Central Neuroplasticity and Pathological Pain

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ABSTRACT: The traditional specificity theory of pain perception holds that pain involves a direct transmission system from somatic receptors to the brain. The amount of pain perceived, moreover, is assumed to be directly proportional to the extent of injury. Recent research, however, indicates far more complex mechanisms. Clinical and experimental evidence shows that noxious stimuli may sensitize central neural structures involved in pain perception. Salient clinical examples of these effects include amputees with pains in a phantom limb that are similar or identical to those felt in the limb before it was amputated, and patients after surgery who have benefited from preemptive analgesia which blocks the surgery-induced afferent barrage and/or its central consequences. Experimental evidence of these changes is illustrated by the development of sensitization, wind-up, or expansion of receptive fields of CNS neurons, as well as by the enhancement of flexion reflexes and the persistence of pain or hyperalgesia after inputs from injured tissues are blocked. It is clear from the material presented that the perception of pain does not simply involve a moment-to-moment analysis of afferent noxious input, but rather involves a dynamic process that is influenced by the effects of past experiences. Sensory stimuli act on neural systems that have been modified by past inputs, and the behavioral output is significantly influenced by the "memory" of these prior events. An increased understanding of the central changes induced by peripheral injury or noxious stimulation should lead to new and improved clinical treatment for the relief and prevention of pathological pain.

INTRODUCTION

The relationship between central neuroplasticity and chronic, pathological pain is not a simple one. Phantom limbs, for example, reveal the complexities of the relationship. It is well known that, after a hand is amputated, punctate stimulation of the skin of the forearm produces sensations not only at the stimulated sites, but also in specific parts of the phantom hand.[1–3] An excellent somatotopic map of the phantom hand is revealed on the forearm which is reasonably assumed to reflect neuroplastic changes in representations of the hand and forearm in the central nervous system from spinal cord to cerebral cortex. These changes in somatotopic maps at both the forearm and brain are found within hours after amputation, suggesting that they are due to the removal of inhibition of existing neurons (rather than growth of

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new neurons) in the hand area, which now respond to stimulation of the forearm. The dynamic changes over time are further revealed as the somatotopic-referred map at the forearm expands greatly to cover almost the whole lower arm, then contracts and undergoes further changes over a period of a year or more.

After these remarkable changes, we would expect that the target cells in the brain must also undergo fundamental changes in the functions they subserve. Several months after amputation of a hand or fingers, the denervated areas of the thalamus and cortex respond exclusively to stimulation of adjacent body areas. However, astonishingly, it seems that stimulation of the denervated brain areas does not produce sensations in the body areas that have "taken over". Despite the neuroplasticity, stimulation of the cortex[4] or thalamus[5] in human paraplegics with major spinal cord injuries produces sensations in anesthetic body areas *below* the spinal transection. This suggests that there is a change in the *input* pattern to these cells, but their *output* pattern retains essential components that produce the perception of the originally innervating part of the body. That is, the neural network—or neuromatrix—of the body-self is partly built-in and partly modified by sensory inputs. The built-in part may explain why the output pattern continues to produce the perception of the genetically determined body part. The marked plasticity in brain representation after amputation may explain telescoping of the phantom and probably some portion of the characteristics of the pain and other abnormal, hyperesthetic experiences reported by amputees. However, we have just seen that the neuroplastic changes in sensory brain areas may hide a built-in, immutable core that continues to send signals for perception and response related to the body area for which it was genetically designated.

Another example of neuronal plasticity that must be examined with caution is the body of evidence that prolonged epidural blocks of sensory input prior to amputation of a limb may prevent or diminish the probability that the patient will suffer phantom limb pain.[6–8] However, the early evidence indicating a marked "preemptive" effect by the presurgical and intrasurgical anesthetic blocks has been challenged by a few failures to replicate the earlier studies.[9] Although the results are contentious,[10–12] this is an exciting, important area for research that has potentially valuable implications for both understanding neuroplasticity and putting that knowledge to use by preventing pathological pain.

These observations teach us that neuroplasticity certainly occurs, but within limits. It is physiologically evident in brain structures, but it does not completely change their functional role in the total activity of the brain. So too, preemptive analgesia does not produce huge clinical effects, but it has been repeatedly demonstrated in well-designed experiments. Clearly, we must keep a balanced perspective on plasticity and genetic determination.

NEURAL PLASTICITY IN HISTORICAL PERSPECTIVE

Pain research and therapy, at any period in history, are determined by the dominant theory of brain function at the time. Until the last half of this century, pain was thought to be produced by a passive, direct-transmission system from peripheral receptors to cortex. There was no place in this concept of the nervous system for plasticity, in which neuronal and synaptic functions are capable of being molded or shaped so that they influence subsequent perceptual experiences. Plasticity related

to pain represents persistent functional changes, or somatic memories,[13] produced in the nervous system by injuries or other pathological events. The recognition that such changes can occur is essential to understanding the chronic pain syndromes, such as low back pain and phantom limb pain, that persist and often destroy the lives of the people who suffer them.

The theory of pain that we inherited in the twentieth century was proposed by Descartes three centuries earlier.[14] It holds that injury activates specific pain receptors and fibers that, in turn, project pain impulses through a spinal pain pathway to a pain center in the brain. The psychological experience of pain, therefore, was virtually equated with physical injury. In the 1950s, there was no room for psychological contributions to pain, such as attention, past experience, and the meaning of the situation. Instead, pain experience was held to be proportional to peripheral injury or pathology. Patients who suffered chronic pain without presenting signs of organic disease were often sent to psychiatrists.

In 1965, Melzack and Wall[15] proposed the gate control theory of pain. The emphasis of the theory on the modulation of inputs in the spinal dorsal horns and the dynamic role of the brain in pain processes had a clinical as well as a scientific impact. Psychological factors, which were previously dismissed as reactions to pain, were now seen to be an integral part of pain processing, and new avenues for pain control were opened. Similarly, cutting nerves and pathways was gradually replaced by a host of methods to modulate the input. Physical therapists and other health care professionals who use a multitude of modulation techniques (including acupuncture) were brought into the picture, and transcutaneous electrical nerve stimulation (TENS) became an important modality for the treatment of chronic and acute pain.[14]

The gate control theory's most important contribution to biological and medical science was its emphasis on central nervous system (CNS) mechanisms. The theory forced the medical and biological sciences to accept the brain as an active system that filters, selects, and modulates inputs. The dorsal horns, too, were not merely passive transmission stations but sites at which dynamic activities—inhibition, excitation, and modulation—occurred. The theory highlighted the CNS as an essential component in pain processes.

Even though the Cartesian concept of direct transmission has dominated our ideas about pain for the past 200 years, descriptions of plasticity related to pain—that is, the idea that injury can produce alterations in CNS function affecting subsequent pain sensitivity—have been proposed by a few courageous clinical observers. MacKenzie[16] suggested that increased pain sensitivity and referred pain could be the result of increased sensitivity of CNS structures. He proposed that sensory impulses arising from injured tissues create an "irritable focus" in spinal cord segments onto which they impinge. In relation to perioperative anesthesia, Crile[17] wrote that patients given inhalational anesthesia still need to be protected by regional anesthesia; otherwise they might incur persistent CNS changes and enhanced postoperative pain. According to Hardy *et al.*,[18] secondary hyperalgesia and referred cutaneous hyperalgesia occur because an injury produces a state of hyperexcitability in the spinal cord. This hyperexcitability is sustained following the activation of a network of internuncial neurons, which produces a spreading facilitation of adjacent neurons in the spinal cord, allowing for the spread of hyperalgesia to uninjured regions of the body. Similarly, Livingston[19] suggested that the afferent activity generated by injured peripheral nerves elicits an abnormal firing pattern within the spinal cord. He

proposed that a disturbance occurs in an internuncial pool of dorsal horn interneurons and results in reverberatory activity which eventually spreads to other parts of the spinal cord, including areas that affect the sympathetic chain. Increased activity in sympathetic efferents would disrupt vasoregulation and induce further hypersensitivity of peripheral tissue, leading to increased afferent input and a vicious circle of peripheral-central activity.

Aside from descriptive references to irritable foci, reverberatory activity, and vicious circles, the above theories do not provide empiral evidence for, or details of, the nature of the CNS changes that occur following noxious stimulation. Only recently has there been specific empirical evidence indicating noxious stimulus-induced changes in CNS function. Kenshalo *et al.*[20] demonstrated that noxious peripheral stimuli produce changes in the sensitivity of dorsal horn neurons to further stimulation, and Woolf and Wall[21,22] provided empirical evidence for a primary afferent input triggering sustained increases in central excitability. Woolf[21] demonstrated that injury-induced increases in spinal cord excitability could be maintained even after local anesthesia of the injured site, providing empirical evidence that acute injury could produce lasting spinal changes. Woolf and Wall[22] showed that the amount of morphine required to prevent the development of this spinal hyperexcitability was 10-fold less than the amount required to reverse it after it was established, and provided the experimental basis for subsequent clinical investigations of the use of preemptive analgesia for the prevention or alleviation of postoperative pain.

These studies indicate that noxious stimulation or injury can produce dramatic alterations in spinal cord function, including sensitization, wind-up, or the expansion of the receptive fields of spinal neurons. Recently, several investigators have proposed detailed theories of how noxious stimuli produce these changes in CNS function. Unlike previous theories of central sensitization, recent theories propose that, in addition to a contribution of neuronal hyperactivity to pathological pain, there are specific cellular and molecular changes that affect membrane excitability and induce new gene expression, thereby allowing for enhanced responses to future stimulation. These studies have recently been reviewed by Coderre *et al.*[23,24] The effect of these changes includes an expansion of dorsal horn receptive fields and hyperexcitability which, if allowed to persist, would presumably produce prolonged changes in excitability that could be maintained without further noxious peripheral input.

PAIN IN PHANTOM LIMBS AND DEAFFERENTATED STRUCTURES

A striking property of phantom limb pain is the persistence of a pain that existed in a limb prior to its amputation. This type of phantom limb pain, characterized by the persistence or recurrence of a previous pain, has the same qualities and is experienced in the same area of the limb as the preamputation pain. Case studies of amputees[13] have demonstrated pain "memories" of painful diabetic and decubitus ulcers, gangrene, corns, blisters, ingrown toenails, cuts, and deep tissue injury. In addition, the phantom limb may assume the same painful posture as that of the real limb prior to amputation, especially if the arm or leg had been immobilized for a prolonged period.[13]

The literature indicates that the proportion of amputees who report that their phantom pains are similar to those felt in the limb before amputation may be as high

as 79%.[13] Reports of pain memories in phantom limbs appear to be less common when there has been a discontinuity, or a pain-free interval, between the experience of pain and the amputation. This is consistent with the observation that relief of preamputation pain by continuous epidural block for 3 days prior to amputation decreases the incidence of phantom limb pain 6 months later.[6] Furthermore, if pain is experienced at or near the time of amputation, there is a higher probability that it will persist in the phantom limb.[13,25]

Pain also persists in patients with deafferentation that does not involve amputation. Patients with brachial plexus avulsion[26] or spinal cord injuries[27] often experience pain in the anesthetic, deafferentated region. For example, Nathan[28] described a patient who continued to feel the pain of an ingrown toenail after a complete spinal cord break. In addition, patients undergoing spinal anesthesia[29] and those with injuries of the brachial plexus[26] or spinal cord[27] sometimes report that a limb is in the same uncomfortable, often painful, posture it was in prior to the injury or block. These postural phantom sensations do not usually persist beyond several days, and in most cases are at least temporarily reversed by competing visual inputs which reveal a dissociation between the real and perceived limb.

A literature also exists on the persistence of painful and nonpainful sensations associated with removal or deafferentation of body structures other than the limbs, including breasts,[30] teeth,[31,32] and internal and special sense organs. Ulcer pain has been reported to persist after vagotomy[33] or subtotal gastrectomy with removal of the ulcer.[34] Similarly, patients have reported labor pain and menstrual cramps following total hysterectomy,[35] rectal and hemorrhoid pain following removal of the rectum,[36] the burning pain of cystitis after complete removal of the bladder,[37] and the pain of a severely ulcerated cornea after enucleation of an eye.[38]

When a missing or completely anesthetic limb continues to be the source of pain which resembles an old injury, it is reasonable to assume that the pain is centrally represented, but it is not clear whether deafferentation per se is necessary for pain memories to develop. The interruption of afferent input associated with deafferentation may facilitate the central neural changes that contribute to the formation of pain memories by removing normal inhibitory control mechanisms. In addition, because amputation also results in the loss of visual and tactile information related to the limb, the central influences that normally inhibit the established pain "traces" may be reduced further by the absence of information from external sources that could confirm or disconfirm the percept arising from the peripheral injury.

There is evidence that in some instances the reactivation of pain memories requires a peripheral trigger. Leriche[39] described a patient who did not experience phantom limb pain until six years after amputation, when an injection into the stump instantly, and permanently, revived the pain of a former painful ulceration of the Achilles tendon. Nathan[28,40] reported a similar phenomenon when applying noxious stimulation to the stump of an amputee who later reexperienced the pain of an ice-skating injury he had sustained five years earlier when the leg was intact. Noordenbos and Wall[41] also described seven patients with partial peripheral nerve injury, and subsequent pain, who underwent complete nerve resection and graft or ligation. Following regeneration and a pain-free period, all redeveloped pain of the same quality and in the same location as the pain they had experienced prior to nerve resection, although in some patients the recurrence of pain was restricted to a smaller area within the originally painful region. These studies and case reports indicate that past

pains may be reactivated months or even years after the original injury, in some cases by a peripheral trigger that provides the input required to activate the central neural structures subserving the memory trace.

Deafferentation by peripheral neurectomy or dorsal rhizotomy in rodents is followed by self-mutilation (autotomy) in which the animals bite and scratch the insensate paw to the point of amputation.[42] There is evidence that autotomy behavior is produced by ongoing pain or dysesthesia, associated with increased neuronal activity, which is referred to the anesthetic region.[43] Autotomy behavior is dramatically affected by alterations in the level of noxious input present at the time of, or prior to, nerve section. Thus, noxious chemical,[44,45] thermal,[46,47] and electrical[47,48] stimulation prior to nerve sections significantly increases the severity of autotomy following neurectomy or rhizotomy. These findings suggest that the prior injury produces central changes that influence nociceptive behavior, after nerve sections, at a time when inputs from the injured region are no longer capable of transmitting their message centrally.

The above findings are similar to clinical reports that phantom limb pain is more likely to occur in amputees who had pain in their limb prior to amputation, and strongly suggest that central neuroplasticity is crucial to the development of phantom limb pain. The clinical relevance of these findings is indicated by the observation that in human amputees the incidence of phantom limb pain at 7 days and 6 months after amputation is significantly greater in patients whose pain is not treated by epidural block with bupivacaine and morphine prior to amputation surgery.[6] In contrast to the effect of increasing noxious inputs at the time of nerve injury, reducing or eliminating the afferent barrage induced by nerve section produces a dramatic reduction in autotomy. When the afferent barrage induced by nerve cuts in rats is blocked by treating the sciatic and saphenous nerves with local anesthetics prior to sectioning them, a significant reduction is found in the incidence and severity of autotomy.[48]

An animal model has recently been developed[47] that parallels the observation that human amputees report similar pains in a limb before and after amputation. In this animal model, rats selectively initiated autotomy in either the lateral or medial half of a hind paw if that particular half had been given a thermal injury prior to sciatic and saphenous nerve sections. The selective attack on the previously injured region, despite the fact that the entire foot was deafferented, suggests that the rats were responding to pain referred to the injured area, which was produced by the prior injury and the central trace it created. Rats injured after neurectomy did not show a similar preference indicating that the rats were not responding simply to peripheral cues associated with the injury.

DENERVATION HYPERSENSITIVITY AND NEURONAL HYPERACTIVITY

Sensory disturbances associated with nerve injury have been closely linked to alterations in CNS function. Markus *et al*.[49] have demonstrated that the development of hypersensitivity in a rat's hind paw following sciatic nerve section occurs concurrently with the expansion of the saphenous nerve's somatotopic projection in the spinal cord. Nerve injury may also lead to the development of increased neuronal

activity at various levels of the somatosensory system. In addition to spontaneous activity generated from the neuroma,[50] peripheral neurectomy also leads to increased spontaneous activity in the dorsal root ganglion[51] and spinal cord.[52] Furthermore, after dorsal rhizotomy, increases in spontaneous neural activity occur in the dorsal horn,[53] the spinal trigeminal nucleus,[54] and the thalamus.[55]

Clinical neurosurgery studies reveal a similar relationship between denervation and CNS hyperactivity. Neurons in the somatosensory thalamus of patients with neuropathic pain display high spontaneous firing rates, abnormal bursting activity, and evoked responses to stimulation of body areas that normally do not activate these neurons.[56,57] The site of abnormality in thalamic function appears to be somatotopically related to the painful region. In patients with complete spinal cord transection and dysesthesias referred below the level of the break, neuronal hyperactivity was observed in thalamic regions that had lost their normal sensory input, but not in regions with apparently normal afferent input.[58] Furthermore, in patients with neuropathic pain, electrical stimulation of subthalamic, thalamic, and capsular regions may evoke pain and in some instances even reproduce the patient's pain.[40,59] Direct electrical stimulation of spontaneously hyperactive cells evokes pain in some, but not all pain patients, raising the possibility that in certain patients the observed changes in neuronal activity may contribute to the perception of pain.[58] Studies of patients undergoing electrical brain stimulation during brain surgery reveal that pain is rarely elicited by test stimuli unless the patient suffers from a chronic pain problem. However, brain stimulation can elicit pain responses in patients with chronic pain that does not involve extensive nerve injury or deafferentation. Nathan[40] describes a patient who underwent thalamic stimulation for a movement disorder. The patient had been suffering from a toothache for 10 days prior to the operation. Electrical stimulation of the thalamus reproduced the toothache.

It is possible that receptive field expansions and spontaneous activity generated in the CNS following peripheral nerve injury are, in part, mediated by alterations in normal inhibitory processes in the dorsal horn. Within four days of a peripheral nerve section, a reduction occurs in the dorsal root potential, and therefore in the presynaptic inhibition it represents.[60] Nerve section also induces a reduction in the inhibitory effect of A-fiber stimulation on activity in dorsal horn neurons.[61] Furthermore, nerve injury affects descending inhibitory controls from brain stem nuclei. In the intact nervous system, stimulation of the locus coeruleus[62] or the nucleus raphe magnus[63] produces an inhibition of dorsal horn neurons. Following dorsal rhizotomy, however, stimulation of these areas produces excitation, rather than inhibition, in half the cells studied.[64]

EFFECTS OF ANESTHETIC OR ANALGESIC PRETREATMENT ON POSTINJURY PAIN

As noted above, deafferentation pain in rats is significantly reduced if the injured nerves are locally anesthetized prior to nerve injury. Thus, autotomy after nerve sections,[48] or hyperalgesia following nerve ligation,[65] is significantly reduced if the sciatic and saphenous nerves are locally anesthetized prior to the nerve injury. Recent evidence indicates that persistent pain induced by tissue injury is also reduced by pretreatment with local anesthetics or opioids prior to the injury, suggesting a

contribution of central plasticity to nociceptive pain. A subcutaneous injection of dilute formalin produces a biphasic nociceptive response with an early phase of intense pain that occurs in the first few minutes and a later tonic phase of moderate pain occurring about 20–60 min after formalin injection.[66] The nociceptive response to subcutaneous formalin is matched by a corresponding biphasic increase in the activity of dorsal horn neurons after formalin injection.[67] Dickenson and Sullivan[68] have demonstrated that intrathecal administration of a μ-opiate agonist significantly inhibits the prolonged increase in dorsal horn activity produced by subcutaneous formalin injection. However, this inhibition occurs only if the drug is given before the formalin injection, and not if it is given 2 min after the injection. These results imply that the dorsal horn activity associated with the late phase of the formalin test depends upon spinal activation during the early phase immediately after formalin injection.

Behavioral studies support the electrophysiological finding that the late phase response to formalin is, in part, dependent on spinal changes generated during the early phase. Tonic nociceptive responses in the late phase of the formalin test (30–60 min after formalin) are not eliminated by complete anesthetic blockade of the formalin-injected area at the time of testing during the late phase, but are virtually abolished if the area was also blocked by local anesthetics at the time of formalin injection.[69] Furthermore, late-phase nociceptive responses are significantly reduced by spinal anesthesia induced immediately prior to formalin injection, but not by spinal anesthesia administered 5 min after formalin injection—that is, after the early phase had already occurred.[69] These results suggest that central neural changes, which occur during the early phase of the formalin test, are essential for the development of the later tonic phase of the formalin test.

Evidence suggests that peripheral tissue injury also induces plasticity in supraspinal structures, which affects persistent pain behavior. This evidence comes from assessing the effects of preinjury treatment with local anesthetics (in this case injected into discrete brain regions) on postinjury pain responses. Nociceptive responses to subcutaneous formalin injection into the rat hind paw are suppressed after focal injection of lidocaine into specific limbic system sites such as the cingulum bundle and the fornix pathway. The lidocaine injection produces analgesia during the late phase of the formalin test (30–70 min after formalin injection) when injected into these areas 10 min before, but not 10 min after, the formalin injection.[70] These results suggest that activity in the cingulum bundle and fornix during the early-phase response to formalin is critical to the development of the late-phase response to formalin. The cingulum bundle and fomix are part of a neural loop that projects from the anterior thalamic nuclei to the cingulate cortex, hippocampus, and mammillary bodies, and returns to the anterior thalamic nuclei.[71] It is proposed that activation of this "closed" circuit during the early phase of the formalin response induces a sensitized state within the limbic system, enhancing responses to subsequent stimulation. Recent physiological evidence supports this concept. Brain stem stimulation has been found to enhance the responsiveness of the anterior thalamic nuclei to stimulation of the mammillary bodies and cingulate cortex.[72] Furthermore, noxious peripheral stimulation produces bursting activity in CAI neurons of the hippocampus.[73] The selective blocking of neural activity in the cingulum bundle or fornix during the early phase of formalin may reduce nociceptive responses by preventing the development of long-term changes in these structures.

POSTOPERATIVE PAIN

The idea that CNS changes produced by tissue damage and noxious inputs associated with surgery could contribute to postoperative pain has existed for several decades.[17] However, it was only after the research by Woolf and Wall[22] provided a sound justification for preemptive treatment that this idea began to receive the clinical attention it deserves. Woolf and Wall[22] demonstrated in experimental animals that opioids are much more effective at reducing stimulus-induced increases in the excitability of the dorsal horn if they are administered prior to, rather than following, C-fiber electrical nerve stimulation. Recent clinical evidence supports the hypothesis that the administration of analgesic agents prior to surgery may prevent the central sensitizing effects of the surgical procedure. In this manner it may be possible to reduce postoperative pain intensity or lower postoperative analgesic requirements for periods much longer than the duration of action of the preoperatively administered agents.

McQuay *et al.*[74] examined the possible prophylactic effect of opiate premedication and/or local anesthetic nerve blocks on postoperative pain. They provided data showing that the time to first request for postoperative analgesics was longest among patients who had received a presurgical treatment with opiates and nerve blocks, and shortest among patients who had received neither. Similar findings have recently been reported by Kiss and Kilian,[75] who showed that opiate pretreatment increased the length of time until request for first analgesic, reduced the percentage of patients requesting analgesics, and decreased analgesic consumption in the first 48 h for patients undergoing lumbar disc surgery. Over the past few years, additional evidence has accumulated to support the hypothesis that preemptive analgesia using a variety of agents (e.g., opiates, local anesthetics, NSAIDs) prolongs the time to first request for analgesics, reduces postoperative pain intensity, or decreases postoperative analgesic requirements among patients undergoing inguinal herniography,[76] oral surgery,[77–79] tonsillectomy,[80] abdominal surgery,[81] orthopedic surgery,[82,83] lower-limb amputation,[6,84] and thoracotomy.[85]

Tverskoy *et al.*[76] clearly demonstrated the benefits of preincisional blockade on postoperative pain. Patients who were undergoing inguinal hemiorraphy received general anesthesia alone, general anesthesia plus subcutaneous and intramuscular injections of bupivacaine prior to surgical incision, or spinal bupivacaine administered preoperatively. All patients received the same regimen of postoperative analgesics. Twenty-four and 48 h after surgery, postoperative incisional pain, movement-associated pain, and pain induced by pressure applied to the surgical wound were all significantly lower in the two groups that had received bupivacaine prior to surgical incision compared to patients who received general anesthesia alone.

Recently, a number of well-controlled, double-blind studies have also shown that preoperative administration of NSAIDs by a variety of routes reduces postoperative pain long after the clinical duration of action of the NSAIDs. Campbell *et al.*[79] found that intravenous diclofenac administered before tooth extraction resulted in less postoperative pain the day after surgery when compared with pretreatment using intravenous fentanyl or a placebo. Similarly, Hutchison *et al.*[78] reported that, compared to patients pretreated with a placebo, significantly fewer patients who received orally administered piroxicam before tooth extraction required supplemental postoperative analgesics and their time to first postoperative analgesic request was longer.

McGlew *et al.*[83] demonstrated that, on days 1 to 3 after spinal surgery, postoperative pain scores and opiate consumption were significantly lower among patients who had received indomethacin suppositories compared with placebo suppositories one hour before surgery.

Taken together, these studies demonstrate that opiate premedication, regional local anesthesia, spinal anesthesia, or systemic NSAIDs administered before incision are more effective than placebo or no treatment controls. The implication of these studies for clinical pathological pain is that changes in central neural function that are induced by surgery alter subsequent perception in such a way that nociceptive inputs from the surgical wound may be perceived as more painful (hyperalgesia) than they would otherwise have been, and innocuous inputs may give rise to frank pain (allodynia).

However, these early studies on the prevention of postoperative pain with preoperative analgesics did not compare the pretreatment with the effects of the same treatments administered after surgery.[86] Demonstrating that pretreatment with analgesics, but not a placebo, lessens pain and decreases postoperative analgesic requirements at a time when the agents are no longer clinically active indicates that the central component of postoperative pain can be prevented or preempted. In the absence of a postincisional or postoperative treatment condition, it is not possible to determine the separate contributions of factors associated with the intraoperative versus the postoperative period to the enhanced postoperative pain experience. It may be that analgesic pretreatments reduce the development of local inflammation, a potential peripheral factor that could contribute to postoperative pain, rather than inhibiting central sensitization induced by noxious inputs during surgery. This may be particularly important in the case of NSAIDs,[78,79,83] which act primarily to reduce peripheral inflammation, but may also be important in the case of infiltration with local anesthetics[76] because local anesthesia would also reduce peripheral inflammation that is dependent on the efferent functions of peripheral nerves (i.e., neurogenic inflammation). Altering the timing of administration of analgesic agents (i.e., before or after incision vs. before or after surgery) may provide clues to the specific intraoperative (e.g., incision, wound retraction) or postoperative (e.g., inflammation) factors that contribute to the central neural changes underlying the enhanced pain.

Recently, studies have been directed at identifying specific intra- and postoperative factors that may contribute to surgically induced postoperative pain and hyperalgesia by comparing the effects on postoperative pain of opiates or local anesthetic agents administered either before or after surgery.[85,87–90] Rice *et al.*[87] found that the timing of a caudal block with bupivacaine relative to the start of surgery had no effect on postoperative pain in a pediatric population undergoing brief (30 min) ambulatory surgical procedures. Dierking *et al.*[89] evaluated the effects of a local anesthetic inguinal field block administered before or after inguinal hemiorraphy on postoperative pain and analgesic consumption. They also found that the timing of the block relative to surgical trauma did not produce differences in postoperative pain or analgesic use. Similarly, Dahl *et al.*[88] reported that postoperative pain and analgesic consumption did not depend on whether a 72-h continuous infusion of epidural bupivacaine and morphine was started before incision or immediately after surgery, approximately 2.5 h later.

ln contrast, Ejlersen *et al*.[90] reported that even though preincisional blockade was not associated with significantly less postoperative pain, fewer patients in the preincisional group, as opposed to a postincisional group, required supplemental postoperative analgesics, and their demand for analgesics was delayed. In addition, Katz *et al*.[85] demonstrated that preincisional treatment with epidural fentanyl in patients undergoing thoracotomy resulted in significantly lower VAS pain scores 6 h after treatment when compared with a postincisional treatment. The significant difference in pain intensity could not be explained by lingering plasma concentrations of fentanyl, which at the time of pain assessment were equally subtherapeutic in both groups, or by PCA morphine consumption, which until this point was virtually identical in both groups. Also, between 12 and 24 h after surgery, the control group self-administered more than twice the amount of PCA morphine than the experimental group, a finding that parallels the studies by Woolf and Wall.[22,91] Recent studies by Katz and his colleagues[92,93] continue to find small, but consistent effects of preemptive analgesia on several types of postsurgical pain.

EXPERIMENTAL EVIDENCE OF CNS PLASTICITY

Damage of peripheral tissue and injury to nerves typically produce persistent pain and hyperalgesia. Recent evidence indicates that hyperalgesia depends, in part, on central sensitization. Hyperalgesia to punctate mechanical stimuli, which develops after intradermal injection of capsaicin, is maintained even after anesthetizing the region where capsaicin was injected.[94] However, if the skin region is anesthetized prior to capsaicin injection, cutaneous hyperalgesia does not develop. Furthermore, hyperalgesic responses to capsaicin can be prevented if the area of skin where the injection is made is rendered anesthetic by a proximal anesthetic block of the peripheral nerve which innervates it. Thus, for hyperalgesia to develop, it is critical that initial inputs from the injury reach the CNS. However, once hyperalgesia is established, it does not need to be maintained by inputs from the injured peripheral tissue.

Further evidence for a central mechanism of hyperalgesia is suggested by clinical and experimental cases of referred pain and hyperalgesia. Referred pain appears to depend on neural mechanisms because local anesthesia of the injured region blocks its expression.[95] Furthermore, the role of central neural mechanisms is supported by the observation that phrenic nerve stimulation causes referred shoulder pain even after the sectioning of all cutaneous nerves from the painful region of the shoulder[96] and by the finding that the injection of hypertonic saline into intraspinous ligaments resulted in pain referred to a phantom arm.[97] It is possible that referred pain depends on the misinterpretation of inputs from an injured region whose axons also branch to the uninjured referred area, or alternatively that axons from the injured and referred regions converge on the same cells in the sensory pathway. If referred pain could be explained exclusively by convergence, then such pains would not provide clear evidence of central sensitization. However, evidence that referred pain is also in part dependent on CNS changes is provided by findings that referred pain and hyperalgesia spread to areas that do not share the same dermatome.[19] For example, it has been shown that pain of cardiac origin is referred to sites as distant as the patient's ear.[98] The fact that pain and hyperalgesia can spread to areas far removed

from the injured region implies that central changes, as opposed to convergence, are involved in the spread of hyperalgesia.

Furthermore, referred pain has often been found to spread specifically to sites of a previous injury. Henry and Montuschi[99] describe a case where the pain of an angina attack was referred to the site of an old vertebral fracture. Similarly, Hutchins and Reynolds[31] discovered that alterations in barometric pressure during high-altitude flights caused many of their patients to complain of pain localized to teeth that had been the site of previous painful stimulation (e.g., fillings, canes, and extractions), in many cases years earlier. Reynolds and Hutchins[32] were able to replicate this finding under controlled conditions. One week after damaged teeth were filled or extracted, pinprick of the nasal mucosa produced pain referred to the previously treated teeth. This phenomenon occurred among patients who had been treated under general anesthesia, but not under the influence of a local anesthetic block. Furthermore, in patients who had received bilateral dental treatment without a local anesthetic, subsequent blocks applied to one side permanently abolished the referred pain ipsilateral, but not contralateral, to the anesthetized side.

Behavioral and physiological studies in animals also demonstrate hyperalgesia or sensitization in response to stimulation of body regions that are at a distance from a cutaneous or deep tissue injury. Cutaneous[21] and deep[100] tissue injury, as well as noxious electrical stimulation of cutaneous and muscle afferent nerves,[101] also produces an increase in the excitability of the ipsilateral and contralateral flexor efferent nerves in response to noxious mechanical stimulation of the hind paw. Since the increased excitability in the contralateral flexor efferent nerve is maintained even after inputs from the injured paw are blocked by local anesthesia, the results suggest that central, not peripheral, changes underlie this effect. In this way, cutaneous hyperalgesia after injury may depend on central hypersensitivity which is produced by inputs from a peripheral injury, but does not need to be maintained by them. Behavioral studies indicate that the spread of hyperalgesia to the hind paw contralateral to the paw that received a thermal injury is unaffected by either deafferentation or anesthetic blocks of the injured hind paw following the injury, but is prevented if deafferentation or anesthetic block precedes the injury.[46] These data provide further evidence that peripheral injury can produce central changes that are maintained even after the inputs from the injury are removed.

Prolonged sensory disturbances associated with tissue injury (secondary hyperalgesia and referred pain, as well as allodynia and persistent spontaneous pain) are believed to result from either a reduction in the threshold of nociceptors or an increase in the excitability of CNS neurons involved in pain transmission. Because there is a large body of evidence documenting the sensitization of peripheral receptors following noxious stimulation, a peripheral mechanism is usually held to be responsible for the hyperalgesia that develops after injury. However, recent experimental studies suggest that sensitization within the CNS also contributes significantly to this phenomenon. Specifically, following injury, noxious stimulation, or C-fiber afferent electrical stimulation, there is a sensitization of neurons in the dorsal horn of the spinal cord and other areas in the somatosensory pathway. This sensitization is reflected by increased spontaneous activity, reduced thresholds or increased responsivity to afferent inputs, and prolonged afterdischarges to repeated stimulation.

In addition to the sensitization and prolonged excitation of dorsal horn cells, noxious stimulation associated with tissue injury also produces an expansion of the receptive fields of dorsal horn neurons. Neurons in the dorsal horn of the spinal cord with receptive fields adjacent to a cutaneous heat injury expand their receptive fields to incorporate the site of injury.[102] Similar receptive field expansions have been observed in spinal cord following mechanical, chemical, inflammatory, and nerve injuries, as well as following the induction of polyarthritis and in response to electrical nerve stimulation.[23] Receptive field expansions have also been observed in brain stem and thalamic neurons.

IMPLICATIONS FOR TREATMENT OF ACUTE AND CHRONIC PAIN

Recent advances in our understanding of the mechanisms that underlie pathological pain have important implications for the treatment of both acute and chronic pain. Since it has been established that intense noxious stimulation produces a sensitization of CNS neurons, it is possible to direct treatments not only at the site of peripheral tissue damage, but also at the site of central changes. Furthermore, it may be possible in some instances to prevent the development of central changes which contribute to pathological pain states. The fact that amputees are more likely to develop phantom limb pain if there is pain in the limb prior to amputation,[13] combined with the finding that the incidence of phantom limb pain is reduced if patients are rendered pain-free by epidural blockade with bupivacaine and morphine prior to amputation,[6] suggests that the development of neuropathic pain can be prevented by reducing the potential for central sensitization at the time of amputation. Although the latter finding is contentious,[9,10] the conclusions by Bach *et al*. remain valid.[11,12] The evidence that postoperative pain is also reduced by premedication with regional and/or spinal anesthestic blocks and/or opiates[74,76,85] suggests that acute postoperative pain can also benefit from the blocking of the afferent barrage arriving within the CNS and the central sensitization it may induce.

Whether chronic postoperative problems such as painful scars, postthoracotomy chest-wall pain, and phantom limb and stump pain can be reduced by blocking nociceptive inputs during surgery remains to be determined. Furthermore, additional research is required to determine whether multiple-treatment approaches (involving local and epidural anesthesia, as well as pretreatment with opiates and antiinflammatory drugs) that produce an effective blockade of afferent input may also prevent or relieve other forms of severe chronic pain such as postherpetic neuralgia and reflex sympathetic dystrophy. It is hoped that a combination of new pharmacological developments, careful clinical trials, and an increased understanding of the contribution and mechanisms of noxious stimulus-induced neuroplasticity will lead to improved clinical treatment and prevention of pathological pain. In particular, these improvements in the treatment and prevention of pain may lead to more effective strategies to treat the distressing pains reported by patients with chemical intolerance and multiple chemical sensitivity. Many of these pains may be due, in part at least, to prolonged pathological changes in the nervous system produced by severe trauma

and stress. Therapeutic advances in pain relief due to a better understanding of neuroplasticity may lead to improvements in treating this population of patients.

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REFERENCES

1. CRONHOLM, B. 1951. Phantom limbs in amputees. Acta Psychiatr. Neurol. Scand. Suppl. **72:** 1–310.
2. DOETSCH, G.S. 1997. Progressive changes in cutaneous trigger zones for sensation referred to a phantom hand: a case report and review with implications for cortical reorganization. Somatosens. Mot. Res. **14:** 6–16.
3. DOETSCH, G.S. 1998. Perceptual significance of somatosensory cortical reorganization following peripheral denervation. NeuroReport **9:** R29–R35.
4. COHEN, L.G., H. TOPKA, R.A. COLE & M. HALLETT. 1991. Leg paresthesias induced by magnetic brain stimulation in patients with thoracic spinal cord injury. Neurology **41:** 1283–1288.
5. LENZ, F.A., H.C. KWAN, R. MARTIN *et al*. 1994. Characteristics of somatotopic organization and spontaneous neuronal activity in the region of the thalamic principal sensory nucleus in patients with spinal cord transection. J. Neurophysiol. **72:** 1570–1587.
6. BACH, S., M.F. NORENG & N.U. TJELLDEN. 1988. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain **33:** 297–301.
7. JAHANGIRI, M., J.W.P. BRADLEY, A.P. JAYATUNGA & C.H. DARK. 1994. Prevention of phantom limb pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. Ann. R. Coll. Surg. **76:** 324–326.
8. SCHUG, S.A., R. BURRELL, J. PAYNE & P. TESTER. 1995. Pre-emptive epidural analgesia may prevent phantom limb pain. Reg. Anesth. **20:** 256.
9. NIKOLAJSEN, L., S. IIKJAER, J.H. CHRISTENSEN *et al.* 1997. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet **350:** 1353–1357.
10. MCQUAY, H.J., R.A. MOORE & E. KALSO. 1998. Phantom limb pain (correspondence). Lancet **351:** 595.
11. KATZ, J. 1997. Phantom limb pain (commentary). Lancet **350:** 1338–1339.
12. KATZ, J. 1998. Phantom limb pain (correspondence). Lancet **359:** 595.
13. KATZ, J. & R. MELZACK. 1990. Pain "memories" in phantom limbs: review and clinical observations. Pain **43:** 319–336.
14. MELZACK, R. & P.D. WALL. 1996. The Challenge of Pain. Penguin. London.
15. MELZACK, R. & P.D. WALL. 1965. Pain mechanisms: a new theory. Science **150:** 971–979.
16. MACKENZIE, J. 1893. Some points bearing on the association of sensory disorders and visceral diseases. Brain **16:** 321–354.
17. CRILE, G.W. 1913. The kinetic theory of shock and its prevention through anoci-association (shockless operation). Lancet **ii:** 7–16.
18. HARDY, J.D., H.G. WOLFF & H. GOODELL. 1950. Experimental evidence on the nature of cutaneous hyperalgesia. J. Clin. Invest. **29:** 115–140.

19. LIVINGSTON, W.K. 1943. Pain Mechanisms. Macmillan. New York.
20. KENSHALO, D.R., R.B. LEONARD, J.M. CHUNG & W.D. WILLIS. 1982. Facilitation of the responses of primate spinothalamic cells to cold and mechanical stimuli by noxious heating of the skin. Pain **12:** 141–152.
21. WOOLF, C.J. 1983. Evidence for a central component of post-injury pain hypersensitivity. Nature **306:** 686–688.
22. WOOLF, C.J. & P.D. WALL. 1986. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci. Lett. **64:** 221–225.
23. CODERRE, T.J., J. KATZ, A.L. VACCARINO & R. MELZACK. 1993. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain **52:** 259–285.
24. CODERRE, T.J., K. FISHER & M.E. FUNDYTUS. 1997. The role of ionotropic and metabotropic glutamate receptors in persistent nociception. *In* Proceedings of the Eighth World Congress of Pain. IASP Press. Seattle, WA.
25. JENSEN, T.S., B. KREBS, J. NIELSEN & P. RASMUSSEN. 1985. Immediate and long-term phantom pain in amputees: incidence, clinical characteristics and relationship to preamputation pain. Pain **21:** 267–278.
26. JENSEN, T.S. & P. RASMUSSEN. 1994. Phantom pain and related phenomena after amputation. *In* Textbook of Pain, pp. 508–521. Livingstone/Churchill. Edinburgh.
27. BERGER, M. & F. GERSTENBRAND. 1981. Phantom illusions in spinal cord lesions. *In* Phantom and Stump Pain, pp. 66–73. Springer. Berlin.
28. NATHAN, P.W. 1985. Pain and nociception in the clinical contex. Philos. Trans. R. Soc. Lond. **308:** 219–226.
29. WALLGREN, G.R. 1954. Phantom experience at spinal anaesthesia. Ann. Chir. Gynaecol. Fenniae **43**(suppl.)**:** 486–500.
30. KRONER, K., B. KREBS, J. SKOV & H.S. JORGENSEN. 1989. Immediate and long-term breast syndrome after mastectomy: incidence, clinical characteristics and relationship to pre-mastectomy breast pain. Pain **36:** 327–337.
31. HUTCHINS, H.C. & O.E. REYNOLDS. 1947. Experimental investigation of the referred pain of aerodontalgia. J. Dent. Res. **26:** 3–8.
32. REYNOLDS, O.E. & H.C. HUTCHINS. 1948. Reduction of central hyper-irritability following block anesthesia of peripheral nerve. Am. J. Physiol. **152:** 658–662.
33. SZASZ, T.S. 1949. Psychiatric aspects of vagotomy: IV. Phantom ulcer pain. Arch. Neurol. Psychiatry **62:** 728–733.
34. GLOYNE, H.F. 1954. Psychosomatic aspects of pain. Psychoanal. Rev. **41:** 135–159.
35. DORPAT, T.L. 1971. Phantom sensations of internal organs. Comp. Psychiatry **12:** 7–35.
36. OVESEN, P., K. KRONER, J. OMSHOLT & K. BACH. 1991. Phantom-related phenomena after rectal amputation: prevalence and clinical characteristics. Pain **44:** 289–291.
37. BRENA, S.F. & E.E. SAMMONS. 1979. Phantom urinary bladder pain—case report. Pain **7:** 197–201.
38. MINSKI, L. 1943. Psychological reactions to injury. *In* Rehabilitation of the War Injured, pp. 115–122. Philosophical Library. New York.
39. LERICHE, R. 1947. A propos des algies des amputees. Mem. Acad. Chir. **73:** 280–284.
40. NATHAN, P.W. 1962. Pain traces left in the central nervous system. *In* The Assessment of Pain in Man and Animals, pp. 129–134. Livingstone. Edinburgh.
41. NOORDENBOS, W. & P.D. WALL. 1981. Implications of the failure of nerve resection and graft to cure chronic pain produced by nerve lesions. J. Neurol. Neurosurg. Psychiatry **44:** 1068–1073.
42. WALL, P.D., J.W. SCADDING & M.M. TORNKIEWICZ. 1979. The production and prevention of experimental anesthesia dolorosa. Pain **6:** 179–182.
43. BLUMENKOPF, B. & J.J. LIPMAN. 1991. Studies in autotomy: its pathophysiology and usefulness as a model of chronic pain. Pain **45:** 203–210.
44. DENNIS, S.G. & R. MELZACK. 1979. Self-mutilation after dorsal rhizotomy in rats: effects of prior pain and pattern of root lesions. Exp. Neurol. **65:** 412–421.
45. CODERRE, T.J., R.W. GRIMES & R. MELZACK. 1986. Autotomy after nerve sections in the rat is influenced by tonic descending inhibition from locus coeruleus. Neurosci. Lett. **67:** 82–85.

46. CODERRE, T.J. & R. MELZACK. 1987. Cutaneous hyperalgesia: contributions of the peripheral and central nervous systems to the increase in pain sensitivity after injury. Brain Res. **404:** 95–106.
47. KATZ, J., A.L. VACCARINO, T.J. CODERRE & R. MELZACK. 1991. Injury prior to neurectomy alters the pattern of autonomy in rats: behavioral evidence of central neural plasticity. Anesthesiology **75:** 876–883.
48. SELTZER, Z., B.Z. BEILIN, R. GINZBURG *et al.* 1991. The role of injury discharge in the induction of neuropathic pain behavior in rats. Pain **46:** 327–336.
49. MARKUS, H., B. POMERANZ & D. KRUSHELNYCKY. 1984. Spread of saphaneous somatotopic projection map in spinal cord and hypersensitivity of the foot after chronic sciatic denervation in adult rat. Brain Res. **296:** 27–39.
50. WALL, P.D. & M. GUTNIK. 1974. Properties of afferent nerve impulses originating from a neuroma. Nature **248:** 740–743.
51. WALL, P.D. & M. DEVOR. 1983. Sensory afferent impulses originate from the dorsal root ganglia as well as from the periphery in normal and nerve injured rats. Pain **17:** 321–339.
52. ASADA, H., W. YASURNO & Y. YAMAGUCHI. 1990. Properties of hyperactive cells in rat spinal cord after peripheral nerve section. Pain Suppl. **5:** S22.
53. BASBAUM, A.I. & P.D. WALL. 1976. Chronic changes in the response of cells in adult cat dorsal horn following partial de-afferentation: the appearance of responding cells in a previously non-responsive region. Brain Res. **116:** 181–204.
54. MACON, J.B. 1979. Deafferentation hyperactivity in the monkey spinal trigeminal nucleus: neuronal responses to amino acid iontophoresis. Brain Res. **161:** 549–554.
55. ALBE–FESSARD, D. & M.C. LOMBARD. 1983. Use of an animal model to evaluate the origin of and protection against deafferentation pain. *In* Advances in Pain Research and Therapy. Vol. 5, pp. 691–700. Raven Press. New York.
56. LENZ, F.A., H.C. KWAN, J.O. DOSTROVSKY & R.R. TASKER. 1989. Characteristics of the bursting pattern of action potential that occurs in the thalamus of patients with central pain. Brain Res. **496:** 357–360.
57. RINALDI, P.C., R.F. YOUNG, D. ALBE-FESSARD & J. CHODAKIEWITZ. 1991. Spontaneous neuronal hyperactivity in the medial and intralaminar thalamic nuclei of patients with deafferentation pain. J. Neurosurg. **74:** 415–421.
58. LENZ, F.A., R.R. TASKER, J.O. DOSTROVSKY, *et al.* 1987. Abnormal single-unit activity recorded in the somatosensory thalamus of a quadriplegic patient with central pain. Pain **31:** 225–236.
59. TASKER, R.R. 1989. Stereotactic surgery. *In* Textbook of Pain, pp. 840–855. Livingstone/Churchill. Edinburgh.
60. WALL, P.D. & M. DEVOR. 1981. The effect of peripheral nerve injury on dorsal root potentials and on transmission of afferent signals into the spinal cord. Brain Res. **209:** 95–111.
61. WOOLF, C.J. & P.D. WALL. 1982. Chronic peripheral nerve section diminishes the primary afferent A–fibre mediated inhibition of rat dorsal horn neurons. Brain Res. **242:** 77–85.
62. SEGAL, M. & D. SANDBERG. 1977. Analgesia produced by electrical stimulation of catecholamine nuclei in the rat brain. Brain Res. **123:** 369–372.
63. OLIVERAS, J.L., G. GUILBAUD & J.M. BESSON. 1979. A map of serotonergic structures involved in stimulation produced analgesia in unrestrained freely moving cats. Brain Res. **164:** 317–322.
64. HODGE, C.J., A.V. APKARIAN, M.P. OWEN & B.S. HANSON. 1983. Changes in the effects of stimulation of locus coeruleus and nucleus raphe magnus following dorsal rhizotomy. Brain Res. **288:** 325–329.
65. DOUGHERTY, P.M., C.J. GARRISON & S.M. CARLTON. 1992. Differential influence of local anesthesia upon two models of experimentally induced peripheral mononeuropathy in rat. Brain Res. **570:** 109–115.
66. DUBUISSON, D. & S.G. DENNIS. 1977. The formalin test: a quantitative study of the analgesic effects of morphine, meperidine, and brain stimulation in rats and cats. Pain **4:** 161–174.

67. DICKENSON, A.H. & A.F. SULLIVAN. 1987. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurones following C fibre stimulation. Neuropharmacology **26:** 1235–1238.
68. DICKENSON, A.H. & A.F. SULLIVAN. 1987. Subcutaneous formalin-induced activity of dorsal horn neurons in the rat: differential response to an intrathecal opiate administration pre or post formalin. Pain **30:** 349–360.
69. CODERRE, T.J., A.L. VACCARINO & R. MELZACK. 1990. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. Brain Res. **535:** 155–158.
70. VACCARINO, A.L. & R. MELZACK. 1992. Temporal processes of formalin pain: differential role of the cingulum bundle, fornix pathway and medial bulboreticular formation. Pain **44:** 257–271.
71. VINOGRADOVA, S. 1975. Functional organization of the limbic system in the process of registration of information: facts and hypothesis. *In* The Hippocampus. Vol. 2, pp. 3–69. Plenum. New York.
72. PARE, D., M. STERIADE, M. DESCHENES & D. BOUHASSIRA. 1990. Prolonged enhancement of anterior thalamic synaptic responsiveness by stimulation of a brain-stem cholinergic group. J. Neurosci. **10:** 20–33.
73. SINCLAIR, J.G. & G.F. LO. 1986. Morphine, but not atropine, blocks nociceptor-driven activity in rat dorsal hippocampal neurones. Neurosci. Lett. **68:** 47–50.
74. MCQUAY, H.J., D. CARROLL & R.A. MOORE. 1988. Post-operative orthopaedic pain—the effect of opiate premedication and local anaesthetic blocks. Pain **33:** 291–295.
75. KISS, I.E. & M. KILIAN. 1992. Does opiate premedication influence postoperative analgesia? A prospective study. Pain **48:** 157–158.
76. TVERSKOY, M., C. COZACOV, M. AYACHE *et al.* 1990. Postoperative pain after inguinal hemiorraphy with different types of anesthesia. Anesth. Analg. **70:** 29–35.
77. TUFFIN, J.R., D.R. CUNLIFFE & S.R. SHAW. 1989. Do local analgesics injected at the time of third molar removal under general anesthesia reduce significantly postoperative analgesic requirements? A double-blind controlled trial. Br. J. Oral Max. Surg. **27:** 27–32.
78. HUTCHISON, G.L., S.L. CROFTS & I.G. GRAY. 1990. Preoperative piroxicam for postoperative analgesia in dental surgery. Br. J. Anaesth. **65:** 500–503.
79. CAMPBELL, W.L., R. KENDRICK & C. PATTERSON. 1990. Intravenous diclofenac sodium: does its administration before operation suppress postoperative pain? Anaesthesia **45:** 763–766.
80. JEBELES, J.A., J.S. REILLY, J.F. GUITIERREZ, E.L. BRADLEY & I. KISSIN. 1991. The effect of pre-incisional infiltration of tonsils with bupivacaine on the pain following tonsilectomy under general anesthesia. Pain **47:** 305–308.
81. MOGENSEN, T., J. BARTHOLDY, K. SPERLING *et al.* 1992. Preoperative infiltration of the incisional area enhances postoperative analgesia to a combined low-dose epidural bupivacaine and morphine regime after upper abdominal surgery. Reg. Anesth. **17**(suppl.)**:** 74.
82. RINGROSE, N.H. & M.J. CROSS. 1984. Femoral nerve block in knee joint surgery. Am. J. Sports Med. **12:** 398–402.
83. MCGLEW, I.C., D.B. ANGLISS, G.J. GEE *et al.* 1991. A comparison of rectal indomethacin with placebo for pain relief following spinal surgery. Anaesth. Int. Care **19:** 40–45.
84. MANN, R.A.M. & W.I.K. BISSET. 1983. Anaesthesia for lower limb amputation: a comparison of spinal analgesia and general anaesthesia in the elderly. Anaesthesia **38:** 1185–1191.
85. KATZ, J., B.P. KAVANAGH, A.N. SANDLER *et al.* 1992. Pre-emptive analgesia: clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology **77:** 439–446.
86. MCQUAY, H.J. 1992. Pre-emptive analgesia. Br. J. Anaesth. **69:** 1–3.
87. RICE, L.J., M.A. PUDIMAT & R.S. HANNALLAH. 1990. Timing of caudal block placement in relation to surgery does not affect duration of postoperative analgesia in paediatric ambulatory patients. Can. J. Anaesth. **37:** 429–431.

88. DAHL, J.B., B.L. HANSEN, N.C. HJORTSO *et al.* 1992. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. Br. J. Anaesth. **69:** 4–8.
89. DIERKING, G.W., J.B. DAHL, J. KANSTRUP *et al.* 1992. Effect of pre- vs. postoperative inguinal field block on postoperative pain after hemiorraphy. Br. J. Anaesth. **68:** 344–348.
90. EJLERSEN, E., H. BRYDE-ANDERSON, K. ELIASEN & T. MOGENSEN. 1992. A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. Anesth. Analg. **74:** 495–498.
91. WOOLF, C.J. & P.D. WALL. 1986. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexion reflex in the rat. J. Neurosci. **6:** 1433–1442.
92. KATZ, J., M. CLAIREUX, B.P. KAVANAGH *et al.* 1994. Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient-controlled morphine consumption after lower abdominal surgery. Pain **59:** 395–403.
93. KATZ, J., M. JACKSON, B.P. KAVANAUGH & A.N. SANDLER. 1996. Acute pain after thoracic surgery predicts long-term post-thoractomy pain. Clin. J. Pain **12:** 50–55.
94. LAMOTTE, R.H., C.N. SHAIN, D.A. SIMONE & E.F.P. TSAI. 1991. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. J. Neurophysiol. **66:** 190–211.
95. ROBERTSON, S., H. GOODELL & H.G. WOLFF. 1947. Headache: the teeth as a source of headache and other head pain. Arch. Neurol. Psychiatry **57:** 277–291.
96. DORAN, F.S.A. & A.H. RATCLIFFE. 1954. The physiological mechanism of referred shoulder-tip pain. Brain **77:** 427–434.
97. HARMAN, J.B. 1984. The localization of deep pain. Br. Med. J. **1:** 188.
98. BRYLIN, M. & B. HINDFELT. 1984. Ear pain due to myocardial ischemia. Am. Heart J. **107:** 186–187.
99. HENRY, J.A. & E. MONTUSCHI. 1978. Cardiac pain referred to site of previously experienced somatic pain. Br. Med. J. **2:** 1605–1606.
100. WOOLF, C.J. & S.B. MCMAHON. 1985. Injury-induced plasticity of the flexor reflex in chronic decerebrate rats. Neuroscience **16:** 395–404.
101. WALL, P.D. & C.J. WOOLF. 1984. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. J. Physiol. (Lond.) **356:** 443–458.
102. MCMAHON, S.B. & P.D. WALL. 1984. Receptive fields of rat lamina I projection cells move to incorporate a nearby region of injury. Pain **19:** 235–247.