechanisms of analgesia. *Pain*, **2**, 379-404.
- ——— and BECKER, D. P. (1975) Neurophysiological characterisation of the anterolateral spinal cord neurons contributing to pain perception in man. *Pain*, **1**, 51-58.
- MELZACK, R. (1973) *The Puzzle of Pain*. Harmondsworth, England: Penguin Education.
- and WALL, P. D. (1962) On the nature of cutaneous sensory mechanisms. *Brain*, **85**, 331-356.
- ——— (1965) Pain mechanisms: a new theory. *Science*, **150**, 971-979.
- MENDELL, L. M. (1966) Physiological properties of unmyelinated fibre projection to the spinal cord. *Experimental Neurology*, **16**, 316-332.
- NATHAN, P. W. (1976) The gate-control theory of pain. A critical review. *Brain*, **99**, 123-158.
- and WALL, P. D. (1974) Treatment of post-herpetic neuralgia by prolonged electric stimulation. *British Medical Journal*, **3**, 645-647.
- NOORDENBOS, W. (1959) *Pain*. Amsterdam: Elsevier.
- OLIVERAS, J. L., REDJEMI, J. M., GUILBAUD, G. and LIEBESKIND, J. C. (1974) Behavioural and electrophysiological evidence of pain inhibition from midbrain stimulation in the cat. *Experimental Brain Research*, **20**, 32-44.
- POMERANZ, B., WALL, P. D. and WEBER, W. V. (1968) Cord cells responding to fine myelinated afferents from viscera, muscle and skin. *Journal of Physiology*, **199**, 511-532.

- PRICE, D. D. and MAYER, D. J. (1975) Neurophysiological characterisation of the anterolateral quadrant neurons subserving pain in *macaca mulatta*. *Pain*, **1**, 59–72.
- REYNOLDS, D. V. (1969) Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science*, **164**, 444–445.
- SATRON, R. and GOLDSTEIN, M. N. (1973) Pain perception: modification of threshold of intolerance and cortical potentials by cutaneous stimulation. *Science*, **180**, 1201–1202.
- SCHOENE, W. C., ASBURY, A. L., ASTROM, K. E. and MASTERS, R. (1970) Hereditary sensory neuropathy. *Journal of Neurological Sciences*, **11**, 463–472.
- SHERRINGTON, C. S. (1903) Qualitative difference of spinal reflex corresponding to qualitative difference of cutaneous stimulus. *Journal of Physiology*, **30**, 39–46.
- and SOWTON, S. C. M. (1915) Observations of reflex responses to single break shocks. *Journal of Physiology*, **49**, 331–345.
- STERNBACH, R. A. and TURSKY, B. (1964) On the psychophysical power function in electric shock. *Psychonomic Science*, **1**, 217–243.
- SZENTAGOTHAÏ, J. (1964) Propriospinal pathways and their synapses. In: *Progress in Brain Research*, **2**, *Organisation of Spinal Cord*. Edited by J. C. Eccles and J. P. Schädé. Amsterdam: Elsevier.
- THOMAS, P. K. (1975) The anatomical substratum of pain. *Canadian Journal of Neurological Science*, **1**, 92–97.
- TOREBJORK, H. E. and HALLIN, R. G. (1973) Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human nerves. *Experimental Brain Research*, **16**, 321–332.
- (1974) Identification of afferent C units in intact human skin nerves. *Brain Research, Amsterdam*, **67**, 387–403.
- TREVINO, D., COULTER, J. D. and WILLIS, W. D. (1973) Location of cells of origin of the spinothalamic tract in the lumbar enlargement of the monkey. *Journal of Neurophysiology*, **36**, 750–761.
- VAN HEES, J. and GYBELS, J. M. (1972) Pain related to single afferent C fibres in human skin. *Brain Research, Amsterdam*, **48**, 397–400.
- WALL, P. D. (1959) Repetitive discharge of neurons. *Journal of Neurophysiology*, **22**, 305–320.
- (1962) The origin of a spinal cord slow potential. *Journal of Physiology*, **164**, 508–526.
- (1967) The laminar organization of dorsal horn and effects of descending impulses. *Journal of Physiology*, **188**, 403–423.
- (1968) Organization of cord cells which transmit sensory information. In: *The Skin Senses*. Edited by D. R. Kenshalo. Springfield: Thomas, pp. 512–533.
- (1973) Dorsal horn electrophysiology. In: *Handbook of Sensory Physiology*, Vol. 2. Berlin: Springer-Verlag, pp. 253–270.
- (1974) The future of attacks on pain. In: *Advances in Neurology. Vol. 4. Pain*. Edited by J. J. Bonica. New York: Raven Press.
- (1976) Modulation of pain by non-painful events. In: *Advances in Pain Research and Therapy*. Vol. 1. Edited by J. J. Bonica. New York: Raven Press.

- WALL, P. D. and GUTNICK, M. (1974*a*) Ongoing activity in peripheral nerves: II. The physiology and pharmacology of impulses originating in a neuroma. *Experimental Neurology*, **43**, 580–593.
- — (1974*b*) Properties of afferent nerve impulses originating from a neuroma. *Nature, London*, **248**, 740–743.
- and SWEET, W. H. (1967) Temporary abolition of pain in man. *Science*, **155**, 108–109.
- WHITE, J. C. and SWEET, W. H. (1969) *Pain and the Neurosurgeon*. Springfield: Thomas.
- ZOTTERMAN, Y. (1939) Touch, pain and tickling. *Journal of Physiology*, **95**, 1–28.

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