Persistent Pain

Modern Methods of Treatment Volume 1

Edited by Sampson Lipton

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SAMPSON LIPTON

Centre for Pain Relief,
Department of Medical
and Surgical Neurology,
Walton Hospital,
Liverpool, England

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Preface

Hitherto there have been two types of books on methods of treating pain. The first type is usually designed for the beginner and attempts to give a comprehensive picture of the subject in a relatively small number of pages. As the space is limited, only a few words, or at most a few pages can be devoted to each topic. The second type covers the whole field of pain adequately but not without inherent problems. The first consideration is the size of the book; it will be at least one thousand large pages in size, and probably fifteen hundred will be needed. Somewhere between three quarters of a million and one and a quarter million words will be required, and this number of words takes so long to put together that they may be out of date before they are in print. There are always some sections which change quickly and therefore need revision. Delays occur because contributors become ill, or die, or are overworking. A compromise has to be reached between what should be included and what can be included, and the book may not contain important recent advances.

It is hoped this series will overcome these defects. The book is written for the practitioner who requires knowledge of modern methods of pain relief and he may be a consultant, or a general practitioner, or even a medical student. The practitioner may not use the actual methods described (though he may where no elaborate apparatus is required) but will learn what is available and certainly be able to give informed advice to his patients.

In each volume a small number of subjects will be discussed in fair depth, the size of the volume being about two hundred and fifty pages. They will be published at approximately eight monthly intervals and as the material will be written and published within this time it should be up to date. Comprehensive coverage of the subject will be provided in five or six consecutive volumes.

No apologia is necessary for the proposed publications. The subject of pain relief is of interest to all, from the self-interest of the patient and

the relatives to governmental concern. It has at last dawned on central administration that the cost of painful illness to the community is enormous. It is now seen that relieving persistent pain and returning even one person to productive activity adds to a nation's resources in a most cost effective way.

In this particular volume no attempt has been made to standardize the chapters. The individual authors are authorities in their own right and the written style, arrangement of the paragraphs, references, and bibliography were left to their discretion. In most cases they have adopted the editor's suggestion that references should be kept to a minimum, but where this has not been done they are printed in full. There has been some standardization as far as the headings have been concerned.

It remains to thank the contributors who, with one exception, produced their chapters on time (more or less); and Miss Norah Brown, who produced beautiful typescript from my mutilated copy; and by no means least my family for letting me get on with the job.

January, 1977

SAMPSON LIPTON

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The Anatomo-physiology of Pain

DAVID BOWSHER

University of Liverpool

I. First and Second Pain

Pain is the sensation induced by noxious (tissue-damaging) stimulation and, together with related experiences such as startle and itch, cannot be quantitatively described in terms of the stimulus, as can touch-pressure, relative temperature, sight, and hearing. It is usual to describe two forms of pain, of which the first (not called painful by all subjects) is pricking sensation, felt only in skin; this is accurately localized, rapidly conducted, and does not outlast the provoking stimulus. Pricking sensation, or first pain, when generated by a suitable stimulus in, for example, a limb, induces a flexion reflex which is part of a withdrawal response, serving a protective purpose by causing part of the whole of the organism to be removed from potential (or further) damage. So-called second pain, felt both in skin and deep tissues, on the other hand, builds up slowly, is diffuse, poorly localized, slowly conducted, and outlasts the provoking stimulus. Second or true pain, when unaccompanied by first pain, as, for example, in the case of a boil on the skin or an internal affection such as appendicitis, may bring about an increase in tonic muscular contraction by reflex action, but does not cause phasic flexion. This tendency to immobilization may also be seen as protective, since, in the absence of iatrogenic interference, it affords the best chance of recovery. The mechanism, however, may outlast or even defeat its own purpose; it then becomes pathological pain.

Most research has been conducted on pricking sensation; whereas it is always second pain (hereinafter called pain) with which the physician is concerned. As will be explained below, information about first or pricking pain is carried in the central nervous system by the spinothalamic tract, while information about second or true pain is transmitted centrally by the spino-reticulo-diencephalic system. Although in the spinal cord both travel in the anterolateral column, they are largely synaptically independent of one another beyond the dorsal horn of the spinal grey matter.

A. Receptors and Primary Afferent Fibres

Pricking receptors are probably mechanoreceptors, though their histological structure, if specialized, is unknown. The peripheral sensory fibres carrying messages generated by pinprick belong to the small myelinated category (Group III or Aδ).

Pain receptors may be bare nerve endings in skin and viscera. They are known physiologically as polymodal nociceptors, because activity in them is induced indifferently by high intensity mechanical, thermal, or chemical stimuli. It is not improbable that they are, in fact, chemoreceptors, in that the agent which actually sets them off is a substance released from damaged tissue—the damage being brought about by the stimuli listed. The peripheral nerves carrying these impulses are partly in the small myelinated (Group III), but chiefly in unmyelinated (Group IV or C) categories. In this context, it is interesting to note that while cutaneous fibres in the cat are connected with many receptor types, it has recently been shown in man that all cutaneous C fibres are linked to high-threshold receptors, i.e. potential nociceptors (Hallin and Torebjörk, 1974). It is of capital importance to bear in mind that peripheral nerves contain many more C fibres than fibres of any other category.

II. The Spinal Cord

So far as non-cerebellopetal sensory modalities are concerned, impulses generated in the periphery are carried upwards by two pathways: the dorsal columns and the anterolateral tract.

The dorsal columns are made up of the long central processes of large

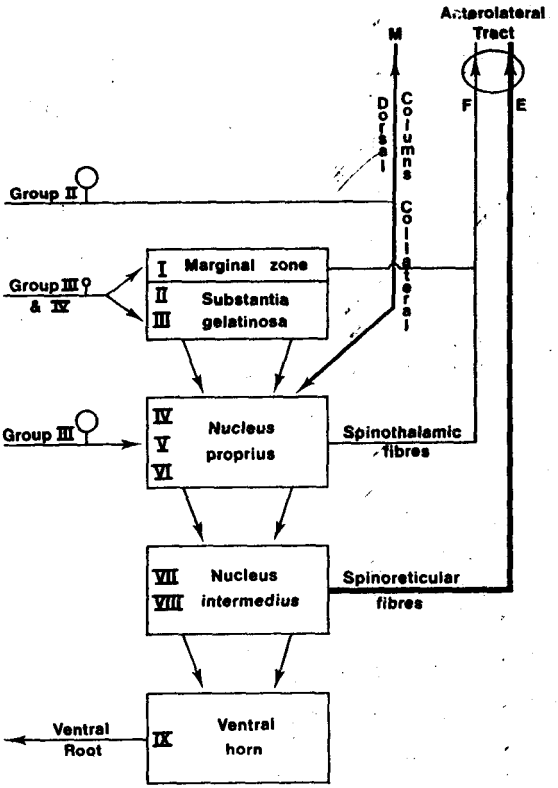

Fig. 1. Peripheral nerves and spinal cord. Groups II, III and IV correspond to large myelinated, small myelinated and unmyelinated primary afferent fibres respectively. The boxes represent the subdivisions of the spinal grey matter, with the laminae of Rexed enumerated on the left-hand side of each box. The arrows between boxes show the direction of convergent impulses, while the thickness of ascending arrows attempts to be vaguely proportional to the number of fibres in the pathways indicated.

primary afferent fibres (Group II) originating from low-threshold tactile and articular mechanoreceptors. Those dorsal column fibres coming from cutaneous mechanoreceptors, at their point of entry into the spinal cord, give off collaterals which make synaptic contact in the dorsal horn of the spinal grey matter.

Unmyelinated peripheral afferent fibres are believed to terminate in the substantia gelatinosa of the dorsal horn, while the small myelinated (Group III) afferents end in the nucleus proprius (lamina V of Rexed). To understand the mechanisms concerned with pain perception, it is

essential to be familiar with the organization of the spinal grey matter, and particularly with its input–output relationships.

1. *Spinal Laminae*

This organization has been clear since Rexed showed that the cells of the grey matter are arranged in nine successive laminae, enumerated from dorsal to ventral (a tenth surrounds the central canal) (Rexed, 1952). As shown in Fig. 1, lamina I corresponds to the marginal zone, II and III to the substantia gelatinosa, laminae IV, V and VI to the nucleus proprius, laminae VII and VIII to the intermediate nucleus, and lamina IX to the motoneurones of the ventral horn. Cells from each lamina converge onto those of the laminae deep to it, while peripheral input and ascending output are related to specific laminae (Wall, 1967).

A lamina which receives a direct peripheral input is, so to speak, dominated by that input; but it is also influenced, or modulated by the converging information coming from more dorsally placed laminae. Thus, for example, lamina V of the nucleus proprius receives small myelinated fibres (Group III) activated by pinprick, hot and cold receptors, while the large cells of the marginal zone (lamina I) receive only noxiously generated activity. The information from these two zones of the spinal grey matter is transmitted through spinothalamic fibres to that same (ventroposterior) thalamic nucleus which receives dorsal column impulses relayed through the medial lemniscus. If, however, the periphery is stimulated more intensely, so as to activate not only Group III but also Group IV (unmyelinated) fibres, the neurones of lamina V will receive convergent excitation from the substantia gelatinosa in addition to direct excitation from Group III peripheral afferents. This will bring about a degree of excitation sufficient to activate neurones in the deeper laminae VII and VIII, resulting in the upward transmission of information through spinoreticular axons, which form the vast majority of fibres ascending in the anterolateral quadrant of the spinal cord (Bowsher, 1957).

2. *Differential Transmission*

Without going into the mathematics of convergence and divergence, the above example can be used to illustrate the very important principles of differential transmission in the spinal cord (Fig. 2). To simplify the

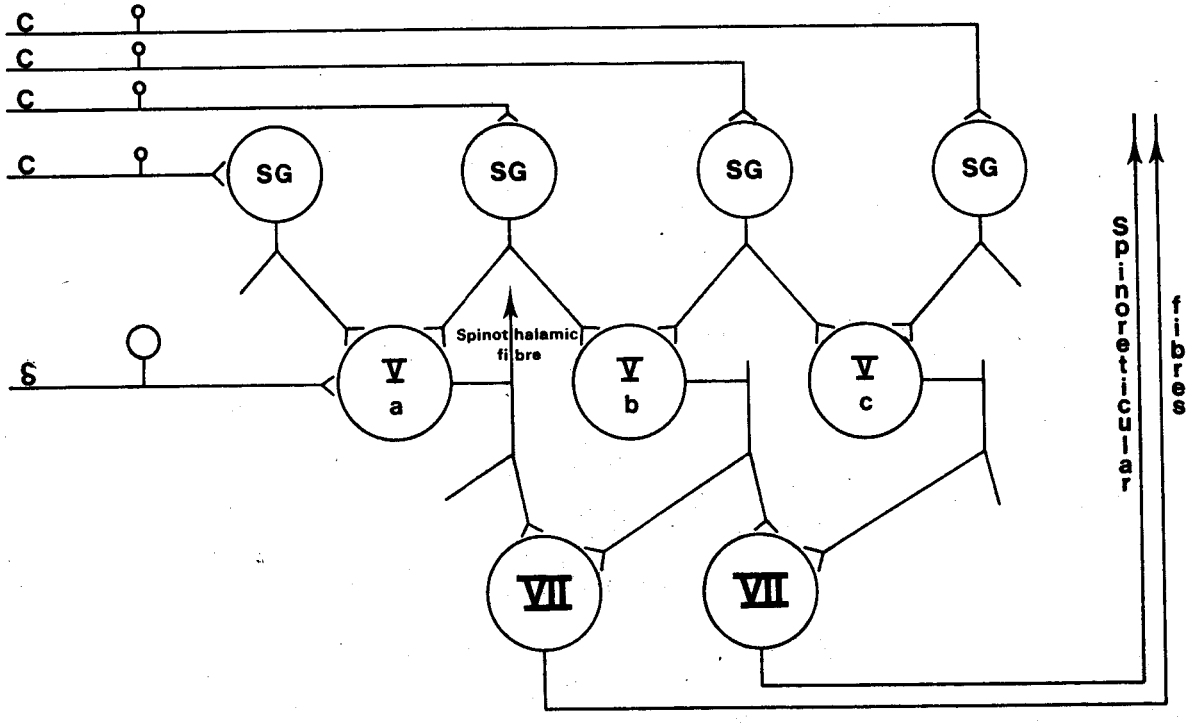

Fig. 2. C = unmyelinated primary afferent fibres; δ = small myelinated primary afferent fibres; SG = substantia gelatinosa; V and VII = fifth and seventh laminae of Rexed. For explanation see text.

situation, suppose that a single peripheral afferent synapse is capable of activating a cell within the dorsal horn, but that the activation of two intramedullary synapses is necessary to generate an impulse in a spinal cord neurone. A low-threshold punctate stimulus (prick) will activate a small myelinated fibre (δ). This in its turn activates the dorsal horn neurone Va, which transmits the information through its ascending axon to the thalamus (Willis, 1976), thence to the somatosensory cortex. Such a system is (i) modality specific, because only the specific receptor and its associated primary afferent fibre are involved; increasing intensity within the specific sub-modality is transduced as increasing frequency of transmission; and (ii) place-specific, because the neurone Va is related only to a specific peripheral receptive field. These are the characteristics of a *specific* or *lemniscal* system, and are also, of course, seen in the dorsal column-medial lemniscus system.

When the intensity of stimulation is increased to tissue-damaging level, nociceptors and their associated small unmyelinated fibres (C) will be brought into play, thus generating impulses in cells of the substantia gelatinosa (SG). These in turn diverge and converge (indirectly) onto cells of lamina V; if enough of these latter (e.g. a, b and c) are excited, they in their turn will activate cells in lamina VII, whence impulses will be transmitted upwards in spinoreticular fibres. This system has properties completely different from those of a lemniscal system, in that (i) modality specificity, in the usual sense of the term, is lost; the cells of lamina VII (and VIII) are not dominated by any single peripheral input (they receive none), but are excited by activity in all those more dorsally-placed neurones which receive all types of peripheral input; and (ii) the peripheral receptive field of such cells is perforce large and rather vague. These are the characteristics of a non-specific or extralemniscal system. Furthermore, there is reason to believe that intensity is expressed by the number of spinoreticular units recruited rather than by the frequency of impulse generation within single units, for it is known that temporal as well as spatial summation is necessary for the activation of some dorsal horn neurones by high-threshold peripheral receptors (Price *et al.*, 1971).

As we shall see, the information carried upwards by spinoreticular fibres undergoes further modification in the brain stem where similar phenomena of recruitment occur. Thus it cannot be stated that any one of the very large number of spinoreticular axons ascending in the anterolateral quadrant of the spinal white matter is a 'pain fibre'. What may rather be stated is that if an appropriate pattern of impulses passes upwards in a sufficiently large number of spinoreticular fibres to activate

a sufficiently large number of ascending reticular neurones the resulting conscious experience will qualify as painful.

3. *Segmental Collaterals*

A further anatomo-physiological phenomenon must be considered before the spinal story can be completed. This concerns the segmental collaterals of dorsal column fibres (Fig. 1). This collateral, under appropriate circumstances, exerts an inhibitory effect in lamina IV on the transmission of information from the substantia gelatinosa across lamina IV to deeper layers of the spinal grey matter, and presumably constitutes the basis of the 'gate control' mechanism of Melzack and Wall (1965). The primary afferents which divide to form dorsal column fibres on the one hand and segmental collaterals on the other are large (Group II) myelinated axons related to low-threshold cutaneous mechanoreceptors, and will therefore be activated by light as well as by intense mechanical stimuli. Thus, in the case of a mechanical stimulus sufficiently intense to activate unmyelinated fibres and gelatinosal cells, some of the information generated by the latter will be prevented from (ultimately) reaching laminae VII and VIII by the concomitant inhibitory action of the segmental collaterals of the large low-threshold fibres.

From the data given above, we are in a position to explain many of the sensory phenomena occurring at spinal cord level. Primacy of place should be given to a modern interpretation (Mumford and Bowsher, 1976) of the classical observations of Henry Head (Head and Rivers, 1908). It will be recalled that he noted that the first cutaneous sensations to be experienced during regeneration following a peripheral nerve lesion tended to be poorly localized and painful, or at least itchy; to this general category he gave the name 'protopathic'. As it is known that small unmyelinated fibres regenerate earlier than the large myelinated axons, it may safely be assumed that Head's protopathic sensations are due to the uninhibited transmission of information from the substantia gelatinosa to deeper layers of the spinal grey matter. With all peripheral fibres intact, it is necessary to generate a much greater barrage of impulses in the substantia gelatinosa before enough information 'breaks through' the inhibition brought about by activity in the collaterals of large low-threshold fibres. Because the pain engendered by, for example, a sharp slap outlasts the actual mechanical stimulus, our species has from time immemorial exploited dorsal horn physiology by rubbing the affected area; this type of stimulus activates (only) the

large low-threshold fibres whose segmental collaterals reduce the amount of information passed on by the excited cells of the substantia gelatinosa.

4. *Peripheral Electrical Stimulation*

More recently, this phenomenon has been made more effective by using electrical stimulation to bring about synchronous activation of the large cutaneous fibres and their collaterals. When the peripheral part of the large fibres is intact, stimulation can be applied to a peripheral nerve, and the synchronous barrage sent orthodromically into the spinal cord (Sweet and Wepsic, 1968). In those instances, such as phantom limb pain, where large peripheral fibres cannot be got at, a stimulator may be placed on or near the dorsal columns, so that a barrage may be delivered antidromically down the ascending dorsal column fibres and into the inhibitory segmental collaterals (Shealey *et al.*, 1967). Both these procedures have proved effective in the relief of certain types of chronic pain (see Chapter 7).

5. *Cordotomy*

The destruction of fibres ascending in the anterolateral columns of the spinal cord by open surgery or percutaneous electro-coagulation is also obviously effective in relieving pain (Chapters 7 and 2). Pinprick and thermal sensibility below and contralateral to the lesions are also lost, because the relatively small number of somatotopically organized spinothalamic fibres are intermingled with the very much larger number of spinoreticular fibres in the anterolateral quadrant (Bowsher, 1957). Cordotomy is, nowadays, usually only used for the relief of pain in terminal malignant disease, because of a tendency for pain to return, usually after about 18 months. Now, if the sensation of pain depends on the number of brainstem reticular neurones activated by an ascending pattern of impulses, it is obvious that when the number of intact spinoreticular fibres is reduced, fewer brainstem neurones will be excited by the remaining fibres. However, in the course of time, either or both of the following may occur: (i) alternative routes, involving spinospinal pathways, may 'open up' so that eventually the afferent barrage reaching brainstem reticular cells becomes quantitatively equivalent to its former level; (ii) undivided (including ipsilateral) spinoreticular fibres sprout so as to reoccupy the synaptic sites left vacant by the de-

struction of other efferents; this would be consistent with the phylogenetic primitiveness of central non-specific neurones (Bowsher, 1974).

III. The Brainstem

1. *Reticular Neurones*

It has been estimated that the brainstem of the cat contains some ten million reticular neurones (Scheibel and Scheibel, 1958); the number in man must be correspondingly greater. Some reticular neurones have descending axons, and eventually exert their influence on the motoneurones of the spinal cord; others have ascending axons, and yet others dichotomizing axons, with one branch passing upwards and one downwards. The ensemble of reticular neurones capable of transmitting impulses in a rostral direction constitute the ascending reticular activating system of Moruzzi and Magoun (1949); it is these cells which are activated by spinoreticular axons. It was shown by Brodal (1957) that ascending and descending reticular neurones are arranged in blocks such that axons of each type pass through the dendritic fields of the other; there thus exists a sort of ladder pattern, with one ascending and one descending upright, the rungs representing the interconnections; the significance of this will be discussed below. Here it should be noted that a significant number of reticular neurones with descending axons (reticulo-spinal neurones) are inhibitory in function.

The axons of non-specific spinoreticular, reticulo-reticular, and reticulo-diencephalic neurones collateralize very widely, in such a way that any one neurone supplies a very small number of terminals to each of a very large number of widely-dispersed secondary neurones (Fig. 3). This is in contrast with the axons of specific, lemniscal neurones, which make multiple, concentrated, contacts with small numbers of closely-grouped secondary neurones. This latter arrangement ensures both the maintenance of topical precision and security of synaptic transmission.

2. *Spatial and Temporal Summation*

Most brainstem reticular neurones are contacted by many thousands of afferent endings, (Bowsher and Westman, 1970), which come from a very large number of different sources. In the very highly simplified diagram of Fig. 3 it is imagined, as in Fig. 2, that two presynaptic

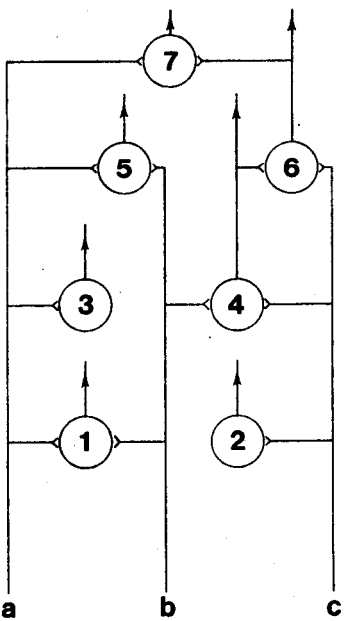

Fig. 3. 1 to 7 are rostrally-projecting ascending reticular neurones, while a, b and c are ascending spinal or reticular afferents. For explanation see text.

endings must be activated in order to fire a neurone. In the diagram, a, b, and c are spinoreticular axons; an impulse in any one of them would be insufficient to generate an impulse in any one of the ascending reticular neurones 1 to 7. Excitation in fibres a and b (but not c) would fire cells 1 and 5; excitation in b and c (but not a) would, in the first instance, fire cell 4, activity in which, added to excitation in a branch of fibre c, would then fire cell 6; activity in fibres a and c alone would have no effect. However, excitation arriving in all three spinoreticular fibres would fire not the four neurones represented by the simple sum of a + b and b + c, but five cells —1, 4, 5, 6 and 7; showing that a whole may be greater than the sum of its parts!

This grossly simplified diagram, which in reality would need to be multiplied many thousand-fold, illustrates two very important properties of the ascending reticular system: (i) it shows how additional cells may be 'recruited' by an increase in afferent activity, and (ii) it shows that activity generated in a pool of neurones is asynchronous, because variable numbers of synapses intervene between the first input

and the final output; thus a peripheral stimulus lasting x milliseconds will produce an evoked potential in the reticular formation lasting n × x milliseconds. Both these phenomena are in quantitative contrast to what happens in specific lemniscal systems.

The recruiting phenomenon as illustrated in Fig. 3 depends on spatial summation; but there is reason to believe that temporal summation may also occur. In any event, the cardinal fact is that the greater the afferent barrage ascending from the spinal cord the greater will be the number of brainstem neurones activated. Animal experiments suggest that in response to mechanical stimulation of the periphery, the number of reticular neurones activated is proportional (though not linearly) to the intensity of the stimulus (Bowsher and Petit, 1970). Thus we may suppose that the whole gamut of 'protopathic' sensation, from itch to agony, depends on the number of ascending reticular neurones activated.

3. *Localization of Pain*

There remains the question of localization of the stimulus (or pain). In the case of painful stimulation of the tegument in the neurologically intact subject, there is no problem, for specific lemniscal neurones with very discrete receptive fields maintained across all central synapses are perforce activated at the same time. But in the case of visceral pain, or peripheral pain arising in the absence of larger fibre activation (postherpetic neuralgia, causalgia, phantom limb pain), it is a matter of everyday clinical observation that the pain is more or less grossly localized by the patient, while recordings made experimentally in the brainstem reticular formation show that its cells can often be activated by stimuli applied to any part of the body. However, careful analysis of the activity of single cells in the reticular formation have shown that, in the cat, less than 25% of the neurones respond by the same discharge pattern to stimuli applied to different regions of the body. Furthermore, since some brainstem reticular neurones have more restricted peripheral fields, it is probable that even if a stimulus of the same intensity applied to different areas of the body were to activate the same total number of ascending reticular cells, stimulation of different regions would activate different sets of neurones within the general reticular pool. Thus the pattern of summed activity ascending from the reticular formation to higher levels of the brain would be characteristic, and different, from each peripheral stimulation site.

Overall, then, it can be said that the ascending reticular system pro-