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## Pain Mechanisms: A New Theory

A gate control system modulates sensory input from the skin before it evokes pain perception and response.

Ronald Melzack and Patrick D. Wall

The nature of pain has been the subject of bitter controversy since the turn of the century (1). There are currently two opposing theories of pain: (i) specificity theory, which holds that pain is a specific modality like vision or hearing, "with its own central and peripheral apparatus" (2), and (ii) pattern theory, which maintains that the nerve impulse pattern for pain is produced by intense stimulation of nonspecific receptors since "there are no specific fibers and no specific endings" (3). Both theories derive from earlier concepts proposed by von Frey (4) and Goldscheider (5) in 1894, and historically they are held to be mutually exclusive. Since it is our purpose here to propose a new theory of pain mechanisms, we shall state explicitly at the outset where we agree and disagree with specificity and pattern theories.

### Specificity Theory

Specificity theory proposes that a mosaic of specific pain receptors in body tissue projects to a pain center in the brain. It maintains that free nerve endings are pain receptors (4) and generate pain impulses that are carried by A-delta and C fibers in peripheral nerves (6) and by the lateral spinothalamic tract in the spinal cord (2) to a pain center in the thalamus (7). Despite its apparent simplicity, the theory contains an explicit statement of physiological spe-

cialization and an implicit psychological assumption (8, 9). Consider the proposition that the skin contains "pain receptors." To say that a receptor responds only to intense, noxious stimulation of the skin is a physiological statement of fact; it says that the receptor is specialized to respond to a particular kind of stimulus. To call a receptor a "pain receptor," however, is a psychological assumption: it implies a direct connection from the receptor to a brain center where pain is felt (Fig. 1), so that stimulation of the receptor must always elicit pain and only the sensation of pain. This distinction between physiological specialization and psychological assumption also applies to peripheral fibers and central projection systems (9).

The facts of physiological specialization provide the power of specificity theory. Its psychological assumption is its weakness. As in all psychological theories, there is implicit in specificity theory the conception of a nervous system; and the model is that of a fixed, direct-line communication system from the skin to the brain. This facet of specificity theory, which imputes a direct, invariant relationship between stimulus and sensation, is examined here in the light of the clinical, psychological, and physiological evidence concerning pain.

*Clinical evidence.* The pathological pain states of causalgia (a severe burning pain that may result from a partial lesion of a peripheral nerve), phantom limb pain (which may occur

after amputation of a limb), and the peripheral neuralgias (which may occur after peripheral nerve infections or degenerative diseases) provide a dramatic refutation of the concept of a fixed, direct-line nervous system. Four features of these syndromes plague patient, physician, and theorist (8, 10).

1) Surgical lesions of the peripheral and central nervous system have been singularly unsuccessful in abolishing these pains permanently, although the lesions have been made at almost every level (Fig. 2). Even after such operations, pain can often still be elicited by stimulation below the level of section and may be more severe than before the operation (8, 10).

2) Gentle touch, vibration, and other nonnoxious stimuli (8, 10) can trigger excruciating pain, and sometimes pain occurs spontaneously for long periods without any apparent stimulus. The fact that the thresholds to these stimuli are raised rather than lowered in causalgia and the neuralgias (10), together with the fact that referred pain can often be triggered by mild stimulation of normal skin (8), makes it unlikely that the pains can be explained by postulating pathologically hypersensitive "pain receptors."

3) The pains and new "trigger zones" may spread unpredictably to unrelated parts of the body where no pathology exists (8, 11).

4) Pain from hyperalgesic skin areas often occurs after long delays, and continues long after removal of the stimulus (10). Gentle rubbing, repeated pin pricks, or the application of a warm test tube may produce sudden, severe pain after delays as long as 35 seconds. Such delays cannot be attributed simply to conduction in slowly conducting fibers; rather, they imply a remarkable temporal and spatial summation of inputs in the production of these pain states (8, 10).

*Psychological evidence.* The psychological evidence fails to support the assumption of a one-to-one relation-

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ship between pain perception and intensity of the stimulus. Instead, the evidence suggests that the amount and quality of perceived pain are determined by many psychological variables (12) in addition to the sensory input. For example, Beecher (13) has observed that most American soldiers wounded at the Anzio beachhead "entirely denied pain from their extensive wounds or had so little that they did not want any medication to relieve it" (13, p. 165), presumably because they were overjoyed at having escaped alive from the battlefield (13). If the men had felt pain, even pain sensation devoid of negative affect, they would, it is reasonable to assume, have reported it, just as lobotomized patients (14) report that they still have pain but it does not bother them. Instead, these men "entirely denied pain." Similarly, Pavlov's (15, 16) dogs that received electric shocks, burns, or cuts, followed consistently by the presentation of food, eventually responded to these stimuli as signals for food and failed to show "even the tiniest and most subtle" (15, p. 30) signs of pain. If these dogs felt pain sensation, then it must have been nonpainful pain (17), or the dogs were out to fool Pavlov and simply refused to reveal that they were feeling pain. Both possibilities, of course, are absurd. The inescapable conclusion from these observations is that intense noxious stimulation can be prevented from producing pain, or may be modified to provide the signal for eating behavior.

Psychophysical studies (18) that find a mathematical relationship between stimulus intensity and pain intensity are often cited (2, 13, 18, 19) as supporting evidence for the assumption that pain is a primary sensation subserved by a direct communication system from skin receptor to pain center. A simple psychophysical function, however, does not necessarily reflect equally simple neural mechanisms. Beecher's (13) and Pavlov's (15) observations show that activities in the central nervous system may intervene between stimulus and sensation which may invalidate any simple psychophysical "law." The use of laboratory conditions that prevent such activities from ever coming into play reduces the functions of the nervous system to those of a fixed-gain transmission line. It is under these conditions that psychophysical functions prevail.

*Physiological evidence.* There is



Fig. 1. Descartes' (76) concept of the pain pathway. He writes: "If for example fire (A) comes near the foot (B), the minute particles of this fire, which as you know move with great velocity, have the power to set in motion the spot of the skin of the foot which they touch, and by this means pulling upon the delicate thread CC, which is attached to the spot of the skin, they open up at the same instant the pore, *d.e.*, against which the delicate thread ends, just as by pulling at one end of a rope one makes to strike at the same instant a bell which hangs at the other end."

convincing physiological evidence that specialization exists within the somesthetic system (9), but none to show that stimulation of one type of receptor, fiber, or spinal pathway elicits sensations only in a single psychological modality. In the search for peripheral fibers that respond exclusively to high-intensity stimulation, Hunt and McIntyre (20) found only seven out of 421 myelinated A fibers, and Maruhashi *et al.* (21) found 13 out of several hundred. Douglas and Ritchie (22) failed to find any high-threshold C fibers, while Iggo (23) found a few. These data suggest that a small number of specialized fibers may exist that respond only to intense stimulation, but this does not mean that they are "pain fibers"—that they must always produce pain, and only pain, when they are stimulated. It is more likely that they represent the extreme of a continuous distribution of receptor-fiber thresholds rather than a special category (24).

Similarly, there is evidence that central-nervous-system pathways have specialized functions that play a role in pain mechanisms. Surgical lesions of the lateral spinothalamic tract (2) or portions of the thalamus (25) may,

on occasion, abolish pain of pathological origin. But the fact that these areas carry signals related to pain does not mean that they comprise a specific pain system. The lesions have multiple effects. They reduce the total number of responding neurons; they change the temporal and spatial relationships among all ascending systems; and they affect the descending feedback that controls transmission from peripheral fibers to dorsal horn cells.

The nature of the specialization of central cells remains elusive despite the large number of single-cell studies. Cells in the dorsal horns (24, 26) and the trigeminal nucleus (27) respond to a wide range of stimuli and respond to each with a characteristic firing pattern. Central cells that respond exclusively to noxious stimuli have also been reported (28, 29). Of particular interest is Poggio and Mountcastle's (28) study of such cells in the posterior thalamus in anesthetized monkeys. Yet Casey (30), who has recently confirmed that posterior thalamic cells respond exclusively to noxious stimuli in the drowsy or sleeping monkey, found that the same cells also signaled information in response to gentle tactile stimulation when the animal was awake. Even if some central cells should be shown unequivocally to respond exclusively to noxious stimuli, their specialized properties still do not make them "pain cells." It is more likely that these cells represent the extreme of a broad distribution of cell thresholds to peripheral nerve firing, and that they occupy only a small area within the total multidimensional space that defines the specialized physiological properties of cells (9). There is no evidence to suggest that they are more important for pain perception and response than all the remaining somesthetic cells that signal characteristic firing patterns about multiple properties of the stimulus, including noxious intensity. The view that only the cells that respond exclusively to noxious stimuli subserve pain and that the outputs of all other cells are no more than background noise is purely a psychological assumption and has no factual basis. Physiological specialization is a fact that can be retained without acceptance of the psychological assumption that pain is determined entirely by impulses in a straight-through transmission system from the skin to a pain center in the brain.

## Pattern Theory

As a reaction against the psychological assumption in specificity theory, new theories have been proposed which can be grouped under the general heading of "pattern theory." Goldscheider (5), initially one of the champions of von Frey's theory, was the first to propose that stimulus intensity and central summation are the critical determinants of pain. Two kinds of theories have emerged from Goldscheider's concept; both recognize the concept of patterning of the input, which we believe (9) to be essential for any adequate theory of pain, but one kind ignores the facts of physiological specialization, while the other utilizes them in proposing mechanisms of central summation.

The pattern theory of Weddell (31) and Sinclair (3) is based on the earlier suggestion, by Nafe (17), that all cutaneous qualities are produced by spatiotemporal patterns of nerve impulses rather than by separate modality-specific transmission routes. The theory proposes that all fiber endings (apart from those that innervate hair cells) are alike, so that the pattern for pain is produced by intense stimulation of nonspecific receptors. The physiological evidence, however, reveals (9) a high degree of receptor-fiber specialization. The pattern theory proposed by Weddell and Sinclair, then, fails as a satisfactory theory of pain because it ignores the facts of physiological specialization. It is more reasonable to assume that the specialized physiological properties of each receptor-fiber unit—such as response ranges, adaptation rates, and thresholds to different stimulus intensities—play an important role in determining the characteristics of the temporal patterns that are generated when a stimulus is applied to the skin (9).

Other theories have been proposed, within the framework of Goldscheider's concept, which stress central summation mechanisms rather than excessive peripheral stimulation. Livingston (8) was perhaps the first to suggest specific neural mechanisms to account for the remarkable summation phenomena in clinical pain syndromes. He proposed that intense, pathological stimulation of the body sets up reverberating circuits in spinal internuncial pools, or evokes spinal cord activities such as those reflected by the "dorsal root reflex" (32), that can

then be triggered by normally non-noxious inputs and generate abnormal volleys that are interpreted centrally as pain. Conceptually similar mechanisms were proposed by Hebb (33) and Gerard (34), who suggested that hyper-synchronized firing in central cells provides the signal for pain.

Related to theories of central summation is the theory that a specialized input-controlling system normally prevents summation from occurring, and that destruction of this system leads to pathological pain states. Basically, this theory proposes the existence of a rapidly conducting fiber system which

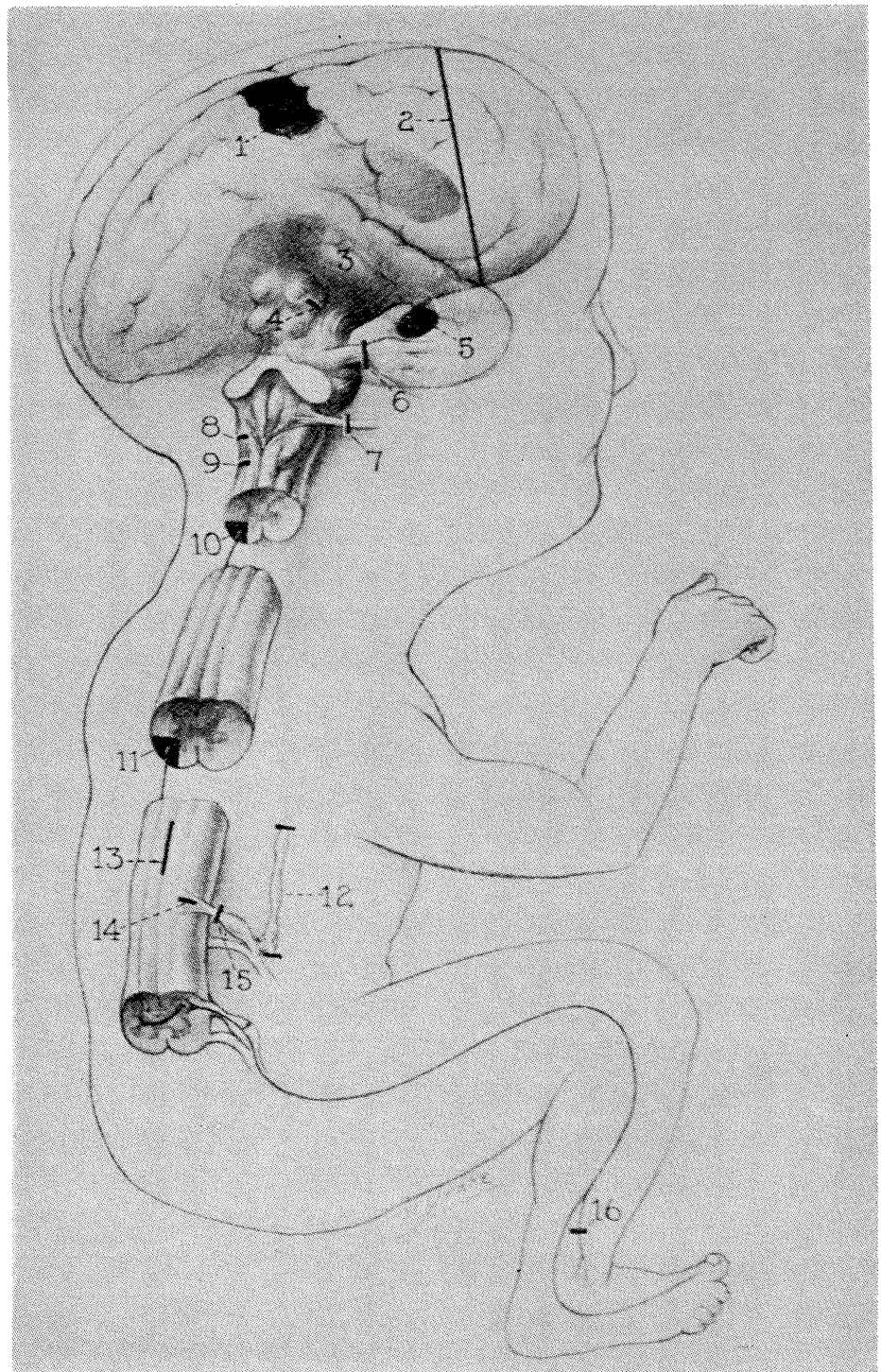


Fig. 2. MacCarty and Drake's (77) schematic diagram illustrating various surgical procedures designed to alleviate pain: 1, gyrectomy; 2, prefrontal lobotomy; 3, thalamotomy; 4, mesencephalic tractotomy; 5, hypophysectomy; 6, fifth-nerve rhizotomy; 7, ninth-nerve neurectomy; 8, medullary tractotomy; 9, trigeminal tractotomy; 10, cervical chordotomy; 11, thoracic chordotomy; 12, sympathectomy; 13, myelotomy; 14, Lissauer tractotomy; 15, posterior rhizotomy; 16, neurectomy.

inhibits synaptic transmission in a more slowly conducting system that carries the signal for pain. These two systems are identified as the epicritic and protopathic (7), fast and slow (35), phylogenetically new and old

(36), and myelinated and unmyelinated (10) fiber systems. Under pathological conditions, the slow system establishes dominance over the fast, and the result is protopathic sensation (7), slow pain (35), diffuse burning

pain (36), or hyperalgesia (10). It is important to note the transition from specificity theory (7, 35, 36) to the pattern concept: Noordenbos (10) does not associate psychological quality with each system but attributes to the rapidly conducting system the ability to modify the input pattern transmitted in the slowly conducting, multisynaptic system.

The concepts of central summation and input control have shown remarkable power in their ability to explain many of the clinical phenomena of pain. The various specific theoretical mechanisms that have been proposed, however, fail to comprise a satisfactory general theory of pain. They lack unity, and no single theory so far proposed is capable of integrating the diverse theoretical mechanisms. More important, these mechanisms have not received any substantial experimental verification. We believe that recent physiological evidence on spinal mechanisms, together with the evidence demonstrating central control over afferent input, provides the basis for a new theory of pain mechanisms that is consistent with the concepts of physiological specialization as well as with those of central summation and input control.

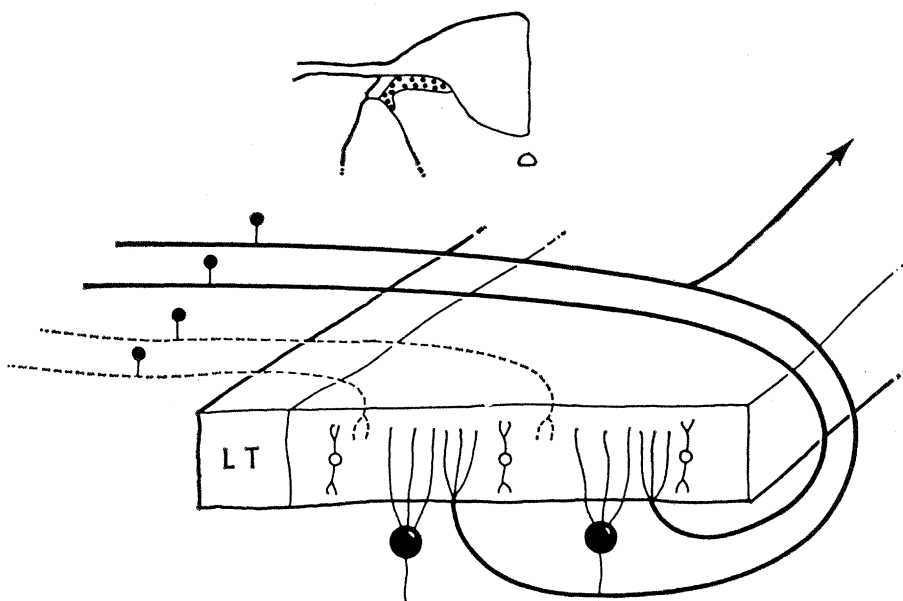
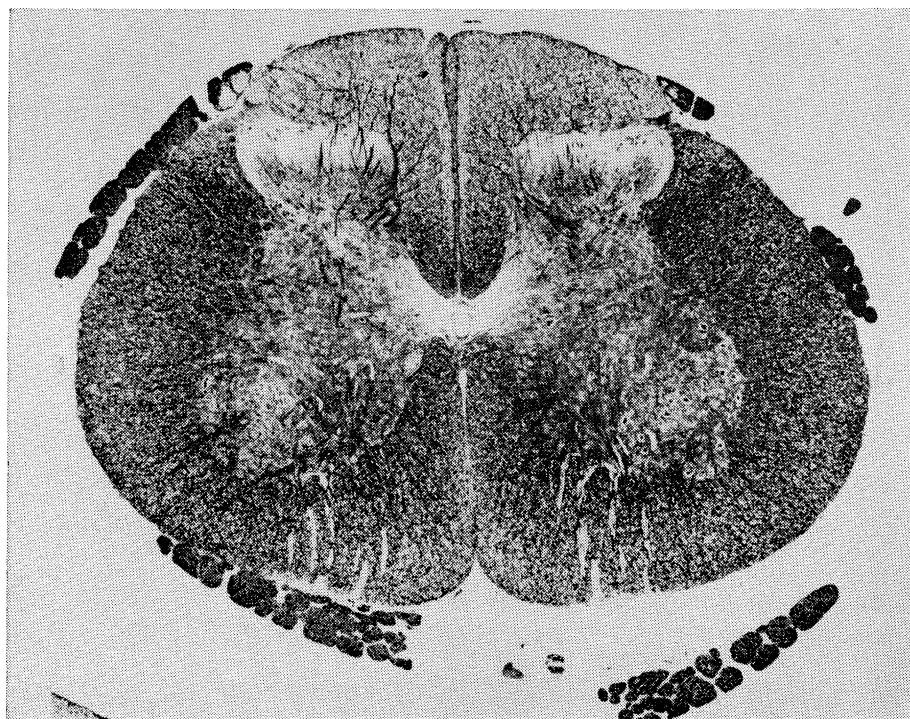


Fig. 3. (Top) A histological section of the cat spinal cord (lumbar region). (Middle) Cross section of the dorsal quadrant. The stippled region is the substantia gelatinosa. (Bottom) Main components of the cutaneous afferent system in the upper dorsal horn. The large-diameter cutaneous peripheral fibers are represented by thick lines running from the dorsal root and terminating in the region of the substantia gelatinosa; one of these, as shown, sends a branch toward the brain in the dorsal column. The finer peripheral fibers are represented by dashed lines running directly into the substantia gelatinosa. The large cells, on which cutaneous afferent nerves terminate, are shown as large black spheres with their dendrites extending into the substantia gelatinosa and their axons projecting deeper into the dorsal horn. The open circles represent the cells of the substantia gelatinosa. The axons (not shown) of these cells connect them to one another and also run in the Lissauer tract (LT) to distant parts of the substantia gelatinosa. [From Wall (37)]

### Gate Control Theory of Pain

Stimulation of the skin evokes nerve impulses that are transmitted to three spinal cord systems (Fig. 3): the cells of the substantia gelatinosa in the dorsal horn, the dorsal-column fibers that project toward the brain, and the first central transmission (T) cells in the dorsal horn. We propose that (i) the substantia gelatinosa functions as a gate control system that modulates the afferent patterns before they influence the T cells; (ii) the afferent patterns in the dorsal column system act, in part at least, as a central control trigger which activates selective brain processes that influence the modulating properties of the gate control system; and (iii) the T cells activate neural mechanisms which comprise the action system responsible for response and perception. Our theory proposes that pain phenomena are determined by interactions among these three systems.

*Gate control system.* The substantia gelatinosa consists of small, densely packed cells that form a functional unit extending the length of the spinal



cord. The cells connect with one another by short fibers and by the longer fibers of Lissauer's tract (37, 38), but do not project outside the substantia gelatinosa. Recent evidence (39) suggests that the substantia gelatinosa acts as a gate control system that modulates the synaptic transmission of nerve impulses from peripheral fibers to central cells.

Figure 4 shows the factors involved in the transmission of impulses from peripheral nerve to T cells in the cord. Recent studies (39-41) have shown that volleys of nerve impulses in large fibers are extremely effective initially in activating the T cells but that their later effect is reduced by a negative feedback mechanism. In contrast, volleys in small fibers activate a positive feedback mechanism which exaggerates the effect of arriving impulses. Experiments (37, 39, 41) have shown that these feedback effects are mediated by cells in the substantia gelatinosa. Activity in these cells modulates the membrane potential of the afferent fiber terminals and thereby determines the excitatory effect of arriving impulses. Although there is evidence, so far, for only presynaptic control, there may also be undetected postsynaptic control mechanisms that contribute to the observed input-output functions.

We propose that three features of the afferent input are significant for pain: (i) the ongoing activity which precedes the stimulus, (ii) the stimulus-evoked activity, and (iii) the relative balance of activity in large versus small fibers. The spinal cord is continually bombarded by incoming nerve impulses even in the absence of obvious stimulation. This ongoing activity is carried predominantly by small myelinated and unmyelinated fibers, which tend to be tonically active and to adapt slowly, and it holds the gate in a relatively open position. When a stimulus is applied to the skin, it produces an increase in the number of active receptor-fiber units as information about the stimulus is transmitted toward the brain. Since many of the larger fibers are inactive in the absence of stimulus change, stimulation will produce a disproportionate relative increase in large-fiber over small-fiber activity. Thus, if a gentle pressure stimulus is applied suddenly to the skin, the afferent volley contains large-fiber impulses which not only fire the T cells but also partially close the presynaptic gate, thereby shortening the barrage generated by the T cells.

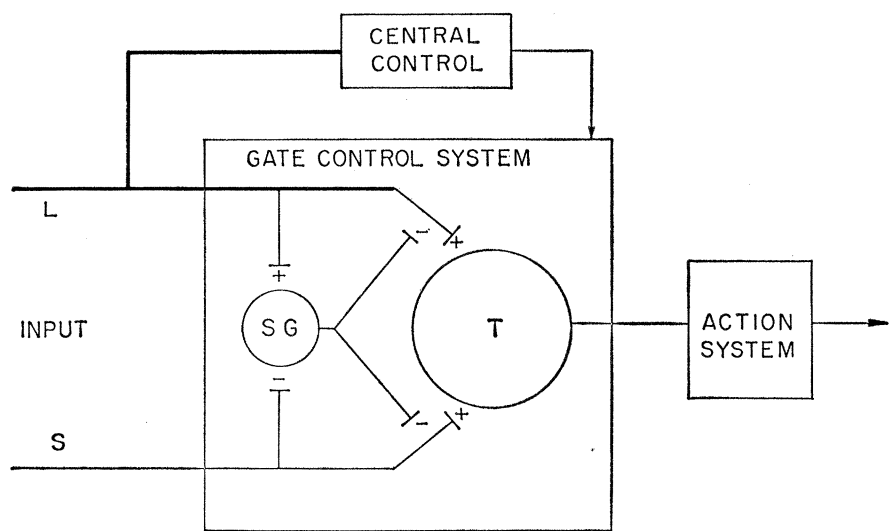


Fig. 4. Schematic diagram of the gate control theory of pain mechanisms: *L*, the large-diameter fibers; *S*, the small-diameter fibers. The fibers project to the substantia gelatinosa (*SG*) and first central transmission (*T*) cells. The inhibitory effect exerted by *SG* on the afferent fiber terminals is increased by activity in *L* fibers and decreased by activity in *S* fibers. The central control trigger is represented by a line running from the large-fiber system to the central control mechanisms; these mechanisms, in turn, project back to the gate control system. The *T* cells project to the entry cells of the action system. +, Excitation; -, inhibition (see text).

If the stimulus intensity is increased, more receptor-fiber units are recruited and the firing frequency of active units is increased (9, 24). The resultant positive and negative effects of the large-fiber and small-fiber inputs tend to counteract each other, and therefore the output of the *T* cells rises slowly. If stimulation is prolonged, the large fibers begin to adapt, producing a relative increase in small-fiber activity. As a result, the gate is opened further, and the output of the *T* cells rises more steeply. If the large-fiber steady background activity is artificially raised at this time by vibration or scratching (a maneuver that overcomes the tendency of the large fibers to adapt), the output of the cells decreases.

Thus, the effects of the stimulus-evoked barrage are determined by (i) the total number of active fibers and the frequencies of nerve impulses that they transmit, and (ii) the balance of activity in large and small fibers. Consequently, the output of the *T* cells may differ from the total input that converges on them from the peripheral fibers. Although the total number of afferent impulses is a relevant stimulus parameter, the impulses have different effects depending on the specialized functions of the fibers that carry them. Furthermore, anatomical specialization also determines the location and the extent of the central terminations of the fibers (24, 41, 42).

There are two reasons for believing

that pain results after prolonged monitoring of the afferent input by central cells. First, threshold for shock on one arm is raised by a shock delivered as long as 100 milliseconds later to the other arm (43). Second, in pathological pain states, delays of pain sensation as long as 35 seconds after stimulation cannot be attributed to slow conduction in afferent pathways (10). We suggest, then, that there is temporal and spatial summation or integration of the arriving barrage by the *T* cells. The signal which triggers the action system responsible for pain experience and response occurs when the output of the *T* cells reaches or exceeds a critical level. This critical level of firing, as we have seen, is determined by the afferent barrage that actually impinges on the *T* cells and has already undergone modulation by substantia gelatinosa activity. We presume that the action system requires a definite time period for integrating the total input from the *T* cells. Small, fast variations of the temporal pattern produced by the *T* cells might be ineffective, and the smoothed envelope of the frequency of impulses—which contains information on the rate of rise and fall, the duration, and the amplitude of firing—would be the effective stimulus that initiates the appropriate sequence of activities in the cells that comprise the action system.

*Central control trigger.* It is now firmly established (44) that stimula-

tion of the brain activates descending efferent fibers (45) which can influence afferent conduction at the earliest synaptic levels of the somesthetic system. Thus it is possible for central nervous system activities subserving attention, emotion, and memories of prior experience to exert control over the sensory input. There is evidence (44) to suggest that these central influences are mediated through the gate control system.

The manner in which the appropriate central activities are triggered into action presents a problem. While some central activities, such as anxiety or excitement, may open or close the gate for all inputs at any site on the body, others obviously involve selective, localized gate activity. Men wounded in battle may feel little pain from the wound but may complain bitterly about an inept vein puncture (13). Dogs that repeatedly receive food immediately after the skin is shocked, burned, or cut soon respond to these stimuli as signals for food and salivate, without showing any signs of pain, yet howl as normal dogs would when the stimuli are applied to other sites on the body (16). The signals, then, must be identified, evaluated in terms of prior conditioning, localized, and inhibited *before* the action system is activated. We propose, therefore, that there exists in the nervous system a mechanism, which we shall call the central control trigger, that activates the particular, selective brain processes that exert control over the sensory input (Fig. 4). There are two known systems that could fulfill such a function, and one or both may play a role.

The first is the dorsal column-medial lemniscus system. The largest and most rapidly conducting A fibers which enter the spinal cord send short branches to the substantia gelatinosa, and long central branches directly to the dorsal column nuclei. Fibers from these nuclei form the medial lemniscus, which provides a direct route to the thalamus and thence to the somatosensory cortex. The striking characteristics of this system are that information is transmitted rapidly from the skin to the cortex, that separation of signals evoked by different stimulus properties and precise somatotopic localization are both maintained throughout the system (46), and that conduction is relatively unaffected by anesthetic drugs (47). Traditionally, the dorsal column system is supposed to

carry two-point discrimination, roughness discrimination, spatial localization, tactile threshold, and vibration (48). Complex discrimination and localization, however, are not a modality; they represent decisions based on an analysis of the input. Indeed, the traditional view is questionable in the light of Cook and Browder's (49) observation that surgical section of the dorsal columns produced no permanent change in two-point discrimination in seven patients.

The second candidate for the role of central control trigger is the dorso-lateral path (50), which originates in the dorsal horn and projects, after relay in the lateral cervical nucleus, to the brain stem and thalamus. This system has small, well-defined receptive fields (51) and is extremely fast; in spite of having one additional relay, it precedes the dorsal column-medial lemniscus volley in the race to the cortex (52).

Both these systems, then, could fulfill the functions of the central control trigger. They carry precise information about the nature and location of the stimulus, and they conduct so rapidly that they may not only set the receptivity of cortical neurons for subsequent afferent volleys but may, by way of central-control efferent fibers, also act on the gate control system. Part, at least, of their function, then, could be to activate selective brain processes that influence information which is still arriving over slowly conducting fibers or is being transmitted up more slowly conducting pathways.

*Action system.* Pain is generally considered to be the sensory adjunct of an imperative protective reflex (53). Pain, however, does not consist of a single ring of the appropriate central bell, but is an ongoing process. We propose, then, that once the integrated firing-level of T cells exceeds a critical preset level, the firing triggers a sequence of responses by the action system.

Sudden, unexpected damage to the skin is followed by (i) a startle response; (ii) a flexion reflex; (iii) postural readjustment; (iv) vocalization; (v) orientation of the head and eyes to examine the damaged area; (vi) autonomic responses; (vii) evocation of past experience in similar situations and prediction of the consequences of the stimulation; (viii) many other patterns of behavior aimed at diminishing the sensory and affective

components of the whole experience, such as rubbing the damaged area, avoidance behavior, and so forth.

The perceptual awareness that accompanies these events changes in quality and intensity during all this activity. This total complex sequence is hidden in the simple phrases "pain response" and "pain sensation." The multiplicity of reactions demands some concept of central mechanisms which is at least capable of accounting for sequential patterns of activity that would allow the complex behavior and experience characteristic of pain.

The concept of a "pain center" in the brain is totally inadequate to account for the sequences of behavior and experience. Indeed, the concept is pure fiction, unless virtually the whole brain is considered to be the "pain center," because the thalamus (7, 25), the limbic system (54), the hypothalamus (55), the brain-stem reticular formation (56), the parietal cortex (57), and the frontal cortex (14) are all implicated in pain perception. Other brain areas are obviously involved in the emotional and motor features of the behavior sequence. The idea of a "terminal center" in the brain which is exclusively responsible for pain sensation and response therefore becomes meaningless.

We propose, instead, that the triggering of the action system by the T cells marks the beginning of the sequence of activities that occur when the body sustains damage. The divergence of afferent fibers going to the dorsal horns and the dorsal column nuclei marks only the first stage of the process of selection and abstraction of information. The stimulation of a single tooth results in the eventual activation of no less than five distinct brain-stem pathways (58). Two of these pathways project to cortical somatosensory areas I and II (59), while the remainder activate the thalamic reticular formation and the limbic system (60), so that the input has access to neural systems involved in affective (54) as well as sensory activities. It is presumed that interactions occur among all these systems as the organism interacts with the environment.

We believe that the interactions between the gate control system and the action system described above may occur at successive synapses at any level of the central nervous system in the course of filtering of the sensory input.

Similarly, the influence of central activities on the sensory input may take place at a series of levels. The gate control system may be set and reset a number of times as the temporal and spatial patterning of the input is analyzed and acted on by the brain.

### Adequacy of the Theory

The concept of interacting gate control and action systems can account for the hyperalgesia, spontaneous pain, and long delays after stimulation characteristic of pathological pain syndromes. The state of hyperalgesia would require two conditions: (i) enough conducting peripheral axons to generate an input that can activate the action system (if, as in the case of leprosy, all components of the peripheral nerve are equally affected, there is a gradual onset of anesthesia), and (ii) a marked loss of the large peripheral nerve fibers, which may occur after traumatic peripheral-nerve lesions or in some of the neuropathies (61), such as post-herpetic neuralgia (10). Since most of the larger fibers are destroyed, the normal presynaptic inhibition of the input by the gate control system does not occur. Thus, the input arriving over the remaining myelinated and unmyelinated fibers is transmitted through the unchecked, open gate produced by the C-fiber input.

Spatial summation would easily occur under such conditions. Any nerve impulses, no matter how they were generated, which converge on the central cells would contribute to the output of these cells. These mechanisms may account for the fact that non-noxious stimuli, such as gentle pressure, can trigger severe pain in patients suffering causalgia, phantom limb pain, and the neuralgias. The well-known enhancement of pain in these patients during emotional disturbance and sexual excitement (62) might be due to increased sensory firing [as a result of an increased sympathetic outflow (63, 64)] which is unchecked by presynaptic inhibition. Conversely, the absence of small fibers in the dorsal roots in a patient with congenital insensitivity to pain (65) suggests that the mechanisms for facilitation and summation necessary for pain may be absent.

Spontaneous pain can also be explained by these mechanisms. The smaller fibers show considerable spon-

aneous activity, which would have the effect of keeping the gate open. Low-level, random, ongoing activity would then be transmitted relatively unchecked (because of the predominant loss of A fibers), and summation could occur, producing spontaneous pain in the absence of stimulation. This is a possible mechanism for the pains of anesthesia dolorosa and the "spontaneous" pains which develop after peripheral-nerve and dorsal-root lesions. Because the total number of peripheral fibers is reduced, it may take considerable time for the T cells to reach the firing level necessary to trigger pain responses, so perception and response are delayed. This same mechanism can also account for post-ischemic pressure-block hyperesthesia and for the delays in sensation of as much as 10 seconds which occur when the large peripheral fibers fail to conduct (66).

We propose that the A-fiber input normally acts to prevent summation from occurring. This would account for Adrian's (67) failure to obtain pain responses in the frog from high-frequency air blasts which fired peripheral nerves close to their maximum firing rate, in an experiment meant to refute the view that summation of the effects of noxious stimuli is important for pain. It is now clear that the air blasts would tend to fire a high proportion of the low-threshold A fibers, which would exert presynaptic inhibition on the input by way of the gate control system; thus the impulses would be prevented from reaching the T cells where summation might occur. The double effect of an arriving volley is well illustrated by the effects of vibration on pain and itch. Vibration activates fibers of all diameters, but activates a larger proportion of A fibers, since they tend to adapt during constant stimulation, whereas C-fiber firing is maintained. Vibration therefore sets the gate in a more closed position. However, the same impulses which set the gate also bombard the T cell and therefore summate with the inputs from noxious stimulation. It is observed behaviorally (26, 68) that vibration reduces low-intensity, but enhances high-intensity, pain and itch. Similar mechanisms may account for the fact that amputees sometimes obtain relief from phantom limb pain by tapping the stump gently with a rubber mallet (69), whereas heavier pressure aggravates the pain (8).

The phenomena of referred pain,

spread of pain, and trigger points at some distance from the original site of body damage also point toward summation mechanisms, which can be understood in terms of the model. The T cell has a restricted receptive field which dominates its "normal activities." In addition, there is a widespread, diffuse, monosynaptic input to the cell, which is revealed by electrical stimulation of distant afferents (41). We suggest that this diffuse input is normally inhibited by presynaptic gate mechanisms, but may trigger firing in the cell if the input is sufficiently intense or if there is a change in gate activity. Because the cell remains dominated by its receptive field, anesthesia of the area to which the pain is referred, from which only spontaneous impulses are originating, is sufficient to reduce the bombardment of the cell below the threshold level for pain. The gate can also be opened by activities in distant body areas, since the substantia gelatinosa at any level receives inputs from both sides of the body and (by way of Lissauer's tract) from the substantia gelatinosa in neighboring body segments. Mechanisms such as these may explain the observations that stimulation of trigger points on the chest and arms may trigger anginal pain (70), or that pressing other body areas, such as the back of the head, may trigger pain in the phantom limb (11).

The sensory mechanisms alone fail to account for the fact that nerve lesions do not always produce pain and that, when they do, the pain is usually not continuous. We propose that the presence or absence of pain is determined by the balance between the sensory and the central inputs to the gate control system. In addition to the sensory influences on the gate control system, there is a tonic input to the system from higher levels of the central nervous system which exerts an inhibitory effect on the sensory input (44, 71). Thus, any lesion that impairs the normal downflow of impulses to the gate control system would open the gate. Central nervous system lesions associated with hyperalgesia and spontaneous pain (7) could have this effect. On the other hand, any central nervous system condition that increases the flow of descending impulses would tend to close the gate. Increased central firing due to denervation supersensitivity (72) might be one of these conditions. A peripheral nerve lesion, then,



would have the *direct* effect of opening the gate, and the *indirect* effect, by increasing central firing and thereby increasing the tonic descending influences on the gate control system, of closing the gate. The balance between sensory facilitation and central inhibition of the input after peripheral-nerve lesion would account for the variability of pain even in cases of severe lesion.

The model suggests that psychological factors such as past experience, attention, and emotion influence pain response and perception by acting on the gate control system. The degree of central control, however, would be determined, in part at least, by the temporal-spatial properties of the input patterns. Some of the most unbearable pains, such as cardiac pain, rise so rapidly in intensity that the patient is unable to achieve any control over them. On the other hand, more slowly rising temporal patterns are susceptible to central control and may allow the patient to "think about something else" or use other stratagems to keep the pain under control (73).

The therapeutic implications of the model are twofold. First, it suggests that control of pain may be achieved by selectively influencing the large, rapidly conducting fibers. The gate may be closed by decreasing the small-fiber input and also by enhancing the large-fiber input. Thus, Livingston (74) found that causalgia could be effectively cured by therapy such as bathing the limb in gently moving water, followed by massage, which would increase the input in the large-fiber system. Similarly, Trent (75) reports a case of pain of central nervous system origin which could be brought under control when the patient tapped his fingers on a hard surface. Conversely, any manipulation that cuts down the sensory input lessens the opportunity for summation and pain, within the functional limits set by the opposing roles of the large- and small-fiber systems. Second, the model suggests that a better understanding of the pharmacology and physiology of the substantia gelatinosa may lead to new ways of controlling pain. The resistance of the substantia gelatinosa to nerve-cell stains suggests that its chemistry differs from that of other neural tissue. Drugs affecting excitation or inhibition of substantia gelatinosa activity may be of particular importance in future attempts to control pain.

The model suggests that the action

system responsible for pain perception and response is triggered after the cutaneous sensory input has been modulated by both sensory feedback mechanisms and the influences of the central nervous system. We propose that the abstraction of information at the first synapse may mark only the beginning of a continuing selection and filtering of the input. Perception and response involve classification of the multitude of patterns of nerve impulses arriving from the skin and are functions of the capacity of the brain to select and to abstract from all the information it receives from the somesthetic system as a whole (7-9). A "modality" class such as "pain," which is a linguistic label for a rich variety of experiences and responses, represents just such an abstraction from the information that is sequentially re-examined over long periods by the entire somesthetic system.

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## The X-ray Analysis of Complicated Molecules

Dorothy Crowfoot Hodgkin

I first met the subject of x-ray diffraction of crystals in the pages of the book W. H. Bragg wrote for school children in 1925, *Concerning the Nature of Things*. In this he wrote: "Broadly speaking, the discovery of x-rays has increased the keenness of our vision over ten thousand times and we can now 'see' the individual atoms and molecules." I also first learnt at the same time about biochemistry which provided me with the molecules it seemed most desirable to "see." At Oxford, seriously studying chemistry, with Robinson and Hinshelwood among my professors, I became captivated by the edifying chemists had raised through experiment and imagination—but still I had a lurking question. Would it not be better if one could really "see" whether molecules as complicated as the sterols, or strychnine, were just as experiment suggested? The process of "seeing" with x-rays was clearly more difficult to apply to such systems than my early reading of Bragg had suggested; it was with some hesitation that I began my first piece of research work with H. M. Powell on thallium dialkyl halides, substances remote from, yet curiously connected with, my later subjects for research.

A series of lucky accidents (a chance meeting in a train between an old friend of mine, A. F. Joseph, and Professor Lowry was one) took me to Cambridge

to work with J. D. Bernal in 1932. There our scientific world ceased to know any boundaries. In a subdepartment of mineralogy, changed during my stay into one of physics, we explored the crystallography of a wide variety of natural products, the structure of liquids and particularly water, Rochelle salt, isomorphous replacement and phase determination, metal crystals and pepsin crystals, and speculated about muscular contraction. Our closest friends were biologists and biochemists. I left Cambridge with great reluctance to try to settle down academically and try to solve at least one or two of the many problems we had raised.

I do not need here to give a detailed account of the theoretical background of structure analysis by the x-ray diffraction of crystals since this was done long ago by W. L. Bragg (1) and again 2 years ago, very beautifully, by Perutz and Kendrew (2). The experimental data we have to employ are the x-ray diffraction spectra from the crystal to be studied, usually recorded photographically, and their intensities estimated by eye. These spectra correspond with a series of harmonic terms which can be recombined to give us a representation of the x-ray scattering material in the crystal, the electron density. The calculation involves the summation of a Fourier series in which the terms have the amplitudes and phases of the

observed spectra; both depend on the positions of the atoms in the crystal, but only the amplitudes are easily measurable. As Perutz and Kendrew explained, the introduction of additional heavy atoms into a crystal under investigation at sites which can be found may make it possible to calculate phase angles directly from the observed amplitudes of the spectra given by the isomorphous crystals. One is then in the position that, from a sufficient number of measurements, one can calculate directly the electron density and see the whole structure spread out before one's eyes. However, the feat involved in the calculations described 2 years ago was prodigious—tens of thousands of reflections for five or six crystals were measured to provide the electron density distribution in myoglobin and hemoglobin. More often, and with most crystals, the conditions for direct electron density calculation are not initially met and one's progress towards the final answer is stepwise; if some of the atoms can be placed, particularly the heavier atoms in the crystal, calculations, necessarily imperfect, of the electron density can be started from which new regions in the crystal may be identified; the calculation is then repeated until the whole atomic distribution is clear. At the outset of my research career, two essential tools became available, the Patterson synthesis and Beevers and Lipson strips. Patterson showed that a first Fourier synthesis calculated directly from the raw data without phase information, represented the inter-atomic vector distribution in the crystal structure (3). This was capable, in simple

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The author is Wolfson Research Professor of the Royal Society in the Chemical Crystallography Laboratory, Oxford University, Oxford, England. This article is the lecture she delivered in Stockholm, Sweden, 11 December 1964, when she received the Nobel Prize in chemistry. It is published here with the permission of the Nobel Foundation and will be included in the complete volumes of Nobel lectures in English, published by the Elsevier Publishing Company, Amsterdam and New York.