Neuronal plasticity associated with burn injury and its relevance for perception and management of pain in burn patients

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Pain Res Manage Vol 5 No 3 Autumn 2000 205

Through the introduction of the gate control theory and various subsequent works, Ronald Melzack has inspired many investigators worldwide to realize two important facts about pain. First, incoming pain messages are subject to both negative and positive modulation, which significantly affect its perception. Second, the progression of knowledge about the basic mechanisms underlying persistent and chronic pain is critically dependent on the increased understanding of the complexity of the symptoms experienced by pain patients. The present paper examines these two very important issues in an effort to understand better the mechanisms that underlie the pain suffered by burn patients. The physiological responses to burn injury involve many different mediators and mechanisms, all of which contribute to pain perception and development of neuronal plasticity underlying short and long term changes in pain sensitivity. While experimental burn injuries in humans and animals are typically well controlled and mild, in burn victims, the severity is much more variable, and clinical care involves repeated traumas and manipulations of the injured sites. Recurrent inputs from damaged and redamaged tissue impinge on a nervous system that becomes an active participant in the initiation of changes in sensory perception and maintenance of long term sensory disturbances. Recently acquired experimental evidence on postburn hyperalgesia, central hyperexcitability and changes in opioid sensitivity provides strong support that burn patients need an analgesic approach aimed at preventing or reducing the ‘neural’ memory of pain, including the use of more than one treatment modality. Burn injuries offer a unique opportunity to combine experimental and clinical research to understand pain mechanisms better. Over the years, Ronald Melzack has insisted that one of the most laudable enterprises in research is to span the gap between these two often separate worlds.

Key Words: Analgesia; Burns; Neuronal plasticity

Plasticité neuronale lors de brûlures et implications pour la perception et le traitement de la douleur chez les patients brûlés

RÉSUMÉ : Grâce à la Théorie du Portillon et aux différents travaux que Ronald Melzack a poursuivis dans le domaine de la douleur, il a inspiré de très nombreux chercheurs à travers le monde en leur faisant réaliser deux faits extrêmement importants. Premièrement, la transmission des messages de douleur est sujette à des influences modulatrices autant négatives que positives qui affectent la perception sensorielle. Deuxièmement, l’amélioration de nos connaissances au sujet des mécanismes fondamentaux qui sous-tendent la douleur chronique sont étroitement reliées à une meilleure compréhension de la symptomatologie des patients, laquelle est souvent extrêmement complexe. Le présent article traite de ces deux aspects fondamentaux dans l’optique de mieux comprendre les mécanismes impliqués dans la douleur que ressentent les victimes de brûlures. La réponse physiologique à une brûlure implique de très nombreuses substances médiatrices et plusieurs mécanismes différents, lesquels contribuent tous...
ensemble à la perception de la douleur et au développement d’une plasticité neuronale entraînant des changements à court et long terme dans la sensibilité à la douleur. Alors que les lésions thermiques effectuées en laboratoire chez l’humain et l’animal sont typiquement circonscrites et mineures, il en va tout autrement chez les victimes de brûlures où la sévérité des blessures est beaucoup plus variable et les soins aux plaies impliquent des manipulations et des traumas répétés. Des signaux récurrents provenant des tissus blessés et re-blessés bombardent le système nerveux et en font un intervenant clé dans le délénçlement de changements dans la perception sensorielle et le maintien de désordres sensoriels chroniques. Les connaissances expé-

rimentales récemment acquises dans les domaines de l’hyperalgesie post-brûlures, de l’hyperréceptibilité du système nerveux central et des changements dans la sensibilité aux opiacés ont clairement ressorti que les patients brûlés nécessitent une thérapeutique analgésique qui s’attache à prévenir ou minimiser la mémoire « neurale » de la douleur et inclut de ce fait plus qu’une modalité de traitement. Les brûlures offrent une opportunité unique pour réunir recherche fondamentale et recherche clinique pour mieux comprendre les mécanismes de la douleur. Au fil des années, Ronald Melzack a insisté que l’une des entreprises les plus louables en recherche est d’essayer de faire le pont entre ces deux mondes souvent séparés.

In the last half of the 1900s, there was a true revolution in thinking of how the nervous system responds to noxious stimuli. Understanding of pain transmission evolved from it being viewed as a passive system, whereby afferent nerves only relayed information from the site of injury to a pain centre in the brain, to an active system that is capable of modulating incoming inputs in various ways that depend on numerous internal and external factors that all contribute to the pain experience. With the publication of the gate control theory of pain in 1965 (1), Ronald Melzack and his colleague Patrick Wall were at the forefront of this revolution. This original theoretical work set the stage for subsequent large-scale waves of experimental activity in various areas such as brain stimulation-produced analgesia, transcutaneous electrical nerve stimulation and cognitive therapies for pain, and perhaps even the search for endogenous opioids. Although much of the early reaction to the gate control theory prompted scientific study about ways that pain can be inhibited, the theory predicted and eventually stimulated global interest in the study of the means by which pain could enhance pain. By allowing us to recognize that pain can be modulated both negatively and positively at virtually all levels of the nervous system, Ronald Melzack has made a major contribution to the understanding of the role of neuroplasticity in chronic pain.

The inspiration for the gate control theory was the realization that numerous clinical pain conditions could not be explained by the activity in a simple stimulus-response afferent pathway. This realization came from a true recognition of the clinical problems faced by patients with chronic pain. Since his early days working as a postdoctoral fellow with WK Livingston, it became apparent that Ronald Melzack was no longer simply interested in science for its own sake, but that for him, pain research was about understanding the puzzles and challenges of patients with chronic pain, and their dedicated physicians and caregivers. It is this motivation that he has passed on to his students and collaborators, and this motivation that has provided many of those he has touched with the insights to perform research that is truly meaningful, not only to the pain field, but also to pain patients and clinicians. In the spirit of science for the sake of the pain patient, this paper attempts to bring together basic research on pain and neuroplasticity with the knowledge about the complex sensory disturbances suffered by patients with burn injuries.

CLINICAL CHARACTERISTICS OF BURN PAIN

Burn pain constitutes a unique pain syndrome because of its multiple components and its changing pattern over time. Burn pain is exceptional because wound care involves repeated traumas or manipulations of the injured sites. This means that the patients not only suffer from the pain due to the burn itself, but also must undergo multiple painful therapeutic procedures. These procedures, which occur daily or even several times a day, include dressing changes, wound cleansing and physiotherapy sessions. Other sources of pain related to treatment include the enforced immobilization of limbs and multiple surgical interventions (wound excision and skin grafting). As healing progresses or when skin grafts are applied, patients may feel less pain at the injury sites, but they now have to endure other pains such as the pain associated with nerve regeneration or the pain at the donor sites (areas of the normal skin that have been harvested for grafting) (2-8).

The severity of burn pain can reach excruciating levels, along with its extreme intra- and interindividual variability, making it difficult to provide adequate analgesia to burn patients (3,9-12). In addition, rapid escalation of the patients’ analgesic needs, especially at times of repetitive dressing changes, is a frequent problem. Anecdotal reports and clinical experience indicate that the dose of opioids required to alleviate pain at rest or during dressing changes may escalate sharply to extraordinary levels (4,13-16).

The depth, size and location of the burns determine the severity of the injury, which, in turn, determines the amount of pain felt and the clinical outcome. More severe burns usually require longer hospitalizations, multiple manipulations and frequent surgical interventions, all of which contribute to increase the patient’s pain. The relationship between burn depth and pain intensity is, however, complex and often inconsistent, even within the same patient throughout a treatment course (3,4,7-9,11,17). Clinically, however, it is generally recognized that superficial second-degree dermal burns are the most painful initially. As the inflammatory response progresses, the pain increases at the wound site and spreads to surrounding areas (hyperalgesia). First-degree burns cause less pain because they damage only the superficial layer of the epidermis, and nerve terminals are not exposed as in superficial second-degree burns. In deep partial-thickness burns (deep second-degree), which usually require skin grafting for healing, nerve terminals can be damaged or
They have been found to produce pain when exposed to the peripheral consequences of burn injury: experimental evidence

Inflammatory response

Burns, like other injuries, produce tissue damage and the local liberation of inflammatory mediators. The damage is reflected by a destruction of cells and nerve endings at the site of the burn. Potassium ions, protons and ATP are released from the cells damaged by burn injury (33,34). These substances sensitize the remaining primary afferent nerve endings (35,36) and likely produce spontaneous pain because they have been found to produce pain when exposed to the base of a blister (34) or directly activate primary afferent C fibres when injected subcutaneously (37,38). After a burn injury, serotonin and bradykinin are released locally from the blood (39,40), and histamine is released from damaged mast cells (41). Serotonin, bradykinin and histamine sensitize primary afferent C fibres (42–44) and produce pain following intradermal injection (34,45,46). Tissue damage associated with burns also causes the production and accumulation of arachidonic acid metabolites (47). The cyclo-oxygenase products of arachidonic acid metabolism, prostaglandins and prostacyclins (48–50), as well as the lipoxygenase products leukotrienes and diHETEs (51–53), sensitize C fibre nociceptors and produce pain or hyperalgesia when administered intradermally or subcutaneously. Burns also stimulate chemokines that attract leukocytes and lymphocytes, which ultimately release cytokines such as interleukin 1-beta and tumour necrosis factor-alpha, which also sensitize nociceptors and induce hyperalgesia (54). Finally, antidiromic nerve impulses in burn-damaged or sensitized primary afferent nerves cause the release of tachykinins such as substance P and neurokinin A from the peripheral terminals in the branches of primary afferent C fibres (55,56), which causes vasodilation (57,58) and plasma extravasation (58,59), as well as nociceptor activation or sensitization (60,61), and pain or hyperalgesia (62,63). Glutamate is also released from the peripheral terminals of activated primary afferent C fibres and can contribute to burn-induced sensory changes (64–66).

Nociceptor sensitization

Concurrent with the local liberation of inflammatory mediators, burn injury increases the excitability of viable primary afferent nociceptors. Thermal injuries produced by repeated heat stimulation result in sensitization that develops within 1 min and lasts for hours (67). Heat sensitization of nociceptors has been demonstrated in the C fibre polymodal nociceptors of rats (68), rabbits (69), monkeys (70) and humans (71). After burn injury, sensitization has also been found in the heat responses of A delta fibre; in high threshold mechanoreceptors in the rabbit, cat (72) and monkey (73); and in the paradoxical heat responses of cold receptors in monkeys (74). Although it has been suggested that, after burn injury, both polymodal nociceptors (75) and high threshold mechanoreceptors (72) are not sensitized to mechanical stimuli, these findings have been questioned (76).

Various studies have attempted to demonstrate a correlation between nociceptor sensitization and reports of hyperalgesia after thermal injury. Some have compared magnitude estimations of hyperalgesia in humans with neurophysiological recordings of nerve fibres in monkeys (73,77). Others have examined the correlation between human sensory judgments and evoked neural responses in the same subjects by using percutaneous recording techniques (71). The results of these studies are controversial. While Meyer and Campbell (73) reported that hyperalgesia after burn injury is associated with a sensitization of A fibres and a desensitization of C fibres, LaMotte et al (77) and Torebjörk et al (71) suggested that hyperalgesia is related to a sensitization of C fibres and...
not of A fibres. This discrepancy may depend on either the type of skin injured (hairy versus glabrous) or the magnitude of the burn injury.

Nociceptor sensitization occurs not only at the site of a burn injury, but also in nociceptors adjacent to the injury, and may explain in part the spread of cutaneous hyperalgesia. Lewis (78,79) was the first to examine extensively the spread of cutaneous hyperalgesia into uninjured tissue. According to Lewis, hyperalgesia spread to uninjured tissue because of antidromic activity in peripheral nerves. Evidence that Lewis’ theory may underlie hyperalgesia after burn injury has been provided by investigators who have found that C fibre polymodal nociceptors were sensitized when the receptive fields were removed from the burn site (60,69). The spreading nociceptor sensitization is dependent on neural activity because a local injection of lidocaine anesthetic blocked its spread (60). Evidence against Lewis’ theory is provided by Thalhammer and LaMotte (80), who found that a heat injury in one-half of a cutaneous nociceptor’s receptive field did not produce heat sensitization in the other half, despite that hyperalgesia spread into this area. Furthermore, nociceptor sensitization associated with burn injury is restricted to about 5 to 10 mm of the site of the injury (72,76), while cutaneous hyperalgesia spreads as far as 10 to 20 cm beyond the site of injury (81).

CENTRAL CONSEQUENCES OF BURN INJURY:
EXPERIMENTAL EVIDENCE

Central sensitization

The observation that hyperalgesia spreads far beyond the site of a burn injury prompted Hardy et al (81) to propose a dual classification of cutaneous hyperalgesia. Accordingly, Hardy et al proposed that burn injury led to both primary hyperalgesia within the injury (mediated by peripheral mechanisms) and secondary hyperalgesia in the undamaged tissue surrounding the injury (mediated by central mechanisms). Subsequent laboratory studies in humans (82-84) have confirmed that secondary hyperalgesia depends mainly on a sensitization of neurons in the central nervous system (CNS), whereas primary hyperalgesia is probably the result of a combination of peripheral and central sensitization. A state of central sensitization is indicated when inputs from the injured peripheral tissue are not required to maintain hyperalgesia once it has been established. Furthermore, the phenomenon can persist for prolonged periods of time, extending from hours to days (85-87).

The contribution of central sensitization to postburn hyperalgesia comes from studies that have shown that, if the skin is anesthetized before the burn injury, hyperalgesia does not develop or is delayed (83,84). Pedersen et al (84) showed that a prolonged pre-emptive anesthetic block of the saphenous nerve initiated before burn injury significantly reduced primary and secondary hyperalgesia in the late period after the injury. The importance of the depth of the block is highlighted by the fact that the same group was not able to demonstrate a similar pre-emptive effect with topical treatment with lignocaine-prilocaine (EMLA, AstraZeneca, Canada). In a study by Dahl et al (83), the hyperalgesic responses were affected not only by preinjury but also by postinjury infiltration with local anesthetics. It is possible that mild burn produces non-neurogenic tissue injury that triggers hyperalgesia after the preinjury anesthetic wears off, and contributes to the maintenance of the hyperalgesia. These findings do not rule out a contribution of central sensitization after burn injury, but stress the notion that ongoing peripheral inputs from injured tissue make it difficult to isolate central mechanisms.

Additional data from animal studies provide consistent support for Hardy et al’s (81) central mechanism of secondary hyperalgesia because thermal injuries have been shown to sensitize neurons in the CNS. Thus, dorsal horn neurons fire with increasing frequency in response to repeated application of a noxious heat stimulus (67,89) or a burn injury (90,91). In addition to the sensitization of dorsal horn cells, noxious stimulation associated with burn 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 (92). Injury-induced receptive field expansions may contribute to enhanced pain by recruiting primary afferent nerve fibres within the newly expanded field, thus increasing the magnitude of the ascending signal into the CNS, or by modality convergence and activation of previously ineffective synapses (93,94). Behavioural and physiological studies in animals have also demonstrated hyperalgesia or an increase in the excitability of flexor efferent responses to stimulation of body regions that are distant from a burn injury. Woolf (95) found that localized burn injuries cause reductions in flexion reflex thresholds to noxious mechanical and thermal stimulation in the limb contralateral as well as ipsilateral to the injury. Burn injuries also produce an increase in the excitability of the ipsilateral and contralateral flexor efferent nerves in response to noxious mechanical stimulation of the hindpaw (96). Because the increased excitability in the contralateral flexor efferent nerve is maintained, even after inputs from the injured paw are blocked by local anaesthesia, the results suggest that central, not peripheral, changes underlie this effect. In this way, cutaneous hyperalgesia may depend on central sensitization that is produced by inputs from a peripheral injury but does not need to be maintained by them. Behavioural studies of thermal withdrawal latencies indicate that the spread of hyperalgesia to the hindpaw contralateral to the paw that received a mild burn injury is unaffected by either deafferentation or anesthetic blocks of the injured hindpaw after the injury, but is prevented if deafferentation or anesthetic block precedes the injury (97,98). These data provide further evidence that burn injury can produce central changes that are maintained even after the inputs from the injury are removed.

Spinal neurochemical changes

Burn injuries initiate their central neural consequences by triggering the release of various neurotransmitters into the
Neuronal plasticity associated with burn injury

Dorsal horn of the spinal cord. Among the most critical of these neurotransmitters are the neuropeptides, including substance P, and the excitatory amino acids such as glutamate and aspartate. Indeed, burn injuries or noxious heat stimuli have been found to increase the spinal dorsal horn release of substance P (99-102), neurokinin A (103), calcitonin gene-related peptide (CGRP) (104) and somatostatin (105-106). Although there is no direct experimental evidence of thermal injury inducing the release of glutamate in spinal cord dorsal horn, spinal glutamate is enhanced after activation of heat-sensitive fibers with either capsaicin (107-109) or mustard oil (110), as well as after chemical injury with formalin (111). Furthermore, the spinal application of the neuropeptides substance P, neurokinin A and CGRP have been found to enhance the release of glutamate and aspartate from the spinal cord dorsal horn (112-114).

Together with Ronald Melzack, we published early evidence that neuropeptides and excitatory amino acids contribute to hyperalgesia after burn injury (115). The secondary hyperalgesia that develops in the hindpaw contralateral to a mild thermal injury is reversed by intrathecal pretreatment with either a substance P or N-methyl-D-aspartate (NMDA) antagonist (115), and is mimicked by intrathecal treatment with substance P, neurokinin A and NMDA. Similar results were reported for secondary hyperalgesia that is expressed in rats in the tail-flick test, after burn injury of the tip of the tail distal to the testing site. Both a substance P (neurokinin-1) antagonist (116) and an NMDA antagonist (117) reverse the secondary hyperalgesia in the tail-flick test. The analgesic properties of NMDA antagonists in animal models of burn pain have been paralleled by successful analgesic trials in a veterinary context (118) or in human subjects with experimental burn injuries (119-122).

Activation of neuropeptide and glutamate receptors has long term neural consequences. Initially, calcium concentrations increase by influx through ligand and voltage-gated calcium channels, and because of increased internal release following activation of guanosine triphosphate-binding proteins. This release is followed by the increased production of various second messengers including prostaglandins, nitric oxide, protein kinase C and tyrosine kinase, which critically influence nociceptive processing (reviewed in 123). Burn injuries have been shown to enhance the translocation of protein kinase C from cytosol to the membrane in spinal dorsal horn (124), and enhance the spinal production of prostaglandin E2 (125). Although there is no direct evidence for an involvement of spinal nitric oxide following burn injury, it has been found to be involved in the hyperalgesia induced by intrathecal application of either NMDA (126) or substance P (127). Importantly, both protein kinase C and nitric oxide have been implicated in the development of opioid tolerance (128,129), and thus may be implicated in the commonly observed resistance of burn patients to the analgesic effects of opioids (4,7,8,13,15). Tyrosine kinase activity is stimulated by growth factors such as nerve growth factor and brain-derived growth factor (130). Growth factors and tyrosine kinase have been implicated in the development of hyperalgesia after both inflammatory and nerve injury (131,132), and thus likely play a critical role in processes contributing to hyperalgesia after burn injury.

Increases in intracellular calcium and in various second messengers also trigger the induction of proto-oncogenes or third messengers such as c-fos. Importantly, the first demonstration of Fos protein induction in spinal cord dorsal horn was in response to noxious heat (133). Evidence suggests that there is a relation between noxious stimulus-induced Fos expression and behavioural hyperalgesia. Thus, heat injury of the rat hindpaw produces immediate hyperalgesia in the injured hindpaw and hyperalgesia in the uninjured contralateral hindpaw, which develops 4 to 24 h after injury (98,115). Similarly, burn injury of the rat hindpaw not only produces an immediate expression of Fos in the spinal cord dorsal horn ipsilateral to the injury, but also produces a ‘second wave’ of Fos (134) activity in both ipsilateral and contralateral dorsal horns 4 to 24 h after the injury. An association of the behavioural hyperalgesia and Fos expression with neural plasticity after heat injury is suggested because both the contralateral hyperalgesia (97) and the Fos expression in the contralateral dorsal horn (134) still develop when the injured hindlimb is locally anesthetized shortly after the injury.

Fos, the protein product of c-fos, forms a heterodimer with Jun, the protein product of c-jun (another proto-oncogene expressed in the spinal dorsal horn after noxious stimulation), which binds to AP-1-like elements to form a DNA-binding site in the promoter region of its target gene (135). There is evidence to suggest that c-fos participates in the regulation of mRNA, encoding various peptides in the rat spinal cord, including dynorphin (136,137), enkephalin (138,139), substance P (140,141) and CGRP (142). Consistent with these observations, after burn injury there is a contralateral upregulation of enkephalins in the superficial lamina of the spinal cord (143).

Clinical implications of burn-induced neuroplasticity

Implications for pain perception

As described above, the physiological responses to burn injury involve many different mediators and mechanisms, all of which contribute to pain perception and the development of neuronal plasticity underlying short and long term changes in pain sensitivity. Experimental burn injuries in both humans and animals are typically well controlled and mild in nature because of ethical considerations. In burn victims, the injury is usually more severe and much more variable, making the consequences for pain and neural plasticity even more complex. Considering that any manipulation of the injury site (eg, dressing changes, movement, surgery) also triggers the previously described neural and chemical mechanisms, it is not surprising that patients’ pain sensitivity increases over time as noted in several clinical reports of adults and children with burns (reviewed in 4). These reports indicate that many patients experience increasing discomfort during the treatment course, manifested by a decrease in pain threshold and/or tolerance, especially during repetitive dressing changes. This

Pain Res Manage Vol 5 No 3 Autumn 2000

209
state of ‘increasing hyperalgesia’ may explain, at least in part, the phenomenon of rapid dose escalation in opioid requirements that is commonly observed in burn patients. This may also be the result of patients’ decreased resistance to pain due to insufficient analgesia, a problem frequently encountered in this population of patients (4,9,14,144). Finally, it is also possible that burn patients simply develop tolerance or resistance to opioid analgesic effects (145), although this is a controversial and complex issue that is beyond the scope of the present paper (4,8,13,145).

Considering the nature of the injury and its consequences on the peripheral and central nervous system, it is not surprising that burn victims also develop chronic sensory problems (pain, paresthesia) at the site of their injuries (28-30). What is more puzzling is that these patients show at the same time objective signs of hypoesthesia in various spheres of cutaneous sensitivity (18,30-32). Importantly, these sensory losses were observed not only in the healed wounds but also in uninjured sites, suggesting permanent modifications in the CNS. The exact mechanisms involved are difficult to identify because the changes can occur at any level of the CNS (spinal, subcortical, cortical level) (reviewed in 31).

The clinical significance of this hypoesthesia (high sensory thresholds) is also difficult to understand in view of the fact that burn patients often experience difficulty, for example, in returning to outdoor work because of intolerance to cold temperatures, which trigger painful sensations in their healed wounds (28-30). The two phenomena – elevated threshold and increased reaction to suprathreshold stimuli – are not, however, incompatible and can be present in the same patient (146). This disorder is called ‘hyperpathia’ and has been reported in patients suffering from peripheral neuropathy of various origins (147-149). In our study (31), burn patients had elevated sensory thresholds, but they may also have had hyperalgesia that could only have been detected with suprathreshold stimuli. We are in the process of testing this interesting hypothesis, which, if confirmed, would provide additional evidence to support the idea that permanent modifications occur in the CNS after burn injury.

**Implications for burn pain management**

An increased understanding of the physiological mechanisms underlying burn injury, and the neuronal plasticity associated with it, will hopefully contribute to improving current analgesic practices and to preventing and/or treating chronic sensory problems in burn patients. In the meantime, basic principles for optimizing analgesic treatment in this population of patients need to be respected. Recently acquired knowledge of postburn hyperalgesia, central hyperexcitability and opioid insensitivity provides strong evidence that burn patients would certainly benefit from an analgesic approach that involves strategies aimed at preventing or reducing the neural ‘memory’ of pain (pre-emptive analgesia) (8,150,151) and include the use of more than one treatment modality (multimodal analgesia) (7,13,152-154). Introduced to improve analgesic efficacy and reduce adverse drug side-effects in postoperative patients, the concept ‘pre-em-

**CONCLUSIONS**

Burn injuries offer a unique opportunity to combine experimental and clinical research to achieve a better understanding of pain mechanisms and identify ways not only to treat pain but also to prevent it. One of Ronald Melzack’s most laudable enterprises has been to try to span the gap between these two worlds by teaching his students not only the fundamentals of basic scientific research, but also the importance of clinical research and humanism, along with the need to consider the true needs of pain patients. Still today, Ronald Melzack insists on the necessity of increasing collaborations between basic and clinical scientists because this is the best way to eradicate the tragedy of needless pain (155).

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Neuronal plasticity associated with burn injury


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