TOWARD A NEUROPHYSIOLOGY OF PAIN

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PAIN COMMANDS attention. It commands the attention of those engaged in brain research because of its fundamental biological significance; it commands the attention of the clinician, for he is asked to alleviate it; and, almost by definition, it commands the patient's attention for, more than any of the other senses, pain has the capacity to tap motivational drives, disrupt thought and behavior, and influence feeling or affect.

WE MUST CONTINUALLY re-examine our working model of pain mechanisms. As in other disorders, intelligent approaches to management and therapy rely upon an understanding of the relevant basic sciences. A better understanding of the brain mechanisms involved in pain sensation would also strengthen our insight into motivational, emotional, and basic sensory processes. To clinician and sensory physiologist alike, no sensation is more important than pain.

THE BASIC neurophysiology of pain, however, is like the skeleton in the family closet; a general uneasiness inhibits discussion. Common clinical experience and observation belies the textbook explanation, but the urgencies of medicine preclude re-writing the textbook. Moreover, recent advances in sensory physiology or brain research are infrequently communicated to the clinical community, often because of a failure to appreciate their relevance. The clinician and the neurophysiologist each have observations and ideas of interest to the other; they are aware of the shortcomings of the long-standing theory of the pain mechanism, but both are reluctant to begin the task of changing some beautifully simple and well-entrenched concepts. This paper represents an effort to initiate such a change by examining the prevailing concept in the light of available evidence and by offering an alternative view.

THE NEED FOR A NEW CONCEPT

THE PREVAILING theory of the pain mechanism, the one taught in most medical schools today, holds that pain is a specific modality like vision or audition, "with its own central and peripheral apparatus."[107] The free nerve endings in the skin are regarded as pain receptors[36] which generate the impulses carried by small-diameter peripheral nerve fibers to the lateral spinothalamic tract and thence to a center in the somatosensory thalamus or cortex. The activation of neurons within this hypothetical center results in the experience of pain.

THERE IS AN embellishment to this idea. Sir Henry Head[41] reasoned that there are two types of pain: the "epicritic" or sharp, subjectively localized pain, and the "protopathic" or dull, boring, poorly localized type. Separate pathways and distinct fiber types have been suggested[13,14,41,107] for each of these types of pain on the bases of anatomical and physiological evidence. But the basic concept is unchanged. Pain, according to the traditional view, is determined by which fiber, which pathway, and which "center" is activated. The experience, then, is determined by the input with little or no allowance for information processing or modification by the central nervous system.

Central Control Determinats

THERE IS NO DOUBT as to the importance of the afferent input as a major determinant of pain sensation. There is convincing evidence, however, that

pain is strongly influenced by "higher central nervous system" activities. Anticipation,[45] anxiety and attention,[46] suggestion and placebos,[11,64] cultural background,[21] environmental factors,[11] hypnosis,[9] early experience,[65] and prior conditioning[84,85] all have a profound effect on pain experience. Beecher, for example, has observed that soldiers wounded in battle experienced significantly less pain or required less meditation than similarly afflicted male civilians.[11] The importance of environmental factors, suggestion, anxiety, and the placebo effect is, in fact, supported by the experience of every physician. The common experience of having been injured without knowing it demonstrates the importance of attention. Controlled animal experiments also emphasize the significance of higher central processes
. Melzack and Scott[65] found that dogs raised in partial sensory isolation would, when observed at maturity, repeatedly injure themselves and fail to withdraw from damaging stimuli with little or no evidence of pain. Pavlov[84,65] found that dogs would not show pain responses to noxious stimuli delivered to one limb if a food reward followed the stimulus. Noxious stimuli to other limbs, however, continued to evoke normal pain responses.

THESE EXPERIMENTAL and clinical observations are often regarded as variations in the "reaction to pain"[40] as though they were secondary considerations in the pain mechanism. Such reasoning leads one to conclude that: (1) the subjects under observation (including Melzack's and Pavlov's dogs) had some mysterious motives for suppressing their behavior, or (2) the pain they experienced was not really painful. The latter conclusion simply states the paradox of non-painful pain,[76] and the conceptual model of pain underlying the entire traditional view suggests that pain is *followed*, not accompanied, by motivation and affect.

AN ALTERNATIVE view, supported by the anatomical, physiological, and psychological evidence to be presented, is that the afferent input, and its effect on critical brain areas, is modified by on-going CNS activity. Indeed, Pavlov's observations indicate that information about the location of the stimulus reached the brain in time to activate these central control processes and thus modify the activity ascending over more slowly conducting pathways.

Motivational-Affective Determinants

SHERRINGTON[99] OBSERVED that "... affective tone is an attribute of all sensation, and among the affective tones of skin sensation is skin pain." The development of sensory physiology and psychophysics since Sherrington's time has emphasized pain as a sensory process and has led to relative neglect of its motivational and affective dimensions. Intense somatic stimuli can hardly be considered painful if they fail to evoke aversive behavior or are devoid of affective quality. Clinical studies of patients with frontal lobe lesions or lobotomy,[34] medical thalamic lesions,[59] congenital insensitivity to pain,[10,33] or pain asymbolia"[93,95] clearly reveal the motivational and affective dimension as an essential component of pain. These patients may have no loss of ability to detect pinprick as sharp, to judge the relative intensities of stimuli, or to localize the stimulus in space and time. The spatio-temporal and intensity aspects of the input are recognized, but there is a lack of the strong aversive drive and negative affect especially associated with clinical pain.[58,105]

CASES OF PERIPHERAL neuropathy or the "thalamic syndrome" emphasize the motivational-affective dimension of pain by revealing the lack of necessary correlation between stimulus intensity and response.[80] Gentle stimuli such as puffs of air or stroking with cotton may evoke prolonged and excruciating pain. The "trigger" phenomenon of trigeminal neuralgia or tic douloureux is another example which highlights the distinction

between the physical properties of the stimulus and the affective quality of experience.

THE TRADITIONAL theory of pain fails to account for the essential motivational-affective dimension. Textbooks of neurology, physiology and psychology characteristically deal with "pain sensation" in one section, and "aversive drives and punishment" in another, with no indication that the latter is an essential component of the former. In the discussion to follow, it will be seen that there is considerable overlap among the brain areas associated with the classical "pain pathway" and those regions now known to play a major role in motivational mechanisms. The neural systems subserving drive and affect must therefore be included in any proposed pain mechanism.

CURRENT EVIDENCE

The Afferent System

THE PREVAILING theory of pain reflects the widespread acceptance of von Frey's[36] contention that free nerve endings are "pain receptors" and that excitation of these ending or afferent fibers results in the sensation of pain. Subsequent physiological[22] and psycho-physiological experiments implicated thinly myelinated and unmyelinated afferent fibers as subserving "fast" or "epicritic" pain and "slow" or "protopathic" pain, respectively. The neural mechanism of pain could thus be no more than adequate stimulation of the appropriate fiber; the "pain fiber" would be the necessary and sufficient determinant of pain.

IT IS NOT POSSIBLE, however, to ascribe one sensation to an anatomically, distinct fiber or nerve ending.[67] Nearly 95% of the hairy surface of mammalian skin appears to be innervated only by free nerve endings.[112] The sensations of touch, pressure and temperature change can be elicited by stimulation of the cornea, which is served exclusively by free nerve endings.[55] Moreover, recent physiological studies;[30,50,51,101] have shown that the small diameter afferents do not, as a group, respond only to strong stimuli. Indeed, the majority of those studied are quite sensitive to thermal or mechanical stimuli, and many are sensitive to both forms of energy.[43] Some of the thinly myelinated afferents have been found to be high threshold mechanoreceptors, but these were not activated by strong chemical or thermal stimulation.[17] At present, a limited number of unmyelinated fibers would seem to function as a very high threshold afferent system, responsive only to intense thermal and mechanical stimuli.[43,51]

BUT THE CRITICAL afferents for pain may not, in fact, possess the physiological characteristic of a high threshold, broad energy spectrum system. Since the hyperpathias or hyperalgesias associated with certain neuropathies or the "thalamic syndrome" show that gentle stimuli may be painful,[80] the small diameter afferents, which recent clinical and human neurophysiological studies have shown to be *necessary* for pain,[23,106] may play their determining role at central levels, in the spinal cord and brain. The peripheral apparatus could then be regarded as an essential, but not exclusive, deterimant of pain. Neurophysiological studies of the spinal cord show, for example, that activity in small-diameter afferents increases the ventral root discharge produced by a large-fiber volley[70] and increases the post-stimulus discharge of neurons responding to gentle somatic stimuli.[20,69] The evidence[70] strongly suggests a *gating mechanism* whereby the output of some neurons in the spinal cord dorsal horn is determined by the proportion of small fibers contributing to the dorsal born input.[68] The sensory and reflex effects of activity in fine afferent fibers, then, are determined not only by the type of receptor stimulated, but, perhaps more importantly, by interaction with other inputs to central cells.

The Ascending Systems

THE SOMATOSENSORY system is composed of two major central pathways:

the dorsal and dorsolateral columns-medial lemniscal pathway (lemniscal system) and the ascending fibers of the antero-lateral spinal cord (anterolateral system). The anatomy of the lemniscal system has been studied and reviewed extensively,[14,71] and neurophysiological studies[88,89] have revealed much about the functional properties of this pathway. In general, the lemniscal system is functionally suited for spatial and temporal discrimination among somatic stimuli. At medullary, thalamic, and cortical levels, these neurons show a somatotopic organization with well-defined and limited receptive fields.[75,89,113] These cells respond to either light pressure, movement of hair, or joint movements; in some cases, the frequency of neural discharge is a continuous function of mild skin indentation or joint position.[74] Many elements of this system adapt rapidly, respond to high rates of stimulation,[73] and transmit their signals rapidly[53,72] to thalamus and cortex.

IN CONTRAST, THE anatomy and physiology of the anterolateral system has been studied less extensively. The recent work of Mehler,[62,63] however, reveals the extensive direct connections of this pathway. On phylogenetic and anatomical grounds, Mehler divides the anterolateral system into a more recently developed *neospinothalamic* part and an older, but persistent *palcospinothalamic* projection. The relatively larger *neospinothalamic* fibers ascend laterally in the brain stem to terminate in the nucleus ventralis posterolateralis of the dorsal thalamus. There is behavioral and physiological evidence[24,81,87,98] that the anterolateral system, by itself, may function in a spatio-temporal discriminative capacity. It is likely that this is achieved *via* the *neospinothalmic* route which projects, with the medial lemniscus, to the ventrobasal thalamus and which may be influenced by the segmental collaterals of the dorsal columns.[91]

THE *paleospinothalamic* fibers form what we shall call a *paramedial ascending system* which projects to the reticular formation of the medulla, midbrain, and medial-intralaminar thalamus. The paramedial ascending system and its associated structures are not organized to provide discrete spatial or temporal information. There is little or no evidence for discrete spatial information transfer to the reticular formation[6,8,12,20,97] or medial thalamus,[4,5,18,54] where somatensory input, though predominant, is mixed with other sensory afferents.[18,94,104]

THE STRIKING FEATURE of the paramedial ascending system is its relation to the *limbic system* and associated structures (Fig. 1). The medial forebrain structures (such as the hippo-campus and amygdala) forming a ring (limbus) around the upper brain stem have strong hypothalamic connections, a property shared by other diencephalic and brain stem areas. The former "rhinencephalon," then, is now known to be a richly inter-connected limbic *system* which plays a major role in non-olfactory, basic behavioral mechanisms.[90] It is now well established that stimulation or ablation of limbic system structures profoundly influences aversive drives or pain-related behavior. At the mesencephalic level, electrical stimulation of a region which includes the central gray, the ventral tectum and dorsal tegmentum produces strong aversive drive and behavior typical of responses to naturally occurring painful stimuli.[28, 49,22,103] Lesions of the central gray and adjacent midbrain tegmentum, in contrast, produced marked decreases in responsiveness to noxious stimuli.[66,102] At the thalamic level, "fear-like" responses, associated with escape behavior, have been elicited by stimulation in the dorsomedial and adjacent medial-intralaminar nuclei of the thalamus,[92] and lesions of the same area have provided relief from intractable pain.[44,59]

LIMBIC FOREBRAIN AREAS have also been implicated in pain-related processes. Electrical stimulation of the hippocampus, fornix, or amygdala may evoke escape or other attempts to stop
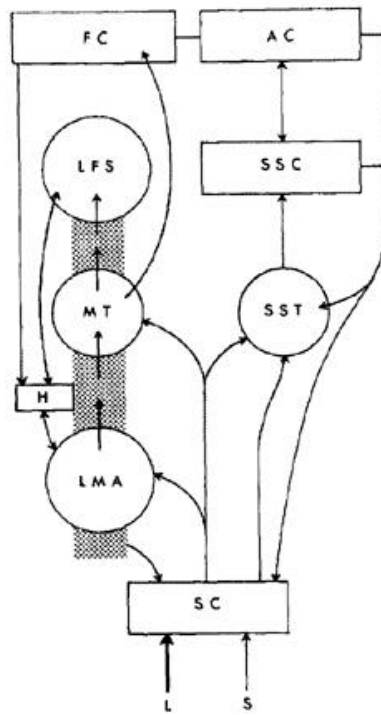
Figure 1

Schematic diagram of the anatomical foundation of the proposed pain model. On the right: thalamic and neocortical structures subserving discriminative capacity. On the left: reticular and limbic systems subserving motivational-affective functions. Ascending pathways from the spinal cord (SC) are: (1) the dorsal column-lemniscal and dorsolateral tracts (right ascending arrow) projecting to the somatosensory thalamus (SST) and cortex (SSC), and (2) the anterolateral pathway (left ascending arrow) to the somatosensory thalamus via the neospinothalamic tract, and to the reticular formation (stippled area), the limbic midbrain area (LMA) and medial thalamus (MT) via the paramedial ascending system. Descending pathways to spinal cord originate in somatosensory and associated cortical areas (AC) and in the reticular formation. Polysynaptic and reciprocal relationships in limbic and reticular systems are indicated. Other abbreviations: FC—frontal cortex; LFS—limbic forebrain structures (hippocampus, septum, amygdala, and associated cortex); H—hypothalamus. (The diagram of limbic-reticular structures is adapted from Nauta, 1958.)

stimulation,[28,29] as well as defensive reactions.[57,47] After ablation of the amygdala and overlying cortex, cats show marked changes in affective behavior, including decreased responsiveness to noxious stimuli.[96] Surgical section of the cingulum bundle, which connects the posterior frontal cortex to the hippocampus, also produces a loss of "negative affect" associated with intractable pain. This evidence indicates that limbic structures, although they play a role in many other functions,[90] provide a neural basis for the aversive drive and affect comprising the motivational dimension of pain.

IT IS PARTICULARLY significant, then, to note that fibers of the *paramedial ascending system* project to the medial brain stem reticular formation and the midbrain central gray.[15,62,63] The midbrain central gray is part of the "limbic midbrain area"[77] that (1) projects diffusely to the adjacent reticular formation, (2) connects reciprocally with the hypothalamus *via* Schutz' fasciculus and thus permits interaction with the limbic forebrain areas by way of the medial forebrain bundle, (3) connects with the medial and intralaminar thalamic nuclei, and (4) receives projections from the granular frontal cortex.[78] Thus, the phylogenetically older paramedial ascending system, separate from but in parallel with the neospinothalamic pathway, gains access to the motivational mechanisms in the limbic system.

The Central Control System

WE HAVE THUS FAR considered the peripheral and ascending central systems and have indicated the physiologically and anatomically distinct neural mechanisms subserving discriminative and motivational affective functions. We have yet to account for the powerful influence of "higher" CNS processes such as attention, anxiety, anticipation, and past experiences.

MANY FOREBRAIN structures can influence the activity of ascending pathways in the spinal cord and reticular formation. Corticofugal influences are known to act, via pyramidal and extra-pyramidal pathways, on portions of the discriminative system such as the ventrobasal thalamus[100] and the dorsal column nuclei.[52,60,113] Descending in-

influences from the cortex[7] and midbrain reticular formation[48] act at dorsal horn levels to modify the synaptic effectiveness of primary afferent fibers and regulate the amount of ascending activity.[37,38] These central control fibers may even determine the type of natural stimulus which excites dorsal horncells.[109]

NEOCORTICAL[2,35] AND limbic forebrain[1,44] areas also act on the brainstem reticular formation. Information from other modalities could enter into the central control process via limbic[19,27] or frontal lobe[26] connections. The frontal lobe projects strongly to reticular and limbic[78,111] structures; the effects of lobotomy, for example, could be due to disruption of descending control on the limbic and reticular areas subserving the motivational-affective dimension of pain.

THE ANATOMICAL and physiological evidence cited above leaves little doubt that complex psychological processes represented in the function of higher levels of the nervous system can influence information transfer at many levels. Some of the central control systems act at the level of the primary afferent endings in the dorsal horn; others may modify ascending activity in the discriminative or motivational-affective systems. We must next ask: How are these central controls activated, and how do we fit the central control process into a single model of the neurophysiology of pain?

A NEW CONCEPTUAL MODEL

THE DETERMINANTS of pain include the primary afferent fibers, the ascending pathways for spatio-temporal discrimination and motivational drive, and the descending, central control system.
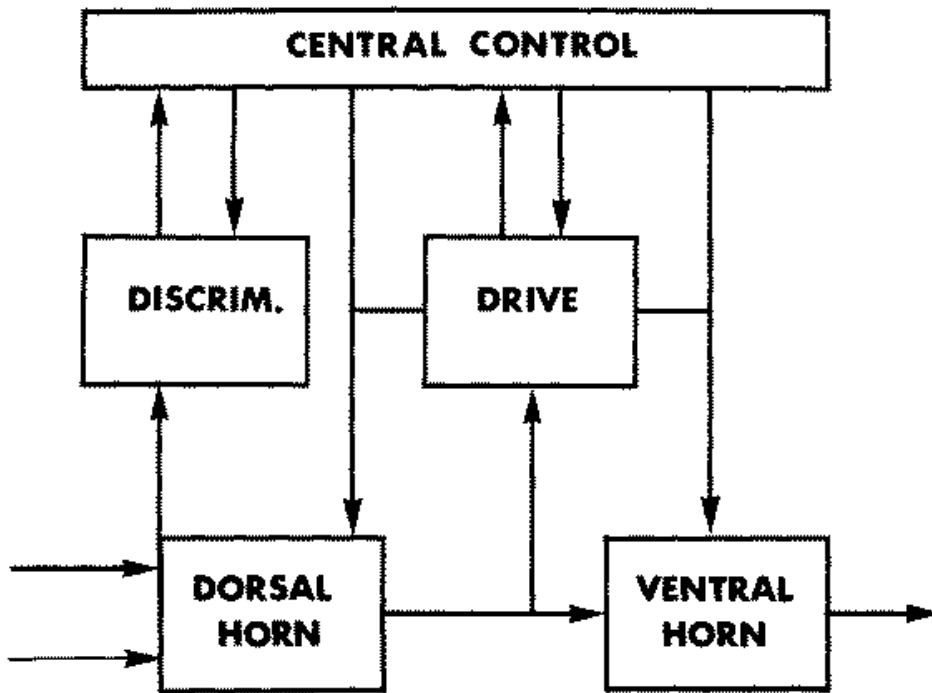

FIG. 2—Conceptual model of the neural mechanisms subserving pain sensation and response. Small and large diameter afferent fibers enter at the spinal cord dorsal horn. Large fibers activate the discriminative system. Both fiber types interact at the dorsal horn to produce a dorsal horn output which activates spinal reflexes (ventral horn) and, via a paramedial ascending system, drive mechanisms in the limbic system. All stages of the system are reciprocally connected with the central control system.

These determinants act in concert to produce the experience of pain and the associated motor and autonomic outputs (Fig. 2). There is no exclusive pain fiber, pathway, or center; there are instead a number of inter-related processes each of which is necessary, but not sufficient, for normal pain experience and response. Pain is a joint function of all these determinants, and cannot be ascribed to any one of them.

THE MODEL IS hierarchically organized and thus reflects a basic functional structure of the nervous system. At the first stage, the appropriate primary afferent input activates nociceptive reflexes (such as the flexion reflex) which are organized at a spinal level. The activity of these spinal reflexes is determined, at the second stage, by components of the motivational drive system. Neurons of the medullary and mesencephalic reticular formation have ascending and descending connections[16,61,114] which are activated by the dorsal horn output and are governed, at the third stage, by limbic forebrain and neocortical controls. The central controls are continuously active and receive input from many sensory afferents via inter-cortical and subcortical pathways. Information about the physical nature and location of a somatic stimulus travels rapidly to higher centers via the oligosynaptic, large-fibered discriminative system. Central control processes may thus be triggered to influence the activity in slower-conducting ascending pathways or spinal reflexes in accordance with the timing, location and physical quality of the stimulus. Each stage of the whole system activates its own controls at higher levels of organization, thus forming a basis for the complexity, flexibility and variability of pain sensation and behavior which is not apparent in the traditional "pain pathway" concept.

The First Stage

THE SMALLER-DIAMETER cutaneous afferents are known to play a major role in the activation of the nociceptive reflexes seen in spinal and decerebrate animals.[31,56,86] Recent neurophysiological studies, in fact, refer to a functionally defined group of "flexion reflex afferents," which includes cutaneous fibers of relatively high electrical threshold.[31,83] Both motor and autonomic outflows reveal a spinal organization sensitive to the diameter spectrum of the afferent input.[70] Since small diameter afferents are not known to have special ventral or intermediate horn connections which would account for their effects, a dorsal horn gating mechanism (Fig. 3) has been proposed.[68] The evidence suggests that small substantia gelatinosa cells[110] depolarize the intramedullary afferent terminals, thereby decreasing their synaptic effectiveness.[39] Large-diameter afferents trigger this pre-synaptic inhibitory mechanism while the smaller-diameter fibers inhibit it. The output of some dorsal horn neurons would, then, be proportional to the ratio of small- to large-diameter afferents. The intramedullary reflex connections of these dorsal horn cells and the supraspinal neurons which receive their output might therefore be expected to reflect this sensitivity to small-diameter cutaneous fibers.

The Second Stage

THE LARGER-DIAMETER afferents ascend in the dorsal columns or, after synapse in the dorsal horn, in the neospinothalamic part of the anterolateral spinal cord. These fibers form the rapidly conducting, topographically organized *discriminative system* which provides higher centers with quick access to information about the physical dimensions of the input.

ANOTHER PORTION OF the dorsal horn output ascends in the anterolateral cord as the *paramedial ascending system*. Recent experiments on *decerebrate* cats[20] show that in the medial medulla, which receives a portion of the spinoreticular input, there are neurons especially sensitive to cutaneous afferent volleys con-
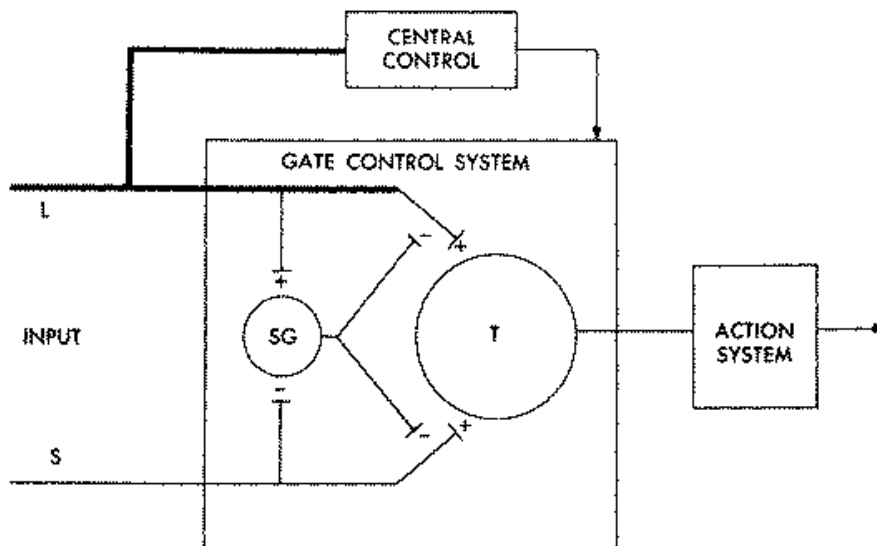
taining finely myelinated fibers (Fig. 4); many of these cells respond only to very strong mechanical cutaneous stimuli. The ascending and descending connections from this region would transfer this information to the spinal cord and to the limbic midbrain and froebrain areas forming the rostral part of the paramedial system. Indeed, many neurons in the medial and intralaminar thalamus of awake monkeys respond most actively (although not exclusively) to stimuli which are behaviorally defined as noxious.[18] These data, together with the lesion and stimulation studies cited previously, strongly suggest that the paramedial ascending system and the limbic structures with which it connects form a *drive* system responsible for the affective dimension of pain. Since these structures also receive inputs from other afferent sources[12,18,94] and show moderate responses to innocous somatic stimuli,[18] the strong aversive drive associated with pain is proposed to be a function of the intensity of neural activity within these areas. This activity, in turn, would reflect the output of that portion of the dorsal horn most sensitive to small-diameter afferents.

The Third Stage

THE *central control system* includes all those neocortical, limbic forebrain, and diencephalic structures known to modulate activity at spinal levels and in the ascending systems. In addition to the neocortical and limbic forebrain influences previously cited, central control fibers from the hypothalamus may act on the drive system to block the aversive aspect of noxious stimuli.[25] All these continuously active descending influences may be triggered by the rapidly conducting large-fiber systems and modulated by changes in wakefulness, other sensory stimuli or by higher order cognitive processes to: (1) alter the discriminative capacity of the system,[3,108] (2) change the effective stimulus for excitation of dorsal horn cells,[109] and (3) alter the responsiveness of reticular and
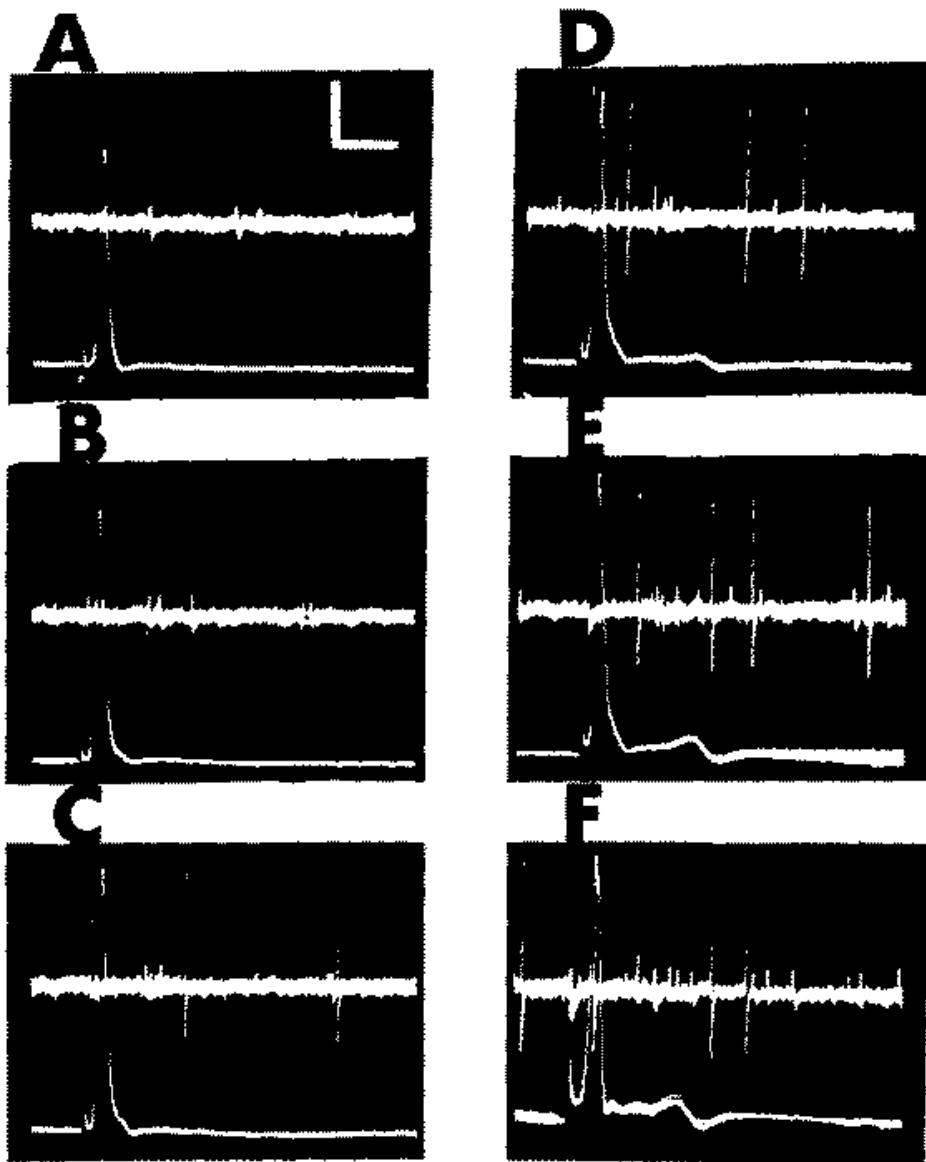
FIG. 4—Neuron in the medial medullary reticular formation sensitive to activation of finely myelinated cutaneous fibers. Top traces: extracellular recording of action potential. Bottom traces: compound action potential of superficial radial nerve of cat. A-B: Cell is not fired by full A-fiber volley. C-E: Increasing post-stimulus discharge as small myelinated fibers are added to the volley. F: Partial block of A-fibers reduces the A wave to the amplitude seen in sample record B; cell continues to respond (smaller fibers were not blocked). Calibration: 200 microvolts, 20 msec. (top trace); 500 microvolts, 2 msec. (bottom trace).

thalamic neurons to noxious somatic stimuli.[18] The activity of central control would, finally, be determined by the past history and the present state of the whole system.

SUMMARY

THE CONCEPTUAL model developed in this paper represents an effort to view the mechanism of pain in terms of neurophysiological processes and neuroanatomical connections which must play a determining role in this important clinical problem. This effort has required the displacement of an older, established, and more simple concept by a model incorporating recent advances in brain research. But pain has not been "explained." Much remains to be done before we can, if ever, specify the brain activities which result in pain experience and response. The model presented here simply indicates some of the neural determinants of pain and sketches their inter-relationships in the form of an integrated, hierarchical system. I hope that, by so doing, the neurophysiology of pain has been brought out of the family closet to form a fruitful foundation for discussion and investigation.

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