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The neural basis of chronic pain, its plasticity and modulation

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Abstract: Dysfunction or injury of pain-transmitting primary afferents' central pathways can result in pain. The organism as a whole responds to such injury and consequently many symptoms of neuropathic pain develop. The nervous system responds to painful events and injury with neuroplasticity. Both peripheral sensitization and central sensitization take place and are mediated by a number of biochemical factors, including genes and receptors. Correction of altered receptors activity is the logical way to intervene therapeutically. [**BERKLEY; BLUMBERG et al.; CODERRE & KATZ; DICKENSON; MCMAHON; WIESENFELD-HALLIN et al.**]

Pain: Spectrum of a biological phenomenon. Though pain is the one of the earliest recognized medical symptoms, its basis in the nervous system was recognized relatively recently (Descartes 1637), and established only in this century (Head & Holms 1911; Melzack & Wall 1965). Whether pain is a sensation or an emotion has been debated throughout medical and philosophical history. The modern consensus is that pain is a sensation with a strong affective component (Merskey & Bogduk 1994).

Pain is not only a sensation, it is also a warning system. It grabs the attention. It strongly triggers negative affective responses. These characteristics set pain apart from other sensory systems such as vision or hearing, which are generally neutral in their emotional content. However, in common with other sensory systems, pain activates specific pathways from primary afferents to the spinal cord and supraspinal cerebral structures. Nociceptive signals are modulated on all levels of neuronal transmission, although the best documented are the modulatory processes at the spinal cord level. Modulation is one of the defining characteristics of pain. Upon arrival at the higher brain centers, pain is treated as a novel stimulus. There, in the brain, pain signals are processed in a distributed fashion (Backonja 1996).

Many thalamic and cerebral areas are involved in the process called pain perception (Backonja 1996; Casey et al. 1996; Talbot et al. 1991; Willis 1985), and they also participate in pain modulation (Dubner 1988). Pain frequently triggers specific motor reactions such as avoidance and protective behaviors, as well as nonspecific behaviors such as withdrawal and negative affect.

For many patients, pain is a disorder which can manifest as one of many painful syndromes. It is no longer a simple sensation, like vision or hearing. When pain becomes a disorder it is rather similar to epilepsy. Analogy with epilepsy is used for two reasons. First, there is phenomenon which does not have to be a disorder, a seizure, and there is a disorder manifesting with the phenomenon of seizure and it is called epilepsy. Second, chronic pain is the result of excitatory amino acid receptor dysfunction, similar to epilepsy (Thomas 1995). The challenge to modern neuroscience and medical practice is to define the moment at which pain ceases to be mere sensation and becomes instead a disorder. Which event in the natural course of this phenomenon changes a sensation into a disorder? This process – neuroplasticity – and many of its elements are only now becoming better understood, as reflected in the series of target articles in this issue.

Neuropathic pain: A manifestation of neuroplasticity. Since S. Weir Mitchell's excellent description of neuropathic pain (1864), it has been recognized that neuropathic pain manifests with more than one type of symptom. His work and the work of clinicians since then categorize neuropathic pain as ongoing pain, spontaneous paroxysms of pain, and hypersensitivity to various stimuli (Fields & Rowbotham 1994; Tasker 1990). Other characteristics of neuropathic pain are referred pain, paresthesias, and sensory deficits, to mention a few. Neuropathic pain varies in intensity but when it is severe it is one of the most difficult pain syndromes to treat, "resistant" to what would be considered high doses of opioids; hence the idea that neuropathic pain is resistant to opioids. Furthermore, it appears that injury to thermonociceptive pathways is mandatory, as it is best documented for the central pain syndrome (Boivie et al. 1989).

Some patients with lesions of the thermonociceptive pathways suffer from pain, but there are those with the same types of injuries who do not develop neuropathic pain. If neuroplasticity is the way the nervous system responds to injury, does this mixed patient response lead one to conclude that neuropathic pain is an example of neuroplasticity gone wrong?

Regardless of where the initial disease process begins – whether in the peripheral nervous system (PNS) or the central nervous system (CNS) – and regardless of the extent of the injury, neuropathic pain frequently presents with similar if not the same symptoms: ongoing pain, hypersensitivity, paresthesias, sensory deficits, autonomic disturbances, and motor disturbances. This characteristic of neuropathic pain disorders leads us to ask: What is the common substrate of various neuropathic pain syndromes? Other than the general answer – neuroplasticity – a more specific answer is called for.

As there are similarities between neuropathic pain syndromes, there are also substantial differences. Upon closer study of the symptoms of neuropathic pain, such as mechanical allodynia and thermal hyperalgesia, it has become more and more convincing that these are distinguishable sensory phenomena. The possibility that each of these pain phenomena has a specific neural substrate has been proposed (Meller & Gebhart 1994). According to this hypothesis, thermal hyperalgesia comes as a result of NMDA receptor activity and mechanical hyperalgesia is a result of AMPA and metabotropic glutamate receptors. However, the evidence for this hypothesis is not strong (Coderre 1994) and we would argue to the contrary, that these phenomena share the same spinal mechanisms (Henry & Radhakrishnan 1994).

The pathophysiological biochemical differentiation would offer specific therapeutic targets. Ample support for this idea has been eloquently presented in three articles in this issue of BBS, by **CODERRE & KATZ, WIESENFELD-HALLIN et al.** and by **DICKENSON.** Most of the data in these articles provide the support for the role of NMDA receptors and CCK receptor activation in the genesis and maintenance of persistent pain states, or what in clinical medicine is called chronic pain disorders. Dysfunction of other neurotransmitter systems, such as GABA, are implicated (WIESENFELD-HALLIN et al.).

Dysfunction of the PNS and of the CNS are the spectrum of a process [CODERRE & KATZ]. CODERRE & KATZ provide an excellent summary of possible peripheral and central nervous system mechanisms seen in a few examples ranging from referred pain to phantom limb pain. There is a strong scientific rationale as well as a concomitant clinical prerogative to make the distinction between peripheral and central mechanisms. These different mechanisms could serve as possible targets for specific therapeutic interventions, as demonstrated earlier in many cases in the CODERRE & KATZ target article and in this commentary as well. Although evidence for many possible different underlying mechanisms is provided, the most common and outstanding phenomenon that could explain most if not all manifestations is central sensitization. The other phenomena probably represent the spectrum within which neuropathic pain can present, since most of the phenomena are seen in neuropathic pain. Another characteristic that is common to all is probably the extent of sensitization, while factors such as the involvement of specific biochemical elements, such as

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Table 1. *Commentators for special pain issue*

	Target article authors					
Commentators	Berkley	McMahon	Dickenson	Coderre & Katz	Wiesenfeld-Hallin et al.	Blumberg et al.
Backonja			[AHD]	[TJC]	[ZW-H]	
Baron & Jänig						[HB]
Benedetti	[KJB]	[SBM]	[AHD]	[TJC]	[ZW-H]	[HB]
Binik	[KJB]					[HB]
Birbaumer & Flor			[AHD]	[TJC]	[ZW-H]	
Brody	[KJB]					
Clarke	[KJB]	[SBM]	[AHD]	[TJC]	[ZW-H]	[HB]
Cleland & Gebhart				[TJC]		
Devor				[TJC]		
Elam						[HB]
Ellermeier	[KJB]					
Gijsbers & Niven	[KJB]					
Gracely	[KJB]	[SBM]	[AHD]	[TJC]	[ZW-H]	[HB]
Han			[AHD]			
Hardcastle	[KJB]	[SBM]	[AHD]	[TJC]	[ZW-H]	[HB]
Hole et al.			[AHD]	[TJC]	[ZW-H]	
Hu & Sessle			[AHD]	[TJC]	[ZW-H]	
Jancsó et al.				[TJC]		
Kupers	[KJB]					
Lautenbacher	[KJB]					
Malliani		[SBM]				
Marchettini et al.			[AHD]	[TJC]		[HB]
Menetrey	[KJB]	[SBM]				
Munafo'	[KJB]					
Noble et al.			[AHD]		[ZW-H]	
Omote					[ZW-H]	
Raja & Wesselmann						[HB]
Roberts						[HB]
Rollman	[KJB]					
Siddall			[AHD]		[ZW-H]	
Stein & Schafer			[AHD]			
Sternberg	[KJB]					
Unruh	[KJB]					
Urban						[HB]
Ursin				[TJC]		
Watkins & Maier			[AHD]	[TJC]	[ZW-H]	
Wesselmann	[KJB]					
Willis				[TJC]		

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excitatory neurotransmitters (Thomas 1995) and genes (Herdegen & Zimmermann 1995) play an important role in the genesis of these distinguishable phenomena.

Morphine can relieve neuropathic pain but more is needed for better pain relief [DICKENSON]. Unraveling the secrets of the mechanisms of neuroplasticity underlying chronic pain leads to specific opportunities for pharmacological intervention. DICKENSON presents a very eloquent review of our current understanding, with the emphasis on NMDA and opioid receptors systems. Time and time again we discover that opioids can relieve pain, even so called "resistant" neuropathic pain. If we employ our knowledge that opioids do not have a maximum dose and that they do not cause end organ damage, their use could be safely increased to the point of therapeutic effect of pain relief or to the point of side effects. However, there are still many questions lurking, such as: Does tolerance to the opioid analgesic and antihyperalgesic effect develop inevitably with chronic opioid use? Does pain really protect against opioid addiction? Some of the preliminary data would suggest that the answers to the questions are no (Backonja et al. 1995), and yes (Vaccarino & Couret 1993) respectively. But definitive answers to these and many related questions are needed before there can be advances in the pharmacotherapy of chronic pain.

Autonomic dysfunction is only a symptom of neuropathic pain, not a cause [BLUMBERG et al.]. The study and analysis of the biological phenomena in the laboratory can lead to very elegant and convincing results, but once the same phenomena are studied in the clinical setting one faces very different and frequently difficult situations. The target article by BLUMBERG et al. provides an excellent example of how complex a task it is to define and test a pain disorder, in this case reflex sympathetic dystrophy (RDS), now known by its new name, complex regional pain syndrome (CRPS). The lack of physiological standards and established technology for the testing of autonomic and pain sensory function make this type of work pioneering. But it is difficult to accept their results as definitive. The main effort of this group was to demonstrate that hyperactivity of the sympathetic nervous system is the cause of RSD and that adequate sympathetic blockade would prove that point. However, as argued earlier in this commentary, dysfunction of the sympathetic system is not the cause of RSD or any other neuropathic pain disorder but rather one of the indicators that segmental spinal reflexes, including autonomic reflexes, are dysfunctional and frequently exaggerated (Backonja 1994). The second argument, that adequate sympathetic blockade would prove that the sympathetic system contributes to RSD, has failed in the past. Furthermore, in its essence it goes against the most significant finding of recent research about pain neuroplasticity – that neuropathic pain has a strong central sensitization component. In addition, even successful nerve blocks, including sympathetic, do not predict successful lasting pain relief from destructive lesions (Boas & Cousins 1988).

New frontiers in pain research and therapy. Approaches to the study of pain as discussed in this issue of BBS hold the promise of improving our understanding of pain processes and should lead to an improvement in pain treatment. Unveiling the secrets held fast within pathophysiological mechanisms and the biochemistry underlying them, will certainly make this promise possible. In addition to the topics of pathophysiology as presented in the articles discussed in this commentary, other approaches, such as an analysis of sex factors as discussed by **BERKLEY,** and the distinction between visceral and somatic pain as discussed by **MCMAHON,** are broadening our view of this biological phenomenon called pain.

Pain can be a sensation or a disorder. A sensation is something we can study in the laboratory dispassionately, but it is quite a different story when we come face to face with the disorder called pain. Chronic pain remains a great puzzle to modern science. Pain is a formidable challenge to clinical practice. We have to understand the components of pain before we can understand pain as a whole. However, as long as pain as is not treated as a whole it will continue to be a vexing problem, because pain, and neuropathic pain in particular is the sum of its parts.

Complex regional pain syndromes: Taxonomy, diagnostic criteria, mechanisms of vascular abnormalites, edema, and pain[1]

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Abstract: Complex regional pain syndromes (reflex sympathetic dystrophy, causalgia) are often characterized by pain and autonomic and motor abnormalities. Pathophysiological mechanisms are in the central and peripheral nervous system. Differences in skin temperature and "the ischemia test" may be used as diagnostic criteria. Sympathetic blocks relieve pain and other symptoms in a subgroup of patients (sympathetically maintained pain, SMP). **[BLUMBERG et al.]**

Introduction. Complex painful disorders (i.e., reflex sympathetic dystrophy, causalgia) may develop as a disproportionate consequence of trauma affecting the limbs with or without obvious nerve lesion. Clinical signs and symptoms are extremely variable. Three major components can be distinguished: (1) Sensory abnormalities, including spontaneous burning pain, hyperalgesia, and allodynia, (2) vascular and sweating abnormalities, edema and trophic changes in skin, subcutaneous tissues, joints, and bone, and (3) motor abnormalities, including impairment of active and passive function, tremor, or dystonia.

In the past the general problem was that no consensus existed about the criteria leading to a reliable diagnosis of these disorders. This was related, first, to the lack of systematic clinical investigations of patients and, secondly, to the lack of quantitative studies of pain, changes of blood flow and sweating, trophic changes, edema, and motor disturbances in these patients. In order to inaugurate a basis for the clinical diagnosis, Consensus Statements were formulated (1) at the 6th World Congress on Pain, Adelaide, Australia 1991 (Jänig et al. 1991) and (2) during a workshop in Orlando, Florida, in 1993 (Stanton-Hicks et al. 1995). As a result of this, a new nomenclature was elaborated and included into the "Classification of Chronic Pain" (Merskey & Bogduk 1994). These disorders are now called complex regional pain syndromes (CRPS). This terminology is also a compromise and will undergo modifications and extension in the future, once we have more quantitative clinical data and better data about mechanisms.

The pathophysiological mechanisms at the base of the symptoms and the role of the sympathetic nervous system in the generation and maintenance of pain, hyperalgesia, allodynia, and associated changes are not clear (Jänig & Stanton-Hicks 1996). Some investigators pointed out that the patients are characterized by sympathetic overactivity in the affected limb. This is erroneously based upon the observation that skin blood flow and temperature are reduced in many patients and that blocking the sympathetic supply to the affected part may relieve the symptoms. In recent studies, patients presenting with similar clinical signs and symptoms, with or without obvious nerve damage, could be distinguished by the effect of sympathetic blockade, regional guanethidine blocks, or intravenous phentolamine injections. Pain relieved by specific sympatholytic procedures is therefore considered "sympathetically maintained pain" (SMP). Thus, SMP is defined to be a symptom of CRPS and not a clinical entity. The only possibility to differentiate between SMP and SIP (sympathetically independent pain) is the efficacy of a correctly applied sympatholytic intervention. **BLUMBERG** deserves credit for his clinical and experimental investigations of patients with CRPS in the last 15 years. However, his article demands some critical comment.

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What is a SMP syndrome? Considering the new terminology it is not feasible to talk of a "sympathetically maintained pain syndrome" as a clinical entity as proposed by **BLUMBERG** (case report 2). On the other hand, case report 2 matches neither the clinical criteria of CRPS I nor those of CRPS II, since a symptom of both CRPS types is the distal generalization. In case report 2, however, spontaneous burning pain, mechanical allodynia, hypoesthesia, and hypoalgesia were clearly restricted to the innervation territory of the left ulnar nerve that showed a proven partial nerve lesion. Independent of these clinical features the pain was definitely sympathetically maintained. As an alternative, a term like ulnar nerve neuralgia with SMP might be more appropriate.

Autonomic abnormalities in case report 2. The chronic pain syndrome presented in case report 2 does not show any signs of autonomic abnormalities. **BLUMBERG** states that "signs of sympathetic hyperactivity are not found in SMP, and autonomic changes, which may be present inside the lesioned area, can be related to denervation and reinnervation of sympathetic effector organs" (sect. 4.2, para. 2). These important clinical findings should be clarified and extended.

A partial nerve lesion was obviously the preceding event of this pain syndrome (cf. case report 2). Therefore abnormalities in skin blood flow, most often vasodilatation in early and vasoconstriction in late stages, within the territory of the lesioned nerve are due to sympathetic denervation. During the first weeks after transection of vasoconstrictor fibers, vasodilation is present within the affected area. Later the vasculature may develop an increased sensitivity to local cold stimuli and to circulating catecholamines, the latter presumably due to up-regulation of numbers or affinity of adrenoceptors or change in postreceptor pathways (Jobling et al. 1992; see Fleming & Westfall 1988). Similar observations were recently described in a chronic nerve constriction model in rats (Wakisaka et al. 1991).

Evidence has also been presented that similar mechanisms are responsible for the cold skin in patients with poly- and mononeuropathy (Ochoa & Yarnitsky 1994). In these patients with a so-called triple cold syndrome, an impairment of sympathetic reflexes has been demonstrated as a consequence of small fiber injury, sympathetic denervation, and consecutive denervation hyper-reactivity. Furthermore, reinnervated blood vessels may maintain the hyper-reactivity to circulating catecholamines and to nerve impulses (Koltzenburg et al. 1995).

Skin temperature (SKT) difference as a diagnostic tool in CRPS I (reflex sympathetic dystrophy)? In contrast to case report 2 and CRPS II, most of the CRPS I patients have only minor trauma without overt nerve injury (see case report 1). Changes in SKT, skin blood flow, and sweating are also present in regions not innervated by the peripheral nerve whose branches might be affected by the minor trauma. They show a generalized distribution and are not restricted to peripheral nerve territories.

The SKT at distal parts of the extremities, that is, those dependent on the overall blood flow through the skin, characteristically shows a difference between sides, with the affected extremity being either warmer or colder. The patients usually report a distorted reaction of SKT to changes in environmental temperature and to emotional stress, for example, the affected hand cools down more slowly or faster than normal. Considering SKT difference as diagnostic tool for CRPS I the following should be stressed.

Systematic measurements show that side differences of SKT are not static descriptors but comprise dynamic changes that critically depend on vasoconstrictor drive and environmental temperature. In contrast to controls, the affected limb has unstable SKTs, typically fluctuating by >2°C. In general, two complex regulation types can be distinguished:

1. Warm patients. Under resting conditions, at 18°C environmental temperature, the affected side is on average 2–3°C warmer. During whole body cooling, the SKT decreases more slowly on the affected side than on the healthy side leading to maximal temperature differences on 4–5°C. During whole body warming, the SKT also increases more slowly on the affected side. Finally, the same level of SKT can be measured on both sides (cf. Fig. 3A in **BLUMBERG et al.**).

2. Cold patients. Under resting conditions in 18°C environment, the affected limb is about 2–3°C colder compared with the unaffected side. After whole body cooling, the SKT on the affected limb decreases more quickly to lower values than on the healthy side. The maximum SKT difference under these conditions may be about 4°C. After whole body warming, no side difference is any longer present.

The findings of **BLUMBERG** and Baron and Maier (1996) show that SKT side differences have to be interpreted with care when defining reliable diagnostic criteria for CRPS I.

Is the "ischemia test" a reliable predictor for CRPS Type I? According to **BLUMBERG** the so-called "ischemia test" is a reliable predictor of CRPS Type I (RSD). He claims that a positive test result (decrease of deep diffuse pain in a minute or less after cuffing the extremity that was largely emptied of blood in the capacity vessels) predicts that blockade of the sympathetic outflow alleviates pain and associated changes. Three critical points have to be emphasized:

(1) The term "ischemia test" is misleading because it implies for most readers that ischemia leads to blockade of activity in primary afferent terminals. This is barely the case. Transducer properties in afferent receptors as well as conduction of afferents are not blocked in such a short time. It is also unlikely that ectopic impulse activity as well as activity in sensitized nociceptors are blocked. **BLUMBERG** himself assumes that afferents stop to fire because the pressure in the deep somatic tissue decreases.

(2) It is assumed that activity in nociceptive afferents from the deep somatic domain is maintained by high pressure in the capillaries and small veins (due to venoconstriction and possibly precapillary vasodilation) and that this activity subsides practically immediately (in a minute) during the test. Consistent with this idea is a positive orthostatic test.

(3) The "ischemia test" has to be verified before it can be recommended. For this purpose, patients with clinically diagnosed CRPS I and CRPS II and a group of patients with neuropathic pain in which the sympathetic nervous system is to our knowledge not involved (e.g., patients with painful diabetic neuropathy) should be tested quantitatively in a double blind study design. Undoubtedly, if the test is positive in CRPS I patients but not in the other groups of patients, it could be a valuable diagnostic tool and would give support to **BLUMBERG'S** hypothesis (see below).

(4) The mechanism of pain in CRPS I patients proposed by **BLUMBERG** implies that cuffing the affected extremity at subsystolic but supradiastolic pressure (preventing in this way venous return) should aggravate the pain. It should be possible to measure this quantitatively in CRPS I patients and in control groups.

The idea of a disturbed microcirculation in CRPS Type I patients needs experimental support. The following idea is suggested by **BLUMBERG:** A changed pattern of activity in sympathetic (vasoconstrictor) neurons innervating blood vessels in deep somatic tissues leads to an increase of interstitial pressure and subsequently to edema and swelling. This activates and/or sensitizes deep somatic nociceptive afferents which in turn sensitize dorsal horn neurons. This results not only in pain and hyperalgesia but also establishes a vicious (positive feedback) circle that can be interrupted by sympathetic blocks. The idea of indirect sympathetic–sensory coupling is interesting and worth pursuing. Unfortunately, it lacks almost any experimental support. Venules and small deep veins are either sparsely or not at all innervated. Increase of interstitial pressure and swelling per se are not painful, that is, are probably not associated with excitation of nociceptive afferents. It is theoretically possible that the initiating event in the CRPS I patients leads to central changes ("central sensitization"), which are then maintained by an afferent input from deep somatic tissues that is normally subthreshold for the central neurons.

This connects to the problem "In which way is the sympathetic outflow to the extremities involved in the generation of swelling in CRPS I patients?" We feel that **BLUMBERG**'s "hydraulic hypoth-

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esis" is too simple to account for the edema and its reversal after sympathetic blocks (BLUMBERG et al. 1994). We agree with Blumberg that it is barely conceivable that the edema (and the increased blood flow and temperature in skin, at least in patients with early CRPS I) is related to neuropeptides released from unmyelinated nociceptive primary afferents producing plasma extravasation at the venular side. Experimental research on animals and humans should focus on the mechanisms by which the edema is generated.

Both case reports clearly support the vicious circle hypothesis. The vicious circle hypothesis of the generation of pain and associated changes (autonomic and motor) goes back to Livingston (1943) and has been elaborated in the Kiel laboratory (see Blumberg & Jänig 1994; Jänig & Stanton-Hicks 1996). The observations reported about both case reports fully support this hypothesis. However, this hypothesis requires neither an increased level of activity in the sympathetic neurons nor a change in activity pattern. If changes occur in the target cells it is in principle possible that the same or a reduced level of activity can maintain the state of the vicious circle. Development of hyper-reactivity of blood vessels after denervation and reinnervation of blood vessels is in favor of this idea. The crucial question is what starts this vicious circle? Can this vicious circle be triggered by central command signals?

NOTE

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The sensory and affective components of pain

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Abstract: Both the sensory and the motivational-affective component of pain must be taken into account in studies on sex differences as well as on neuropathic, postoperative, sympathetic, and visceral pain. In all these cases, therapeutic strategies should be aimed at controlling the peripheral, central, and psychological mechanisms underlying the global pain experience. Similarly, it should be recalled that some neuropeptides act on both sensory and affective pain mechanisms. **[BERKLEY; MCMAHON; DICKENSON; CODERRE & KATZ; WIESENFELD-HALLIN et al.; BLUMBERG et al.]**

Although the six target articles address very important topics in current pain research and therapy, I was surprised to find little or no mention of the affective side of pain perception. Nobody would disagree that the nociceptive input alone is not sufficient to produce the final experience of pain. Striking examples are the placebo effect, where expectations and beliefs can modulate pain perception (Benedetti & Amanzio 1997), and stress analgesia, where a stressful situation may induce the suppression of pain (Wall 1979). In this commentary I would like to stress that whenever we talk of pain we must consider both its sensory and its motivational-affective components. Since pain is a multidimensional experience involving sensory inputs and psychological states, I will discuss several issues that must be taken into account in studies related to sex differences, nociceptive and neuropathic pain, sympathetic nervous system, and neuropeptides.

Sensory and affective sex differences. The target article of **BERKLEY** describes several sex differences, from hormones and neurotransmitters to growth factors and visceral afferents. Hormonal and sensory mechanisms, however, are not the only factors that may undergo inductive and deductive analysis. The inductive analysis must also take into account the psychological counterpart of pain. It is surprising that pain of psychological origin is quoted in Table 1 as the last item of female prevalence. I wonder whether psychological differences between sexes might represent one of the most important factors. For example, it is worth considering the twofold greater prevalence of unipolar depression in women than in men. Similarly, anxiety disorders, such as panic disorder and generalized anxiety disorder, show a female to male ratio of approximately 2 to 1. Further, in the somatization disorder we find a twentyfold greater prevalence in women than in men. It should be recalled that these psychiatric disorders are often characterized by painful somatic symptoms.

On the other hand, deductive analysis must also consider psychological factors, such as the emotional effects of pregnancy and childbirth on the psychological state of women. Nor are sex differences in responses to treatment merely deductive. This difference is a reality. Whereas **BERKLEY** correctly reminds us that women are more likely than men to benefit from behavioral treatments, it should also be remembered that some pharmacological treatments can be more beneficial for women than for men. An example is Gear et al.'s recent finding (1996) that kappa-opioids produce greater analgesia in women than in men.

Sensory and psychological determinants of postoperative pain. **CODERRE & KATZ** talk of the importance of peripheral and central hyperexcitability, pointing out that treatments should target both peripheral and central sources of pathology. However, it should be stressed that "central" does not mean only "sensory" but also "higher order" brain processing, such as nociceptive emotional integration in the limbic system. Hence it should be stressed that treatments ought also to target psychological sources of pathology. Although CODERRE & KATZ describe hyperalgesia, referred pain, neuropathic pain, and postoperative pain, I will, for the sake of brevity, consider only postoperative pain.

Postoperative pain is a striking demonstration that many variables whose sensory aspects are described by **CODERRE & KATZ** are involved in the severity of a painful condition. However, a survey of the available literature shows clearly that psychological factors play a very important role in the severity of postoperative pain. For instance, Taenzer et al. (1986) demonstrated that anxiety, extraversion, depression, educational level, previous chronic pain syndromes, and bias toward using medications are capable of influencing the course of pain after surgery. In particular, trait anxiety and neuroticism are directly related to increased pain perception and can be used as predictors of postoperative pain severity. Not surprisingly, these psychological factors have also been found to affect the analgesic requirements after surgery.

Since non-medical factors may influence postoperative pain, it seems clear that whenever we test the effectiveness of therapeutic strategies such as pre-emptive analgesia, these psychological influences must be taken into account. As **CODERRE & KATZ** emphasize, therapies should target both peripheral and central mechanisms. However, in order to plan a correct and effective pain management, psychological mechanisms must also be considered.

Sympathetic nervous system and emotions. **BLUMBERG et al.** should be aware that other investigators (e.g., Ochoa & Verdugo 1995; Verdugo & Ochoa 1994; Verdugo et al. 1994) claim that the apparent pain relief with sympathetic nerve block is attributable to psychological factors. These investigators suggest that sympathetic blockade is a placebo response and that many patients diagnosed with SMP suffer from a disorder that is primarily psychogenic.

In any case, taking into account the theory of James and Lange, we must be aware that the sympathetic nervous system is involved in the perception of emotion. This appears to be particularly important in the article by **MCMAHON.** In fact, sympathetic afferents arising from viscera do represent a special case for pain perception. In view of the importance of the affective component of pain and the relationship between visceral inputs and emotions, some differences between somatic and visceral pain could also be attributable to differential activation of the limbic system. **BERKLEY** emphasizes this, suggesting that sex differences in visceral input might also result in different emotional influences on pain.

Pain, anxiety, and neuropeptides. The complex interactions between the sensory and affective mechanisms in pain perception must also be taken into account at the biochemical-

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pharmacological level. For example, the tricyclic antidepressant amitriptyline is an effective drug in different painful conditions, however, the mechanisms of its analgesic effects are not completely understood. Amitriptyline could act as an antidepressant drug, thus relieving the depressive symptoms (effects on mood), or otherwise could increase pain inhibition through neurotransmitters such as serotonin (sensory effects).

The interesting and exciting target articles by **DICKENSON** and **WIESENFELD-HALLIN et al.** describe several neurotransmitters or neuromodulators in the control of pain. Although these authors are concerned mainly with sensory aspects, I would again like to stress the importance of the affective component of pain. For the sake of brevity my comment will focus on two neuropeptides: opioids and cholecystokinin (CCK).

In considering the target articles by **DICKENSON** and **WIESENFELD-HALLIN et al.,** we must note that opioids and CCK act at both the sensory and the anxiety level. Since anxiety is strictly related to pain perception (anxiety increase may induce pain increase), the intricate mechanisms underlying such a relationship may confound the effects of opioids and CCK on the affective component of pain. For example, a recent study by König et al. (1996) in mutant mice indicates that the lack of enkephalins has both behavioral and sensory consequences. These authors disrupted the pre-proenkephalin gene to generate the enkephalin-deficient mice *enk*$^{-/-}$. Mice with the *enk*$^{-/-}$ genotype are more anxious, more aggressive, and show an altered supraspinal responsiveness to painful stimuli. It is interesting to see that nociception at the spinal level is not affected by the pre-proenkephalin mutation, and the behavioral changes can be described as an exaggerated response to painful or threatening stimuli. It is therefore likely that the enkephalin-deficient mice have an important change in the affective component of their pain.

As with opioid neuropeptides, CCK may act at both the sensory and the affective level. CCK shows both anti-analgesic and anxiogenic effects. The sensory anti-opioid effects of CCK are well described by both **DICKENSON** and **WIESENFELD-HALLIN et al.,** whereas the anxiogenic effects of CCK are not mentioned. For example, the CCK tetrapeptide (CCK-4) is panicogenic in humans, an effect that is blocked by CCK antagonists (Bradwejn et al. 1994). Thus CCK antagonists may act as analgesics or anxiolytics. We addressed the problem of this intricate pharmacological effect in a recent study showing that nocebo hyperalgesia, a phenomenon opposite to placebo analgesia, can be relieved by the CCK antagonist proglumide through a mechanism not involving opioids. We suggested that in this case proglumide could act as an anxiolytic (Benedetti et al. 1997). The complex action of the CCK antagonists is also shown by their potentiation of placebo analgesia (Benedetti 1996; Benedetti et al. 1995).

As in the cases of sex differences, postoperative pain, and visceral afferents, it is important to consider the actions of some neuropeptides on both the sensory and the affective component of pain. Here too, new pharmacological therapies must be developed, taking into account both sensory and psychological factors.

Pain, pleasure, and the mind

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Abstract: The target articles by **BLUMBERG et al.** and **BERKLEY** reflect some of the recent major theoretical and clinical advances in two areas of pain research. These two articles also represent two very different approaches to which type of variables are considered relevant to the study of pain. These different approaches are contrasted in the context of the different emphases in pain and pleasure research.

From the perspective of a relatively new pain researcher but a longtime investigator of pleasure (particularly sexual pleasure), it was fascinating and instructive to review the target articles in this *BBS* series. I was immediately struck by at least one major difference in emphasis between the study of pain and the study of pleasure. Pleasure research is focussed on the brain (and often on the mind) while pain research only occasionally gets past the dorsal horns of the spinal cord. It is interesting that pain and pleasure research do meet in the sexual arena and I will suggest at the end of my commentary that the overlap is instructive. I was also immediately struck by two apparently very different approaches to the biological study of pain underlying the different papers in this series. One approach appears reductionistic and seems to limit itself to the study of relatively peripheral mechanisms. The other is very "mindful" of the brain and central mechanisms. These diverging points of view are manifest in the articles by **BLUMBERG et al.** and the one by **BERKLEY.**

BLUMBERG ET AL. summarize some impressive theoretical, classificatory, and clinical advances this group has made in the understanding of the sympathetic mechanisms of pain. Difficult to treat "complex regional pain syndromes" often associated with other inexplicable symptoms now seem open to empirical analysis and clinical intervention without resorting to concepts like hysteria, malingering, and so on. On the other hand, the cost of these advances appears to be a severe limiting of the kinds of information considered relevant to the problem.

This limiting becomes apparent in **BLUMBERG et al.**'s choice of information considered pertinent to the illustrative case histories presented in the article. One remarkable aspect of both case histories is that they are comprehensive lists of affected body parts, symptoms, and clinical interventions with almost no indication of a real human being. In case history 1, for example, the only personal piece of information given about the patient is that he is a 72-year-old working man. This information is ignored for the remainder of the case history but one cannot help but wonder about the following: How usual is it for a 72-year-old to be working? Was it necessary for him to work to support himself or his family? Did he previously work with his now affected hands? How did he cope financially and emotionally in the period when he couldn't work? How did all of this affect his pain?

After 7 intravenous regional guanethidine blockades over a 21 day period, the patient became "free of pain and swelling along with an improvement of all the other symptoms." He returned to work and at a 9-month follow-up was free of symptoms. It is hard to argue with clinical success, but there is a strong message in this case history that emotions, stressors, social and familial support, and the meaning of the pain to the patient are not relevant. Even if **BLUMBERG et al.**'s sympathetic-sensory coupling hypothesis is correct, should it not recognize some of the above factors which clearly affect sympathetic activation, not to mention the experience and report of pain?

The reluctance of **BLUMBERG et al.** to include the "mind" or at least the brain as a potential contributor to pain is reflected in the last two sentences before the conclusion: "In addition, one has to consider the possibility of so-called psychogenic pain mechanisms. In all such cases, which may be called atypical RSD, even complete sympathetic blocks may give unsatisfactory results." The logic of inferring psychogenic mechanisms from poor therapeutic outcome to sympathetic blocks is not clear to me. Surely these blocks might be giving unsatisfactory results because our presumed understanding of the mechanisms – whether biological, psychological, or both – may be incomplete. These speculations could be supported or dismissed empirically with a well-controlled treatment outcome study.

BERKLEY maintains the biological emphasis of the series without an underlying reductionist stance. There is a comprehensive review of potential anatomic and physiological factors which may influence sex differences, but the analysis does not stop there. Concepts like attitudes, coping, self-report bias, and so on, are considered and included in BERKLEY's analysis. The fact that pain may often be situationally affected or maintained is acknowledged

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and developmental, social learning, motivational, and interpersonal influences are reviewed and integrated into the argument.

Although **BERKLEY** does not present any case histories, there is little doubt from the following quotation that her method would be quite different from that of Blumberg et al:

> It is clear, however, that when patient A appears in a health care facility to report that she or he is experiencing, say, chest pain, a large number of variables have already contributed to that report that may seem to have a remote relation to the cause of A's pain. On the other side of the scene, a large number of seemingly remote factors also enter into the response of health care worker B, who is faced with A's report of chest pain. These remote factors operate together to have a large impact on A's overall health.

Underlying these lines seems to be the assertion that it is unlikely that any single pain intervention will reliably "cure" chronic pain and that a more "mindful" approach is necessary.

Aristotle suggested that pain and pleasure mechanisms should be understood by including both the material and immaterial, the peripheral and central. It seems to me that pain and pleasure researchers have something to learn from each other and from Aristotle. Consider the following phenomena where pleasure and pain are closely intertwined. (1) A male is being whipped to orgasm by his sexual partner when the partner unexpectedly changes a part of the "script" and the pleasure turns to pain (Weinberg 1994). (2) A woman reports severe dyspareunia with one partner during vaginal intercourse but intense pleasure with another (Meana & Binik 1994). Understanding these phenomena and many similar ones involved in chronic pain (and pleasure) will require a complete understanding of peripheral sensory mechanisms at a molecular level but they will also require an understanding of the mind.

A leg to stand on: Learning creates pain

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Abstract: The persistence of both inflammatory and neuropathic pain can only be explained when learning processes are taken into account in addition to sensitizing mechanisms. Learning processes such as classical and operant conditioning create memories for pain that are based on altered synaptic connections in supraspinal structures and persist without peripheral input. [**CODERRE & KATZ; DICKENSON; WIESENFELD-HALLIN et al.**]

Several target articles in this *BBS* special issue on pain address the question of how neuropathic pain can be explained. Whereas many of the mechanisms in musculoskeletal pain syndromes and inflammatory pain have been elucidated, neuropathic pain states continue to remain a puzzle and are often resistant to pain treatment. The target articles by **CODERRE & KATZ, DICKENSON,** and **WIESENFELD-HALLIN et al.** all address different aspects of the sensitization processes that might be involved in the initiation of neuropathic pain. They all fail to address the important role of learning processes and pain memories in the chronicity process.

CODERRE & KATZ provide an admirable overview of the physiological literature on hyperexcitability of the nociceptive system until 1992. Their "model" (which is rather descriptive than explanatory) and conclusions, however, are too general to allow specific predictions for sensitizing mechanisms in the development and maintenance of chronic pain. One major problem with the review is the neglect of the substantial literature on learning and neuronal plasticity (e.g., Merzenich & Sameshima 1993) and pain memories. To state that peripheral injury barrage may cause first peripheral and then CNS hyperexcitability is as well known as the fact that central excitability can be maintained by ongoing peripheral inflow or in some cases may become autonomous even at the CNS-level without lasting peripheral nociceptive input. Such a "model" is not specific for pain, it is true for any sensory modality. Strong auditory input, for example, causes hyperexcitability from the cochlea up to the cortical projection areas leading to phenomena such as tinnitus, partial deafness and hypersensibility to tones with particular frequencies (Mühlnickel et al., in press; Zenner 1993).

The problem is not hyperexcitability alone; specific questions are: (1) What are the different physiological mechanisms underlying peripheral, spinal, and cortical-subcortical hyperexcitability? (2) In the case of central hyperexcitability, why and how is pain maintained without peripheral input? (3) At which anatomical levels of the CNS can differential cellular and systemic mechanisms be observed and what are the consequences of the different neurophysiological expressions for chronic pain?

None of the above questions can be answered without including learning and conditioning since they are an integral part of all sensitizing mechanisms in animals and humans. The accumulated knowledge of the neurobiological mechanisms of learning and memory can then be used to specifically predict the behavioral and physiological consequences of sensitizing conditions.

Any experimental or clinical procedure that uses sensitizing stimuli as described by the authors such as capsaicin injection, nerve section, or surgery can be treated in a classical Pavlovian conditioning model. These procedures may be viewed as unconditioned stimuli (US) and the simultaneously present environmental, visceral, and somatic stimuli, particularly those in close vicinity to the US-body region, serve as conditioned stimuli (CS). After several (or in some instances a single, cf. Garcia & Koelling 1966) pairings of the US and the CS, the CS may come to elicit the same (or in some instances, cf. Siegel 1975, the opposite) response as the unconditioned response which consists of the pain experience and its accompanying physiological responses. Later presentations of the CS may induce hyperalgesia or hypoalgesia based on the type of conditioning that occurs in a given learning situation (Maier 1989; Maier et al. 1992). In numerous animal experiments, changes in nociceptive sensitivity have been induced by Pavlovian and Skinnerian condition (cf. Greeley 1989; Maier 1989; Weinberger et al. 1991). These learning-induced alterations have not only been demonstrated for behavioral expressions of pain but also for accompanying physiological and neurochemical changes and the central mechanisms for these learned changes in pain sensitivity have been investigated (Watkins et al. 1993; Weinberger & Diamond 1987).

Generalization in learned pain sensitivity from a particular body location to another region, which may not be even remotely related to the same dermatome, such as described in the section on referred pain, can be responsible for these otherwise difficult to explain phenomena. In chronic pain patients, we have found conditioned acquisition and extinction of pain-related muscle tension increases which were not confined to the original position of US application (Flor & Birbaumer 1994). Furthermore, it has been shown that these learning processes lead to cortical memories for pain that subsequently increase pain sensitivity (cf. Birbaumer et al. 1995; Flor et al., in press; Lutzenberger et al. 1997). The cortical pain memories are present in primary and secondary somatosensory cortex (Flor et al. 1995; Flor et al., in press) but also seem to be related to association cortex (Knost et al., in press; Larbig et al. 1996). This literature is consistent with animal work that showed expansion or shrinking of primary somatosensory areas induced by behavioral training (Jenkins et al. 1990; Recanzone et al. 1992), deafferentation (Pons et al. 1991), and amputation (Merzenich et al. 1984).

The behavioral relevance of these cortical reorganizational mechanisms has been demonstrated: in chronic back pain patients, chronicity of pain is positively related to expansion of cortical representational areas (Flor et al., in press); in phantom limb pain, the magnitude of the pain is linearly associated with the amount of expansion observed in SI (Flor et al. 1995). Whereas

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lesion-induced changes in cortical reorganization are probably related to alterations in the periphery, the spinal cord, or the thalamic level (cf. Florence & Kaas 1995; Pons et al. 1991), behavior-induced cortical pain memories should result from the strengthening of synaptic connections via Hebbian learning (Birbaumer et al. 1995; Braitenberg & Schüz 1993; Diamond et al. 1994; Kaas 1995; Rauschecker 1991; Wang et al. 1995).

A recent experiment in our laboratory suggests that peripheral and central mechanisms may contribute in varying degrees to the reorganizational changes that were observed in phantom limb pain and points toward a causal role for these changes (Birbaumer et al. 1997). After local anesthesia of the amputated site (arm and shoulder region), two types of responses can be observed in phantom limb pain: one shows pain reduction as a consequence of anesthesia and consequently a return "movement" of cortical representations to the symmetric position as measured with neuroelectric source imaging. The second group does not respond to anesthetic block and the pathological cortical reorganization remains. The nonresponsive phantom limb pain group does not need any peripheral influx into the deafferented zone for the maintenance of pain. However, studies on the spinal and thalamic influences in this group have not yet been completed.

Several important consequences would follow from the inclusion of learning processes in the hyperalgesia related to hypersensitivity: blocking or delay of conditioning can be induced by either presenting the CS alone prior to conditioning (latent inhibition) or by presenting the CS with another CS that has previously acquired signal value for the response to be learned (blocking); see Rescorla 1988. Extinction requires frequent presentation of all or nearly all CSs without the US. Simple anesthesia or externally produced analgesia of the involved body area will not and cannot result in relief of enduring pain if learning processes were involved because the conditioned stimuli are not presented in an extinction-analogous situation.

Both **DICKENSON** and **WIESENFELD-HALLIN et al.** have described the role of cholecystokinin in antagonizing opioid efficacy and the development of opioid tolerance. Wiertelak et al. (1992) have shown that classical conditioning can abolish morphine-induced analgesia in the presence of safety-signals and that this process is mediated by cholecystokinin (Wiertelak 1994a). Although Dickenson mentions this study, he does not refer to the enormous potential that learning processes may have in inducing this response. Maier and co-workers (Maier et al. 1992; Wiertelak et al. 1994b) have also shown that illness-induced hyperalgesia may be conditioned to innocuous stimuli and that it induces plastic changes similar to those reported for physiological sensitization (e.g., NMDA involvement).

Associative mechanisms are inextricably intermingled with non-associative hyperexcitability in most types of pain described in the target articles. The lack of a clear relationship between most pharmacological agents and pain relief is obvious from the clinical as well as animal literature cited by the authors. Hyperexcitability at the CNS level is not blocked by any single substance: neither opioid, NMDA or AMPA, nor cholinergic mechanisms were found to be solely responsible. The literature on conditioning suggests that convergence of cholinergic, aminergic, and glutamatergic inputs to plastic cortical dendrites from subcortical sources causes lasting plastic changes (Pirch et al. 1992). Therefore a single specific depolarizing agent is extremely unlikely in the production of lasting pain (Weinberger et al. 1991).

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Vaginas yield far more pleasure than pain

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Abstract: **BERKLEY**'s pathogen model of sex differences in pain is inconsistent with women outliving men by several years. The vagina is far more resistant to pathogens than is the rectum. Vaginal stimulation produces intense analgesia in rats and humans. Possible evolutionary and cardiovascular factors are also noted.

The model which **BERKLEY** proposes (of women being more susceptible to pathogens) is inconsistent with women living far longer than men (a large effect size, unlike sex differences in pain), unless one assumes that these pathogens make for real morbidity but decrease mortality, or as Nietzsche put it, "that which does not kill me makes me stronger."

Despite **BERKLEY**'s equation of the orifices, the vagina is far more resistant to viral invasion than the anus (rectum). Homosexual men (who have a higher rate of anal intercourse than women) have a much greater prevalence of pathogens than heterosexual men or women (Root-Bernstein 1993). Although women may be more affected by some pathogens such as chlamydia, they are less affected by more serious infections. In particular, the ability of fragile viruses, such as HIV, to be transmitted through vaginal intercourse (as opposed to anal intercourse or injection) to healthy persons of childbearing age is near zero (Brody 1995a; 1995b; 1997). The relative resistance of the vagina is due to many factors, including histological differences affecting permeability and the ambient pH (the vaginas of healthy women of childbearing age are sufficiently acidic to inactivate HIV; Voeller & Anderson 1992).

No teleological argument is required to see that the purpose of the vagina is to receive the penis (which **BERKLEY** revealingly terms a "potentially damaging object"; sect. 3.1, para. 3). In addition to the intense pleasure that healthy humans experience during intercourse, there is also the analgesia afforded by the stimulation of the vagina. Sensitivity to these reinforcers may be among the main determinants of intercourse frequency (Brody 1997).

The magnitude of analgesia produced by cervical probing of female rats is greater than that of 2 mg/kg morphine (Komisaruk et al. 1976). More intense probing produces more intense analgesia (Crowley et al. 1976), and the effect is potentiated by estradiol augmentation (Rothfeld et al. 1985). Cervical probing suppresses thalamic responses to noxious but not innocuous stimuli (Ross et al. 1979). The analgesic effect of cervical probing has been used to operantly train female rats to solicit probing during painful stimuli (Ross et al. 1979).

Whipple and Komisaruk (1985) found that human vaginal stimulation increased pain detection (47–53%) and tolerance thresholds (36–47%). Among the subgroup of women who orgasmed during the session, the pain detection threshold increased 106% and the tolerance threshold 74%. A variety of controls eliminated the possibility that the results were due to distraction, global anesthesia, or counter-pain phenomena. In a replication and extension, Whipple and Komisaruk (1988) found that simple pressure on the anterior vaginal wall increased pain tolerance (26%), but posterior wall and clitoral pressure did not. However, when subjects applied stimulation so as to produce pleasure and not merely pressure, all genital stimulus zones produced increases in pain tolerance (27–36%). Similarly, pain detection thresholds increased (35%) during anterior wall pressure but not at other genital zones, while detection thresholds increased (39–48%) at all genital sites with pleasurable stimulation.

Orgasmic dysfunction has been reported to be common in women who go on to develop chronic back pain, and the development of back pain results in an exacerbated prevalence of dysfunction, as well as a decrease in frequency of coitus (Maruta & Osborne 1978; Sjogren & Fugl-Meyer 1981).

As a separate issue, another possible contributing factor to sex differences in pain might be related to blood pressure being lower

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in women than men. Resting blood pressure has been found to be positively associated with higher pain thresholds (Brody et al. 1997; Rau et al. 1994).

Finally, in a speculative vein, there may be an evolutionary basis for higher pain thresholds in men: during our long evolution, women needed to be aware of more minor injuries that might harm their fetuses, but men needed to endure more pain during combat and hunting. **BERKLEY** noted that sex differences are greater for pressure stimuli than for thermal stimuli. Developing means of dealing with mechanical but not thermal pain may have been adaptive for those who carried heavy weight or did battle (Rau et al. 1994).

More inhibition and less excitation needed in the fight against pain

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Abstract: Recent pain research has concentrated heavily on excitatory processes. However, noxious stimuli activate excitatory *and* inhibitory systems. As failure of inhibition could underlie some forms of pathological pain, it may be argued that a full understanding of the mechanisms underlying the development of pain states can only come from a consideration of all the central sequelae of injurious stimuli. **[BERKLEY; BLUMBERG et al.; CODERRE & KATZ; DICKENSON; MCMAHON; WEISENFELD-HALLIN et al.]**

It is evident that analgesia may be produced by reducing the effects of the excitatory processes contributing to pain transmission or by increasing the inhibition impinging upon it. Currently the most effective centrally acting pharmacological tools for combatting pain are agents which increase inhibition, that is, opioids, α_2-adrenoceptor agonists, and tricyclic antidepressants. Notwithstanding this situation, recent pain research has concentrated heavily on excitatory processes, a bias which is reflected in the content of these target articles. As a consequence, research into inhibitory mechanisms has been less vigourously pursued than in the past. It is informative in this respect to note that two of the major reviews of opioid function cited in the target article by **DICKENSON** date from the mid-1980s. The attenuation of interest in inhibition is evident in the slow progress towards development of δ-selective opioids, despite their promising profile of activity (Dickenson, sect. 4.1), and in the fact that some very important questions concerning opioids remain unanswered. For instance, we still do not know if changes in descending inhibition make a significant contribution to the antinociceptive action of systemically-administered opioids. This is a question central to the understanding of opioid efficacy, yet the literature on the subject is so rife with contradictions (Dickenson, sect. 4.4), that the supraspinal effects of opioids remain largely a matter of opinion rather than fact. On a related point, our understanding of endogenous pain control systems, including those which may or may not be activated by opioids, is incomplete. Amongst these the monoamine-containing bulbo-spinal pathways remain the most likely potential targets for therapeutic intervention. Unfortunately, investigations into the functions of these systems have been complicated by the pharmacology of the transmitters involved (Dickenson, sect. 4.4, para. 4), and by the fact that their influence on motor systems is often opposite to their effects on sensory transmission. This last factor can confound pain measurements dependent on motor responses (i.e., most animal behaviour experiments). Nonetheless, it remains the case that identifying the spinal receptors through which descending pathways exert their actions will provide important indicators for the development of new analgesic therapies.

A significant feature of endogenous pain suppression systems is that they can be activated by externally applied stimuli, including those of a noxious nature. The behavioural significance of stimulus-activated antinociceptive systems in animals is well accepted (e.g., Harris 1996), and they almost certainly underlie the many forms of counter-irritation analgesia practised in humans. Afferent inflow from the site of an injury ought to activate both excitatory *and* inhibitory systems acting on different parts of the nervous system (see the article by **CODERRE & KATZ,** also Clarke et al. 1992). *Both* aspects of the central consequences of injury need to be understood to appreciate the development of pain states, particularly as failure of inhibition probably contributes to pain pathologies (**WIESENFELD-HALLIN et al.,** sects. 3.2 and 4.4). Furthermore, the late ontogeny of inhibitory systems is likely to have important consequences for the development of pain sensitivity in neonates (**DICKENSON,** sect. 8).

One problem associated with centrally-acting analgesics is that they are not equally effective in all pain states. Thus, the dose-response curve for morphine is shifted to the left in inflammatory pain (**DICKENSON,** sect. 5, para. 1) and to the right in neuropathic conditions (DICKENSON, sect. 5, para. 2; **WIESENFELD-HALLIN et al.,** sect. 4). Both of these target articles invoke the "anti-opioid" peptide CCK as a possible mediator of these changes. Although it is difficult to imagine what sort of evolutionary pressures would have led to the development of such an arrangement, the data supporting an anti-opioid effect of CCK are good. Changes in opioid receptor populations are also likely to contribute (DICKENSON, sect. 3.1, para. 4). Contemplating this last point led me to consider whether inputs from so-called "silent nociceptors" (see **MCMAHON,** sect. 3.2.3) might be particularly sensitive to opioids. Such a situation could explain the enhanced potency of opioids in inflamatory states, assuming that recruitment of these nociceptors really does contribute to pain evolving from such conditions.

In arguing that inhibition has not received sufficient attention in recent years, I do not wish to imply that the efforts expended on studies of excitatory processes have been misdirected. We now have a good understanding of the mechanisms underlying enhanced pain transmission after injury, as evidenced in the target article from **CODERRE & KATZ.** These authors have developed a credible, testable hypothesis for the genesis of hyperalgesia, allodynia, and their more problematic sequelae. The key new ingredient in their model is the consideration of persistent nociceptive afferent inflow after injury. It is intuitive to imagine that nociceptors in damaged tissue will continue to fire long after the original stimulus has been applied, but there has until recently been relatively little thought given to the consequences of such activity. As recognised by CODERRE & KATZ the afferent barrage emanating from injured or inflamed tissue *must* have significant central effects, particularly when one considers the fact that long-lasting alterations in withdrawal reflexes can be evoked by just a few C-fibre strength electric shocks applied to peripheral nerves at low frequency (Wall & Woolf 1984). Further, the central actions of the barrage should change as the neuropeptide content of the primary afferents alters in the post-injury period, with possible consequences for the susceptibility of the pain to pharmacological intervention (see **WIESENFELD-HALLIN et al.,** sect. 4).

A satisfying feature of the **CODERRE & KATZ**'s hypothesis is that differing levels of initial central sensitization and ongoing afferent inflow can be built into the model to explain a wide variety of pain phenomena, in particular referred (sects. 3.3, para. 2) and neuropathic pain (sect. 4.3, para. 1). CODERRE & KATZ argue that the referral of pain from deep to superficial structures is dependent on convergence of visceral and cutaneous afferents onto common populations of second order neurones in the spinal cord. Assuming that these neurones are the site at which central sensitization is effected, once they become sensitized by input from one source (e.g., the viscera), they should show increased responsiveness to signals from all sources. An unsatisfactory component of the CODERRE & KATZ theory is the idea that referred pain relies on tonic inputs from the area of referral. It is not clear how such inputs might be generated, or what level of activity would be required to maintain the referred sensation. Few action potentials

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are recorded from afferent nerves in unstimulated skin, but of course the referral regions may be subject to low level stimulation from contact with clothing and so on. Clearly, we need to know more about the patterns of activity from receptors in referral areas before this aspect of the hypothesis can be accepted.

MCMAHON (sect. 2.5) agrees with **CODERRE & KATZ**'s view that referral of pain from the viscera is dependent on viscerosomatic convergence, but in so doing creates a difficulty for his cautiously proffered argument that the perception of pain from viscera depends on summation of inputs from all receptors ("intensity coding"), rather than activation of specific nociceptors as is claimed to happen for the skin (sect. 3.2, para. 3). If this is a fundamental difference between somatic and visceral sensory systems, cells receiving converging inputs would be accepting one type of pain coding from the skin and a different one from visceral tissue. Perhaps activation of the tiny number of visceral nociceptive afferents is sufficient to set a "pain context" for central interpretation of signals arising from lower threshold receptors. Activity in a few nociceptive afferents could enhance responses of second order cells to the inputs from lower threshold receptors, as has been shown for limb withdrawal reflexes (Clarke et al. 1989), pushing their output into the range identified in the brain as "painful." Such a mechanism would not be contrary to existing evidence on the processing of somatic sensation and might apply to all inputs to viscerosomatic neurones.

The very interesting article by **BLUMBERG et al.** shows that there are still major problems in diagnosis for pain related to activity in the sympathetic nervous system. The finding that sympathetically-maintained conditions can be associated with hot and swollen (as well as cold) extremities is astonishing to this nonclinician. The author's suggestion that this might be due to overactivity in vasoconstrictor fibres directed at post-capillary sphincters is ingenious but is not supported by any evidence. Warm extremities indicate increased blood flow through the tissue: damming the blood supply up on the venous side of the capillaries would not allow this to happen. Perhaps the swelling comes from effects on capillary permeability or changes in lymphatic flow. I suspect the key to sympathetic-sensory coupling lies in the orthostatic component of reflex sympathetic dystrophy: this suggests that tissue pressure is an important stimulus in generation of pain in this condition.

BERKLEY makes an heroic attempt to summarize an unsummarizable subject. Her contribution correctly implies that studies on gender differences in pain perception can only progress once we understand what happens in females during the menstrual/oestrus cycle. It would be amazing if the large changes in the circulating levels of neuroactive compounds (i.e., sex steroids) did not alter some aspects of nociception. Indeed, a recent carefully-controlled study has shown oestrus-related variations in tail flick latency in rats (Sapsed-Byrne & Holdcroft 1996).

Finally, I would like to express my appreciation of these target articles. They are all excellent, and the scope of their coverage will make them a valuable educational resource for some years to come.

Does central nervous system plasticity contribute to hyperalgesia?

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Abstract: Hyperalgesia can arise from peripheral sensitization, on-going peripheral activation, and central plasticity. In the target article, **CODERRE & KATZ** argue that all three mechanisms contribute to hyperalgesia. In contrast, we believe that existing experimental evidence suggests that central plasticity plays only an insignificant role in most experimental models and clinical presentations of hyperalgesia induced by tissue injury or chemical activation of sensory receptors.

Hyperalgesia can arise from three sources: peripheral sensitization, on-going peripheral activation (*ongoing central sensitization* in **CODERRE & KATZ**'s target article) and central plasticity (*initial central sensitization* in the target article). CODERRE & KATZ argue that all three mechanisms contribute to hyperalgesia, with the relative contributions varying according to the type of hyperalgesia and degree of peripheral tissue injury. In contrast, although central plasticity can be induced by electrical stimulation of peripheral nerves (Woolf & Wall 1986), we will argue that existing experimental evidence suggests that central plasticity plays an insignificant role in most experimental models and clinical presentations of hyperalgesia induced by tissue injury or chemical activation of sensory receptors. We believe that our different conclusion arises from consideration of additional studies not cited in the target article and appreciation of critical technical limitations.

Two types of evidence address the relative contributions of peripheral and central mechanisms of hyperalgesia. *Indirect* evidence arises from either the recording of afferent activity (e.g., Puig & Sorkin 1996) or neuromediator (Dubner & Ruda 1992) and structural (Woolf et al. 1992) alterations of the dorsal horn during the development and maintenance of hyperalgesia. Indirect studies, however, only provide supporting evidence or suggest specific mechanisms; they fail to critically test either of the three mechanisms of hyperalgesia. In contrast, the relative contribution of each source can be *directly* tested by two experimental paradigms; *pre-injury* block (also known as pre-emptive analgesia) and *post-injury* block, as shown in Figure 1.

In the post-injury block paradigm, hyperalgesia is induced by injury or natural activation of sensory receptors (e.g., inflamma-

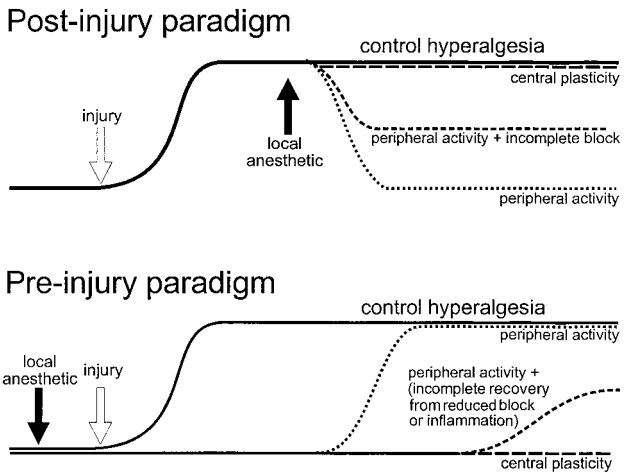


Figure 1 (Cleland & Gebhart). Experimental paradigms to assess the relative contributions of central and peripheral mechanisms. In the post injury paradigm, tissue injury induces hyperalgesia, indicated by the thick black line. Once hyperalgesia is established, blockade of sensory receptors at the site of injury distinguishes between central and peripheral mechanisms. If hyperalgesia is unaffected (long dashed line), central plasticity is sufficient, but if hyperalgesia is completely abolished (dotted line), persistent peripheral activity is necessary. It is important to note that incomplete local anesthetic block (short dashed line) can erroneously suggest central plasticity. In the pre-injury (preemptive) paradigm, local anesthetic is transiently applied during injury presumably to prevent establishment of central plasticity. If hyperalgesia is abolished once the local anesthetic wears off (long dashed line), the transient burst of afferent activity during injury and hence central plasticity is necessary, but if comparable hyperalgesia occurs (dotted line), peripheral activity is sufficient. If the local anesthetic block has not completely worn off or inflammation has been reduced by the local anesthetic block (short dashed line), then central plasticity can be erroneously suggested.

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tion, C-fiber excitation, chronic nerve damage, or clinical insult). Once the hyperalgesia is fully developed, any on-going activity of sensory receptors arising from the induction process is *completely* blocked (e.g., local anesthetic, nerve cut, cold) without altering either the test stimulus (e.g., electrical nerve stimulation or natural stimulation outside the injured area) or response (perception, withdrawal reflex, neural activity). If the hyperalgesia is abolished (dotted line), then on-going peripheral activity was necessary for hyperalgesia. On the other hand, if the hyperalgesia is unaffected by the blockade (long dashed line), then central plasticity induced by the initial activation of sensory receptors was sufficient for full expression of hyperalgesia.

In the pre-injury block paradigm, hyperalgesia is again induced by injury or natural activation of sensory receptors. However, blockade is applied before the induction and allowed to wear off *completely* and *without altering peripheral inflammation*, before the presence and magnitude of hyperalgesia is assessed. If hyperalgesia is prevented, then central plasticity induced by the initial sensory activation was necessary for expression of hyperalgesia, but if hyperalgesia is unaffected, then peripheral mechanisms were sufficient for expression of hyperalgesia.

There are two important issues regarding these experimental designs. First, showing that on-going peripheral activation is necessary does not imply that on-going peripheral activity *causes* hyperalgesia. For example, central plasticity could nonlinearly contribute to hyperalgesia so that it is only expressed in the presence of on-going sensory input. To reasonably demonstrate causality (Kupfermann & Weiss 1978), one must show both necessity and sufficiency. Thus, to show that on-going peripheral activation causes hyperalgesia, one must show that post-injury blockade abolishes hyperalgesia and that pre-injury blockade does not prevent the development of hyperalgesia.

The second issue is that both experimental designs depend critically on technical considerations. In the pre-injury paradigm, local anesthetic must completely silence *all* induced on-going activity *at the time* of measurement; otherwise, a contribution of central plasticity would erroneously be suggested (Fig. 1, upper short dashed line). In the post-injury paradigm, the effects of the block must completely wear off by the time of measurement; otherwise, a contribution of central plasticity would again erroneously be suggested (Fig. 1, short dashed line). Additionally, in the pre-injury paradigm, the block must not diminish the development or magnitude of inflammation; otherwise, once again a contribution of central plasticity would erroneously be suggested (Fig. 1, lower short dashed line).

Returning to the experimental evidence, we believe that (1) there is a preponderance of evidence showing that on-going peripheral activity is necessary and sufficient for secondary hyperalgesia, and that (2) many studies favoring central plasticity failed to adequately describe controls for the completeness of blockade at the time of measurement.

In the post-injury blockade paradigm, studies using formalin (Dallel et al. 1995; Dickenson & Sullivan 1987; Taylor et al. 1995), carrageenin (Kayser & Guilbaud 1987), intra-articular irritants in spinalized animals (Ferrell et al. 1988; Cleland & Gebhart, unpublished observations), nerve damage (Sheen & Chung 1992), topical C-fiber excitatant (Grönroos & Pertovaara 1993; LaMotte et al. 1991, for brush only) and clinical pathology (Gracely et al. 1992; Koltzenburg et al. 1994), found that local anesthetic blockade or nerve section completely (seven studies) or nearly completely (≥82%, three studies) abolished hyperalgesia or hyperreflexia. In the three studies in which some hyperalgesia persisted following blockade, incomplete local anesthesia could have been partially responsible.

In contrast, although **CODERRE & KATZ** mention some of these results, they also cite eight recent studies (Coderre & Melzack 1985; 1987; Coderre et al. 1990; LaMotte et al. 1991; Torebjörk et al. 1992; Wall & Woolf 1984; Woolf 1983; Woolf & Wall 1986) as obtaining the opposite result; significant hyperalgesia or hyperreflexia persisted following blockade. However, in all but one of these studies either technical or interpretative problems call the results into question. Four studies (Coderre & Melzack 1987; Coderre et al. 1990; Woolf 1983; Woolf & Wall 1986) failed to fully document that all irritant-induced activity of sensory receptors was absent at the time of measurement. In this regard, it is important to note that thermal anesthesia can be obtained without mechanical anesthesia, inflammation can increase anesthetic washout and therefore shorten the duration of anesthesia, and the duration of complete block can be brief (Fletcher et al. 1996), especially in the absence of epinephrine. Of the four remaining studies, in one study conditioning (Wall & Woolf 1984) was with acute nerve section, an artificial stimulus more like nerve electrical stimulation than tissue injury. In another study (Codere & Melzack 1985), results were only weakly significant. Lastly, Torebjörk et al. (1992) used local anesthetic to block afferent activity, but they blocked the skin innervated by the electrical test stimulus, not the skin affected by capsaicin (thus the on-going activity would not have been eliminated). Thus, of eight recent studies, only one (LaMotte et al. 1991) obtained unassailable evidence for central plasticity, but then only for punctate and not brush stimulation.

In the pre-injury blockade paradigm, there are far more studies, especially clinical, and greater difficulties in interpretation. Ignoring the many difficulties with clinical studies, we are still left with a uniform problem in interpreting the results of experimental studies; the pre-injury blockade may have decreased the development of peripheral inflammation, either by acting on spinal cord autonomic neurons, axonal flare or local inflammatory mechanisms, depending on the site of local anesthetic administration, thus erroneously indicating a contribution of central mechanisms engaged by the initial sensory receptor activation. Pre- versus post-injury blockade comparisons do not solve this problem because the injury preceding local anesthetic blockade may increase local blood flow, thereby decreasing the efficacy of the post-injury block relative to the pre-injury block (e.g., Dahl et al. 1993; Fletcher et al. 1996). Thus, it is particularly noteworthy that several studies have nevertheless shown that pre-injury blockade does not alter the eventual development of hyperalgesia induced by intra-articular mustard oil (Dahl et al. 1993; Fletcher et al. 1996; Yashpal et al. 1996 for high formalin concentrations; Cleland & Gebhart, unpublished observations). Although it remains possible that following recovery from the anesthetic block, activation of nociceptors by tissue injury could then induce central plasticity, it would be unlikely that the hyperalgesia would reach post injury levels (Woolf & Chong 1993), as reported in these studies.

In summary, in the post-injury block paradigm, eleven studies showed that blockade abolished hyperalgesia, while one study showed that punctate hyperalgesia was unaffected, and in our opinion the remaining seven either did not adequately verify that local anesthetic blockade was complete at the time of measurement or were open to question for other reasons. In the pre-injury paradigm, results are more difficult to interpret, but at least four studies have shown that blockade does not prevent the eventual development of hyperalgesia. In addition, there is indirect evidence from human psychophysical studies (Andersen et al. 1995) and afferent recordings (McCall et al. 1996; Puig & Sorkin 1996) that various conditioning stimuli can induce hyperalgesia cause spontaneous activation of nociceptors with a time course consistent with hyperalgesia.

Thus, we believe that although central plasticity can be induced by electrical nerve stimulation (Woolf & Wall 1986) or acute nerve section (Wall & Woolf 1984), secondary hyperalgesia (acute and chronic) arising from tissue injury or chemical stimuli is predominantly caused by on-going activity of peripheral sensory receptors, with central plasticity providing an insignificant contribution in most instances. Whether central plasticity plays a greater role in as yet unexplored experimental models of hyperalgesia, especially primary hyperalgesia, awaits further, carefully controlled, studies.

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Central versus peripheral substrates of persistent pain: Which contributes more?

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Abstract: evidence that central sensitization needs to be maintained in an ongoing manner by nociceptive input from the periphery makes the peripheral drive, rather than the central amplification process, the highest priority target for understanding and control. To stop the peripheral drive is to kill two birds with one stone. Moreover, the amplification that central sensitization does provide is selective and not necessarily striking in intensity. A "magic bullet" that neutralized central sensitization would probably be less effective in controlling persistent pain than many investigators would like to believe. **[BERKLEY; BLUMBERG et al.; CODERRE & KATZ; DICKENSON; MCMAHON; WEISENFELD-HALLIN et al.]**

CODERRE & KATZ have added some novel emphases to a model that is rapidly becoming the consensus view in the pain research community. Briefly, noxious peripheral inputs (nociceptive, inflammatory, or ectopic/neuropathic) are thought to set up, and if continued, sustain a state of "central sensitization." In the presence of this state, subsequent peripheral inputs are amplified and remarkably Aβ[A-beta] inputs, normal and ectopic, are rendered painful. Does this mean that if we could control the central sensitizing process we could defeat persistent pain?

Which contributes more? In their summary, CODERRE & KATZ state that "persistent pain depends not only on central sensitization, but also on inputs from damaged peripheral tissue". This phrasing captures well the currently favored notion that chronic pain is mostly a central affair. In the model, however, excess peripheral input clearly takes precedence. It both triggers the central amplification and provides the signal that is amplified. We are looking at a serial process. A "magic bullet" that blocked central amplification might reduce persistent pain, but it would not provide complete relief as the excess, painful input from the periphery would remain. On the other hand, block of the peripheral input would "kill two birds with one stone," stopping both the peripheral and the central contributions to the persistent pain process. All else being equal, if I were investing in a new drug, I'd chose one that promises to bring the peripheral abnormality under control.

N-methyl-D-aspartate (NMDA). The reduction of pain with NMDA receptor antagonists instantly makes one think that the process must involve central sensitization. For some it is enough to mention these four letters as if they were a mantra. Here is a call for sobriety. Glutamate is a major excitatory neurotransmitter in the brain, and blocking any of its receptors is expected to suppress spinal network activity. The same holds for other suppressive agents like barbiturates, lidocaine, GABA, or glycine. If one wants to claim that an NMDA receptor antagonist such as MK-801, 5APV or ketamine are acting on a specific process such as central sensitization, one must demonstrate selectivity, and not just suppression.

Selectivity of central amplification. CODERRE & KATZ point out correctly that secondary hyperalgesia is not *the same* as central sensitization. It is a consequence of central sensitization. I would say the same about neuropathic pain evoked by ectopia in Aβ [A-beta] afferents. Note, however, that the area of primary hyperalgesia is also subject to central sensitization! Therefore, everyday tenderness in bruised or burned skin must be due to both (peripherally) sensitized nociceptors and exaggerated central amplification. How can we tell whether peripheral or central sensitization predominates?

Consider the following: cutaneous stimuli in the area of primary hyperalgesia evoke hypersensibility by virtue of peripheral *plus* central sensitization. In the area of secondary hyperalgesia, central sensitization acts alone. The *difference* between the two should roughly indicate the contribution of peripheral sensitization. This difference is not the same for all types of stimuli. For example, on light brushing allodynia in the area of primary hyperalgesia is not much more severe that in the area of secondary hyperalgesia. This implies that for light brush stimuli, central sensitization plays the more important role. Heat allodynia, on the other hand, is much more severe in the area of primary than the area of secondary hyperalgesia. This implies that for moderate thermal stimuli peripheral sensitization is the more important. Deep aches, even when quite intense, only rarely trigger dramatic allodynia and hyperalgesia in the skin. Therefore, if they evoke central sensitization at all, it probably doesn't much amplify cutaneous input from corresponding dermatomes.

Central pathology? The CODERRE & KATZ conclude that "therapies should target peripheral and central *sources of pathology*" (my emphasis). Tissue and neural injury are indeed pathology, and are fitting subjects for corrective intervention. Central sensitization, on the other hand, is not pathology. By all indicators it is a normal somatosensory process that appears to have evolved in order to generate tenderness (mechanical allodynia) and hence protect against further tissue damage. It is the flip side of descending inhibition. Descending inhibition reduces the distraction of pain in emergency, fight or flight situations. Central sensitization augments pain when the organism has the luxury of attending to its wounds. We employ opiates and psychological interventions to exploit the descending inhibition circuitry in the interest of pain relief. We might be able to exploit NMDA receptor antagonists in the same way to reduce central sensitization. Such maneuvers, however, are qualitatively different from treating tissue pathology.

Pain "stamped in"? Like descending inhibition, central sensitization vanishes rapidly when its usefulness has passed. Its it true, as Weir Mitchell is quoted as stating, that when pain is severe it becomes "so stamped upon the sensorium as to forbid its erasure by any future impression"? In modern parlance, can central sensitization become independent of sustaining peripheral drive? In support of the widely held belief that it can, the authors recall some classic anecdotes of 19th century (and current) amputees, as well as some evocative animal research. While there is no proof one way or the other, I recommend a healthy skepticism. "Pain memories" thought to become "stamped in" in this way are said to include corns, blisters, bunions, and ingrown toenails. How much more intense, and in some cases more prolonged, are pains associated with gall stones, arthritic hips, and childbirth. Yet these very common, severe pains are never (or hardly ever) reported to become indelibly "stamped in" when definitive relief of the peripheral drive is eventually achieved. Pain relief is almost always instant and sustained. What is there about the theory of central sensitization that would predict "stamping in" of an ingrown toenail, but not an episiotomy scar? In most cases I suspect that the "pain memories" of amputees are just that, memories, rather than specific sensations. These memories may be triggered by neuroma/DRG/spinal tinglings in the same way that memories of grandma's cooking can be triggered by a passing aroma.

A paradox. The Gate Control theory of pain (Melzack & Wall 1965) proposed that Aβ input should "close the gate on pain." The pain relief provided by gently rubbing a wound, TENS, and dorsal column stimulation are well accounted for in this way. If central sensitization is indeed triggered whenever the skin is injured, and it indeed reliably renders Aβ [A-beta] input painful, then none of these "counterstimulation" approaches should work. Indeed, they should all evoke intense pain! An adequate resolution of this inconsistency is still lacking. Despite the central euphoria currently raging in the pain research community, we appear still to be a long way from understanding the actual role of central sensitization in clinical pain states.

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Is reflex sympathetic dystrophy a valid concept?

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Abstract: Patients with reflex sympathetic dystrophy (RSD) affecting one limb show similar sympathetic traffic in nerves supplying the affected and unaffected limb, despite unilateral autonomic effector dysfunction. This argues against the notion that RSD is mediated by a reflex change in the pattern of sympathetic discharge and underlines the fact that autonomic effector disturbances give little information about underlying nerve traffic. **[BLUMBERG et al.]**

BLUMBERG et al. highlight the need for quality control of sympathetic blocks when used for differentiating sympathetically dependent versus independent pain. The recommendation of skin temperature measurements is, however, debatable since skin temperature changes are sluggish and affected by a number of nonsympathetic factors (cf. below). Monitoring of reflex changes in skin vasomotor or sudomotor function seems a more adequate approach.

The main topic of this commentary is the term reflex sympathetic dystrophy (RSD) and the mechanistic concept it implies. Clinically, RSD or sympathetically maintained pain (SMP) are suspected when a painful region shows autonomic effector dysfunction (i.e., regional differences in skin temperature, blood flow, or sweat production). However, sympathetic effector organs can also be affected by nonsympathetic neurons and non-neural factors. Consequently, sympathetic effector dysfunction does not necessarily suggest altered sympathetic nerve traffic (Wallin & Elam 1993). In fact, the few recordings of sympathetic nerve activity which have been performed in patients with RSD or SMP have not shown abnormal patterns of sympathetic discharge. Wallin and coworkers (1976) found a normal skin sympathetic nerve activity (SSA) in a patient with causalgia, albeit with only minor autonomic symptoms. A recent case report on a patient with SMP and very marked vasoconstriction in one hand demonstrated a low baseline SSA in the nerve innervating the affected region and stimulus-induced increases in SSA were not associated with increased pain (Casale & Elam 1992).

One problem with the interpretation of these reports is that normal SSA is highly variable. Resting activity is determined by the thermoregulatory state, and nonthermoregulatory stimuli which transiently affect SSA include respiratory and arousing stimuli. Due to the marked sensitivity to environmental stimuli, a normal range of SSA is difficult to define. When investigating patients with regional autonomic dysfunctions, this problem can be bypassed by simultaneous intraneural recordings from affected and unaffected limb, as suggested by **BLUMBERG et al.**

Below are case reports on three patients with clinically suspected RSD/SMP, all with marked autonomic dysfunction in one limb. Intraneural recording of SSA was performed in the median (Case 1) or common peroneal nerve (Cases 2, 3) bilaterally, from cutaneous fascicles with similar innervation territories in both limbs. Skin electrical resistance changes, indicating sudomotor function, were monitored within the innervation territories bilaterally. Skin perfusion was monitored with bilateral laser Doppler flowmetry and skin temperature with a multi-channel thermometer.

Case 1: A 44-year-old man suffered a minor crush injury engaging the tip of his right index finger. He slowly developed a constant burning pain and mechanical and cold allodynia involving the whole hand. The affected hand was discoloured, showed varying degrees of edema and skin temperature was usually several degrees lower than in the contralateral hand but could occasionally also be higher. Sympatholytic treatment had a clear analgesic effect.

Case 2: A 72-year-old man suffered a partial lesion of the left sciatic nerve during hip surgery, documented with electromyography. Postoperatively, the patient rapidly developed a spontaneous burning pain, mechanical and cold allodynia and a constant coldness of the affected limb (3–5°C colder than the contralateral limb). Pain was abolished and the temperature assymmetry was markedly reduced during intravenous α-adrenoceptor blockade.

Case 3: After a trauma on the back of the left foot, a 48-year-old woman developed a marked regional vasomotor disturbance with edema, redness, and increased skin temperature. Sympathoexcitatory stimuli such as mental stress, arousal, or even single inspiratory gasps induced large and longlasting vasodilatations in the affected, but not the contralateral, foot. The patient reported no spontaneous pain but a feeling of discomfort and weak mechanical allodynia. Although hardly qualifying for a SMP diagnosis, this case is included because of its marked regional vasomotor disturbance.

Despite marked sympathetic effector dysfunction, with all three patients showing a pronounced skin temperature assymmetry during the recording session, simultaneous bilateral nerve recordings demonstrated similar resting SSA and stimulus-induced bursts of SSA in the two limbs in all three patients (for example, cf. Fig. 1). Sympathetic bursts were followed by similar skin resistance changes recorded within the innervation territories bilaterally. Skin perfusion changes were usually more pronounced, and more variable, in the affected limb. None of the patients reported an augmentation of sensory symptoms during stimulus-induced sympatho-excitation. The main message is that a marked regional autonomic dysfunction does not necessarily indicate an underlying change in pattern of sympathetic nerve activity. In addition, the findings argue against an altered pattern of sympathetic discharge mediating RSD/SMP.

Multi-fiber recordings of sympathetic nerve traffic do not quantitate the number of active fibers. Thus, the possibility remains that different proportions of sympathetic fibers were active in the two limbs. This is important when considering patients with a documented nerve lesion and thus probably a reduced number of sympathetic fibers. It is interesting to note that regional plasma concentrations of norepinephrine and its neuronally derived metabolite 3,4-dihydroxyphenylethyleneglycol have been found to be *lower* in affected versus contralateral unaffected limb of patients with RSD (Drummond et al. 1991), arguing in favor of a lower amount of active fibers in the affected limb. Thus, one possible mechanism for regional vasoconstriction after partial nerve lesion is development of denervation supersensitivity to norepinephrine.

Supersensitivity to norepinephrine can explain a cold but not a warm affected region. One possible mechanism for vasodilatation is of course a loss of sympathetic vasoconstrictor fibers after nerve lesion. The highly variable vasomotor dysfunction of some RSD patients could depend on a vasodilatation at rest, due to few remaining vasoconstrictor fibers, interrupted by marked vasoconstrictions when these few fibers are activated in a supersensitive tissue. An alternative vasodilatory mechanism is the release of vasoactive peptides from activated thin afferent nociceptive fibers.

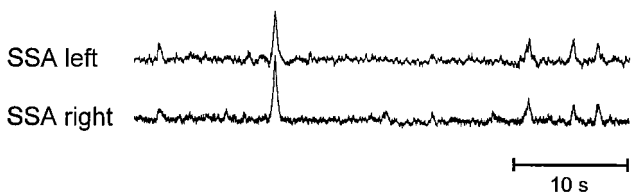


Figure 1 (Elam). Bilateral records of SSA (mean voltage neurograms) from the peroneal nerves, showing similar sympathetic nerve firing patterns at rest despite a constant, marked autonomic effector disturbance in the left foot/leg. Example taken from Case 2.

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In conclusion, direct sympathetic nerve recordings highlight the fact that cutaneous vasomotor function or skin temperature cannot be considered as safe indicators of underlying sympathetic nerve activity. Existing microneurographic and biochemical data from humans suffering RSD/SMP do not support the notion of an increased or altered pattern of sympathetic nerve activity mediating these syndromes.

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On separating pain from the willingness to report it

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Abstract: Signal-detection methodology may be used to disentangle sensory from judgmental effects when analyzing sex differences in pain. An illustrative example is given by reanalyzing a published category-scaling experiment in terms of detection-theory indices. As a result, the apparent sex difference is recast in terms of a judgmental bias. **[BERKLEY]**

In the "inductive" part of her argument, **BERKLEY** succinctly summarizes the literature on sex differences in pain. In reviewing the studies of experimentally induced pain (sect. 1) and endogenous pain (sect. 2), however, she recognizes a problem that may render the evidence inconclusive: "Willingness to report is also a likely factor in pain ratings, but the issue is difficult to resolve because of the difficulty in separating sensory from response factors" (sect. 1, para. 5).

Clearly, the standard solution to this problem would be to apply signal-detection theory, which provides independent measures of the observer's sensitivity and response bias. Though the suitability of this appraoch to the study of pain has been questioned by Rollman (1977), a more recent proposal (Irwin & Whitehead 1991) has elaborated the circumstances under which signal-detection methodology may be meaningfully applied to the study of pain.

The present analysis serves to illustrate the usefulness of the detection-theory approach to the problem raised in **BERKLEY**'s target article by reanalyzing an existing data set and pointing out how the more sophisticated methodology leads to conclusions that are markedly different from those based on taking pain ratings at face value (details and alternative analyses will be presented in a paper in preparation). In working with this data set, the emphasis is not on the typicality of the outcome; rather it is on the generality of the methodological problem addressed.

Ellermeier and Westphal (1995) had 20 subjects (10 male, 10 female) rate the painfulness of four levels of pressure applied to the finger on a rating scale ranging from "no pain at all" to "severe pain." Mean category ratings showed a highly significant gender difference, in that female subjects rated higher pressure levels as more painful than did males, with no difference evident at low pressure levels. This finding is qualitatively consistent with measurements of pain and tolerance thresholds, and with other direct scaling studies (e.g., Lautenbacher & Rollman 1993).

The key feature of the re-analysis advocated here is to refrain from taking the category ratings as direct indicators of sensation magnitude, but instead to treat them like *confidence ratings* in a signal detection experiment. Such ratings serve to trace out a receiver operating characteristic curve from which two parameters may be derived: an index reflecting the sensory discrimination of the stimuli, and another, independent index reflecting the subject's use of the response categories.

The top portion of Figure 1 depicts the discrimination indices

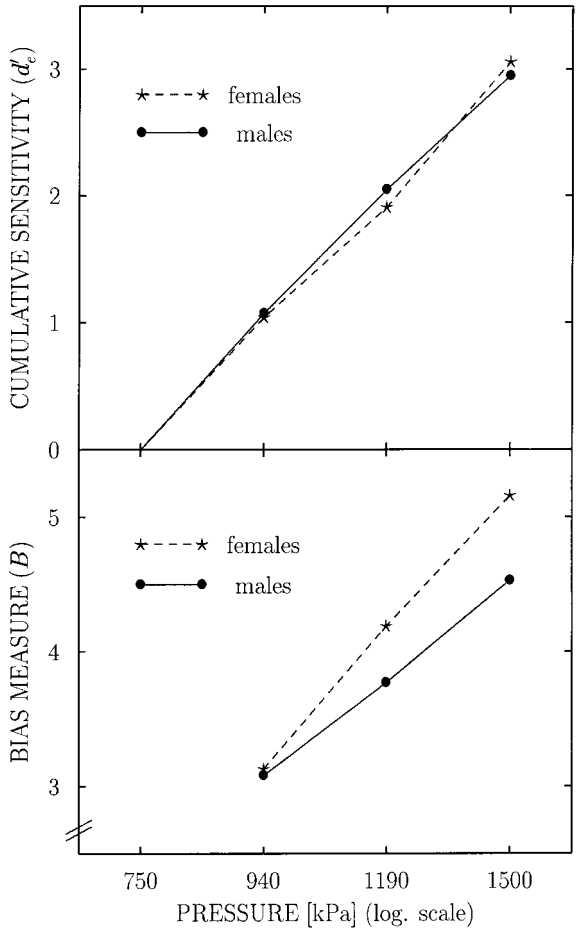


Figure 1 (Ellermeier). Cumulative discriminability (d'_e, top) of painful pressure stimuli and a measure of response bias (B, bottom), computed for pairs of adjacent levels. Results of a pooled ROC analysis of category scaling data from 10 male and 10 female subjects.

(here d'_e) accumulated over the stimulus range, the bottom portion shows the associated response bias measures (B, see McNicol 1972), separately for males and females. The result is unequivocal: cumulative d′ curves are indistinguishable for male and female subjects, suggesting equal sensory discrimination, while the "bias" to assign higher pain ratings grows more strongly in females than in males. This outcome suggests that all of the sex difference present in the original ratings is due to different (judgmental) modes of assigning pain sensations to response categories, while discrimination of the stimuli – both local, and global – is the same.

The crucial question in evaluating this result is whether cumulative discriminability may be interpreted as a measure of sensation magnitude, thus justifying the conclusion that neither discrimination nor the sensation of pain distinguishes males and females. On theoretical grounds, Irwin and Whitehead (1991) have argued to interpret cumulative d′ in this way, quite in line with the Thurstonian (or Fechnerian) idea of constructing a psychophysical scale from units of discriminability. Their point is further strengthened by a validational study (Irwin et al. 1994) showing that a known anesthetic did affect cumulative d′ functions in the way expected of a measure of pain intensity.

The remaining sex difference reflected in the diverging bias measures (see lower portion of Fig. 1) must be due to some judgmental factor not contributing to the discriminability of the stimuli. Further investigations might indeed trace it to variations in the "willingness to report pain," to different ways of signaling

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the experimenter about what constitutes an acceptable stimulus range in a laboratory experiment, or to different levels of anxiety that men and women bring into the pain laboratory (cf. Rollman 1995).

Obviously, if the outcome of the present re-analysis were representative of similar studies, it would deepen rather than reduce the gap between the "inductive" and "deductive" approaches to sex differences in pain that have been so convincingly pursued by **BERKLEY.** In contrast to traditional scaling or threshold approaches, however, which result in unknown mixtures of sensory and judgmental effects, signal-detection methodology might clarify at what psychological level sex differences in pain will have to be conceptualized.

Psychobiological sex differences in pain: Psychological as much as biological

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Abstract: The argument of **BERKLEY** for the existence sex differences in pain is based on biological factors. We suggest that the psychological evidence for such differences is more substantial.

Overall, **BERKLEY** is skeptical about the behavioural ("inductive") evidence for a sex difference in pain sensitivity. She prefers to weight her argument for the existence of such differences on so-called "deductive" evidence of a primarily biological nature, arguing persuasively that there is a physiological basis for differences between the sexes in pain sensitivity. Thus, BERKLEY apparently concludes that there is only weak behavioural evidence for sex differences in pain despite the presence of a number of biological factors which should predispose us in that direction. We would argue that she underemphasises the behavioural evidence, so well reviewed in her target article.

Female hyperalgesia, demonstrated under laboratory conditions, is remarkably consistent with the evidence for sex differences in the occurrence of a range of clinical pain. The fact that much of this evidence is incidental to the main purpose of the surveys involved would seem to increase rather than decrease the significance of the data (sect. 2, para. 1). Moreover, although it is undoubtedly true that sex differences in clinical pain interact with "situational, temporal, attitudinal, and social factors," these psychosocial factors may in themselves be subject to sex differences, which act either to exaggerate or minimise the effects of physiological differences. For example, the greater use of behavioural coping strategies by women (Jensen et al. 1994) may reduce female pain experience just as the greater readiness of male physicians to diagnose angina in men may increase the reporting of chest pain in males.

In contrast to her skepticism about the human data, **BERKLEY** seems sympathetic to the evidence for sex differences in pain sensitivity in nonhuman species. But these responses might likewise be modulated by differences in emotions and behaviours provoked in male and female animals by the testing procedures rather than straightforward demonstrations of fundamental physiological differences in nocicepitive mechanisms.

BERKLEY's focus on physiological mechanisms and on deductive analysis has the unfortunate effect of distracting attention from the psychological mechanism which may be an important source of sex differences. This can be seen most clearly in the analysis of sex differences related to the reproductive organs and to sex hormones and their temporal features. Whereas we would agree with BERKLEY that many of the observed sex differences in pain are psychobiological consequences of the specific role of women in reproduction, we feel that these consequences are as much "psycho" as "bio" in nature. BERKLEY emphasises the possibility that the regular experience of menstrual pain in otherwise healthy young women could result in the sensitisation of nociceptive mechanisms – a conclusion with which we would readily concur (Gijsbers & Niven 1993). However, some of our recent findings would point to the beneficial effects of previous pain experience, in that we found that women in childbirth utilise a range of behavioural and mental strategies which they have effectively exercised during previous painful experiences (Niven & Gijsbers 1996). This psychological effect may offset physiological "disadvantages."

BERKLEY does discuss one major psychological mechanism in her review of temporal conditioning, but we wonder what evidence would support the kind of learned time-locked nociception which Berkley relates to the periodic hormonal variations experienced by women. Most women with regular menstrual cycles have diminished levels of menstrual pain after giving birth to their first child. Why should this be the case if it is the cycling sex hormones that are providing "discriminative stimuli for conditioning" (sect. 3, para. 6)? What is needed in this context is a long-term behavioral study of pain in women, which encompasses menstruation, pregnancy, parturition, post-natal menstruation, and menopause.

BERKLEY's target article is a useful contribution to the understanding of biological mechanisms that might (we emphasise "might") underlie sex differences in pain perception. In agreeing with the appropriateness of her quotation from Irigeray (1993) regarding the critical importance of the issues she addresses, we feel that she undervalues the adage that the proper study of woman lies in the study of women. Only through such study will we come to understand the extent to which individual differences in suffering are dependent on generalisable sex differences. It is these differences in the experience of clinical pain which are of critical importance in the recommendations for treatment.

The complexity of the interactions between the biological and psychosocial factors involved in pain perception, report, and response are such that we would echo **BERKLEY**'s conclusion that it is as yet inappropriate to call for "different overall treatment regimens for females and males" (sect. 2, last para.). Equality of treatment is much more important, and achieving it remains a significant problem (Niven & Carroll 1993). However, we would base our conclusions not on the insignificance of sex differences in behaviour and perception but on their complexity.

Persistent pain: Trim the branches or fell the tree?

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Abstract: In patients with pain characterized by a painful focus and allodynia, the painful symptoms arise from altered central processing that is initiated and subsequently maintained by persistent input from nociceptive afferents. Treatments directed at this normal consequence of persistent input are inherently limited. The most efficacious treatments will target the pathology, the various sources of ongoing nociceptor input. **[BLUMBERG et al.; CODERRE & KATZ; DICKENSON]**

Both clinical and experimental studies provide converging lines of evidence for endogenous processes that both exacerbate and attenuate pain. While a host of animal models have furthered our understanding, it is important to focus on evidence from the ultimate target of this research, the underlying mechanisms of intractable pain syndromes.

BLUMBERG et al. discuss differences in patients with sympathetic involvement; one group presents with warm swollen extremities, another group presents with spontaneous pain, allodynia, and often an identifiable pain focus associated with

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Table 1 (Gracely). *Key features of a model of persistent pain*

1. Persistent input from nociceptive afferents maintains and modulates altered central processing.
2. There are multiple sources of persistent input: neuropathic or nociceptive, with and without sympathetic involvement. A patient can have more than one type.
3. The initiating and the subsequent maintaining input of ongoing central sensitization, can be different, and likely result in different central mechanisms.
4. Following natural or experimental injury, the altered central processes are initiated by nociceptive input and may exist independent of this input for a period of time.
5. The chronic pathology is not the central sensitization but the persistent input that maintains this sensitization.

Source: Gracely, Linch, & Bennett, 1992.

surgery or injury. We studied the latter group in our laboratory and on the basis of sensory assessments and diagnostic blocks proposed a model of persistent pain (Gracely et al. 1992). In their review, **CODERRE & KATZ** describe the key features of our model, which are shown in Table 1. We proposed that the symptoms in these patients resulted from altered central processing that is maintained dynamically by persistent input from nociceptive afferents. This dependence on ongoing input is dynamic in that it is coupled temporally and influenced by the magnitude of the input. We found that symptoms quickly disappeared after a block of the persistent input and just as quickly reappeared after this block waned. Symptoms also were modulated by the amount of input; continued stimulation of painful areas exacerbated both spontaneous and evoked pain. Thus, in the chronic phase, it appears that the persistent input is directly responsible for central processes that account for many features of the syndrome including allodynia, hyperalgesia, and other sensory and motor abnormalities.

Initially, we focused on these central processes as the crux of the problem. Our first figures actually identified "abnormal sensory processing." Subsequently, it became clear that these central processes are not abnormal; they are natural mechanisms that promote immobility and protection after traumatic injury. As noted by Wall (1979), the initial escape response is followed by a prolonged period of immobilization. Once hit by a car, the dog first runs wildly into the bushes, then remains there, curled up and unmoving. If all proceeds well, the wounds heal and the dog resumes its activities. The painful input and the altered processing return to normal. Thus, the pathology in our patients was not the central sensitization, but the persistence of "acute" painful input. We changed our figure to read "altered central processing" and as **CODERRE & KATZ** point out, redirected the blame to the periphery. Prolonged nociceptive input, however achieved, is the real culprit.

Varieties of persistent input. As shown in Table 1, there is no restriction on the sources of this pathological input. It can arise from normal nociception or from neuropathic sources such as neuromas or injured nerves. It may be influenced by sympathetic activity or independent of this influence. Thus common features of spontaneous pain, allodynia and hyperalgesia, may result from very different pathologies. In our study the input was assumed to be from damaged nerves following surgery, and may have been influenced by sympathetic activity in 3 of the 4 cases. In a more recent study, we observed that minuscule (0.1 to 0.2 cc of 2% lidocaine) infiltrations of local anesthetic into the major vestibule glands relieved some or all of the mechanical allodynia in women suffering from vulvodynia (Turner et al. 1995). This finding strongly suggested that the painful symptoms in this condition resulted from altered central processing maintained by nociceptive input from these glands. Unlike our previous study, the maintaining input in these cases may not be neuropathic in nature but mediated by nociceptors activated by local inflammation. However, a neuropathic component cannot be ruled out.

Limitations of broad spectrum central treatment. How can the pain from these varied syndromes be treated? Since they share a final common pathway, it might be efficient to attack the common central consequences of persistent nociceptive input. In a sense, nociceptive or neuropathic pains, be they sympathetically maintained or not, could be treated by a "broad spectrum" agent that attenuates the resultant common central sensitization. The NMDA receptor has been strongly implicated in central sensitization and as **DICKENSON** (sect. 6.1.2) points out, is the target of numerous therapeutic investigations. Both new experimental drugs and commonly used agents (ketamine, dextromethorphan) have demonstrated NMDA antagonism in animal models and/or in human studies (DICKENSON, sect. 7.1). In addition, DICKENSON elaborates on potentiation of opioid therapy by a variety of agents including the NMDA antagonists. A similar argument can be made for the NMDA antagonist class, combinations of drugs that reduce central sensitization with conventional analgesics, which may provide effective relief in a number of syndromes that involve central sensitization. However, the ultimate effectiveness of these central strategies is limited because they reduce only the sensitized component of the experienced pain, and will likely exert unintended actions resulting in untoward side effects.

The pathology is in the periphery, peripheral control is efficient. It is noted by **DICKENSON** and others that the very design of endogenous analgesic systems suggest that an impressive biological efficiency is obtained by attenuating pain at its primary afferent source, before it has a chance to spread to multiple neural and neuropharmacological branches. Opioid activation of supraspinal receptors do not attenuate conveniently located ascending spinothalamic tracts; instead, these systems descend back down the cord to attenuate messages before they spread out among the numerous projection systems. Similarly, presynaptic inhibition reduces pain input by a simple single mechanism, avoiding the necessity of intercepting the multiple post-synaptic systems activated by the primary afferent. Central pain syndromes are particularly intractable because the pathology is located after these major sites of pain inhibition. The patients described here are the fortuitous cases in which the lesion is before the dorsal horn. Perhaps we can learn from the *Wisdom of the Body* (Cannon 1939) and effectively cut off pain at its source, to fell the afferent message at its trunk before it activates numerous ascending branches. The most effective therapy, in terms of both efficacy and reduced side effects, will silence the persistent peripheral nociceptive input.

Acute pain management. The growing literature on preemptive analgesia indicates that the tactic of peripheral control is already being applied to the management of procedural pain. As we and **CODERRE & KATZ** (sect. 2.5) stress, it is critically important to distinguish between the original nociceptive event that initiates altered central processing, and subsequent inputs that maintain it. Both animal and human evidence suggests that in the initiation phase, altered central processing can become independent of the initiating input. With time, the clinical evidence suggests that the central processes become dependent on this input, although chronic altered processing independent of this input can never be completely ruled out. The autonomy observed during initiation suggest the treatments for acute procedures, such as preemptive surgical analgesia, must be relentless. They must block input during the procedure and probably block input in the immediate postoperative period. A lapse of anesthesia during the period may allow the initiation of central processes that are difficult to control by further local anesthetics and subsequently maintained by minor, postoperative nociceptive inputs.

Chronic pain management. Treatment of chronic patients will require identification of the type of persistent input and the development of treatments that target each type. In addition to the focus on the exciting and increased understanding of central pain

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plasticity, there should be renewed efforts to cure neuromas, to quiet ectopic discharge, to uncouple adrenergic receptors, and to remove inflammatory and other forms of persistent nociceptor activation.

Cholecystokinin (CCK): Negative feedback control for opioid analgesia

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Abstract: Negative feedback is an important mechanism whereby the organism maintains its balance in a complicated system. It may be regarded as a modern version of the ancient Eastern wisdom of Yin and Yang balance. Control of pain and analgesia, is no exception: CCK seems to serve as a built-in mechanism for the modulation of opioid analgesia system **[DICKENSON]**.

DICKENSON has provided a comprehensive account of the plasticity of nociceptive transmission in the dorsal horn of spinal cord as controlled by the interaction of many pharmacological systems, including opioid and nonopioid transmitters/mediators. Considerable attention has been paid to the interaction between opioids and cholecystokinin (CCK) since this has been amply shown to play a key role in determining the efficacy of opioid analgesia at both spinal and supra-spinal levels. Here I would like to make three points to supplement the opioid/CCK mechanisms for modulating pain and analgesia.

1. CCK reverses mu and kappa, but not delta opioid analgesia. In section 5.2, paragraph 1, **DICKENSON** pointed out that CCK prevents mu- but not delta-mediated neuronal inhibition. In our hands, CCK antagonizes not only mu, but also kappa, except for the delta receptor mediated opioid effect. Thus, i.t. injection of 4 ng of cholecystokinin octapeptide (CCK-8) produced a right shift of the dose-response analgesic curve induced by i.t. injection of mu agonist PL017 or kappa agonist 66A-078 [(N-MeTyr^1, N-MeArg^7, D-Ala^8)Dynorphin (1-8) amide], but not that induced by delta agonist DPDPE (Wang et al. 1990b)

2. Mechanisms of CCK antagonism of opioid effect. In section 5.2, paragraph 4, **DICKENSON** mentions a possible mechanism by which CCK attenuates the antinociceptive effect of morphine, that is, CCK mobilizes calcium from intracellular store (Wang et al. 1992) via IP_3 pathway (Zhang et al. 1992) to counter the opioid suppression of the rise in intracellular calcium produced by depolarization. We now have direct evidence that in a patch clamping study on dissociated rat dorsal root ganglion neuron, opioid-induced suppression of voltage-gated calcium current could be almost completely reversed by CCK-8. That the effect of CCK is achieved by the activation of the CCK receptor is shown by the fact that the CCK effect can be readily reversed by the CCK-B receptor antagonist L-365260. Again, CCK antagonizes mu (Liu et al. 1995) and kappa (Xu et al. 1996) rather than delta opioid effect.

Another aspect of CCK/opioid interaction seems to take place at the receptor level ("receptor-receptor cross-talk"). Wang et al. (1989) were the first to show that CCK suppressed brain membrane binding to ^{3}H-etorphine, the universal opioid agonist. Further study revealed that CCK decreased the Bmax of mu binding and increased the Kd of kappa binding without affecting delta binding (Wang et al. 1990a). Uncoupling of the opioid receptor from G protein may serve as another mechanism of CCK antagonism of opioid activity (Zhang et al. 1993). The molecular events underlying the anti-opioid effect of CCK in the CNS have been summarized in a recent review article (Han 1995a).

3. CCK as a negative feedback control for opioid analgesia. In paragraph 9 of section 5.2, **DICKENSON** concludes that CCK may be an endogenous "brake" applied to the antinociceptive action of morphine. In a recent review article (Han 1995b) I called this "negative feedback control," based on five lines of evidence: (1) Systemic morphine produced an 89% increase of the CCK immunoreactivity in the perfusate of the rat spinal cord, an effect completely reversed by naloxone (Zhou et al. 1993b). (2) Peripheral electrical stimulation produced a naloxone reversible analgesia accompanied by a marked increase of the content of CCK in rat spinal perfusate with a frequency rank order of 100 Hz = 15 Hz > 2 Hz; i.t. administration of CCK-B antagonist L-365260 markedly potentiated the stimulation-produced analgesia with the same rank order of 100 Hz > 15 Hz >> 2 Hz (Zhou et al. 1993). (3) An increase of CCK release in rat spinal perfusate can be triggered by mu- or kappa- but not delta-opioid agonist (Sheng et al. 1995). (4) Repeated morphine administration increased the abundance of brain CCK mRNA as measured by the Northern blotting (Zhou et al. 1992) or *in situ* hybridization (Pu et al. 1994). (5) I.c.v. injection of CCK antisense plasmid vector significantly delayed the development of morphine tolerance (Tang et al., in press).

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Pains are in the head, not the spine

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Abstract: The authors presume that activity in the dorsal horn or nociceptors is well correlated with pain sensations and behavior. This overlooks the myriad of interactions between cortex and our spinothalamic tract. It is better to think of our nociceptors, the dorsal horn, and the pain centers in our brain as all components in one larger and complex pain sensory system. **[BERKLEY; BLUMBERG et al.; CODERRE & KATZ; DICKENSON; MCMAHON; WIESENFELD-HALLIN et al.]**

Back in 1911, Head and Holmes proposed a dual system of afferent projections in our pain sensory system: an *epicritic* system that processes information regarding intensity and precise location, and a *protopathic* system that delivers the actual pain sensations. Eighty-five years later, we still believe they were fundamentally right. We have a "sensory discriminative" subsystem, originating with the A-δ fibers, that computes the location, intensity, duration, and nature (stabbing, burning, prickling) of stimuli. We also have an "affective-motivational" subsystem, beginning with the well-known C-fibers, which supports the unpleasant part of painful sensations. As the authors all indicate, each subsystem has a set of neurons that resides in the dorsal root ganglion of the spinal column. These neurons extend their axons to whatever tissue they innervate and receive input there; they also have a second axon that projects across to the dorsal horn. However, pain processing does not end there. The now classic view of our basic pain system continues up through cortex. In brief, the axons in the dorsal horn connect with a second set of neurons housed in the dorsal horn whose axons run out of the spinal column and up to the thalamus. And there is a third set of neurons that projects from the thalamus to the postcentral gyrus in cerebral cortex.

I trust that the six target article authors all know these facts; however, their writing does not reflect this and, in my humble opinion, it should. With two exceptions,[1] the authors assume that activity in the nociceptors, dorsal horn, or some interaction of the two is directly correlated with an animal's experience of pain (or, in some cases, with producing pain behavior in an animal). This assumption is mistaken. The authors show convincingly that our pain system is quite complex; however, they overlook that it gets even more complex once we move beyond the spine.

Very roughly speaking, once pain information exits the dorsal horn, it travels either to the reticular formation in the brain stem or

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to the thalamus. Laminae I and V project to the lateral nuclei in the thalamus (Craig et al. 1994), and laminae I, V, and VI project to the medial nuclei. Each type of nucleus underwrites a different sort of information; the lateral nuclei process discriminative information (the so-called "fast pain"), while the medial nuclei and reticular connections process affective-motivational information ("slow pain"). The two thalamic streams remain separate on their trip to cortex as well. Pain neurons in the lateral nuclei synapse in somatosensory cortex, which can then compute the location and characteristics of the pain; those in the medial nuclei synapse in the anterior cingulate gyrus in the frontal lobe, which figures in our emotional reactions to pain. The frontal lobe (and its connections) process our actual suffering.

These higher centers of pain are very important. Consider how our emotional states influence the degree of pain we feel, quite independently of actual injury: stories of athletes and soldiers continuing to function without pain even though severely injured are legion. Psychogenic pains have been documented for quite some time (cf., Roy 1985). Hypnosis allows some subjects to engage in what would otherwise be painful activities without being in pain. [See Spanos: "Hypnotic Behavior: A Social-Psychological Interpretation of Amnesia, Analgesia, and 'Trance Logic'" *BBS* 19(3) 1986.] Evoked potential recordings of painful stimuli under hypnosis indicates that at least activity in the frontal lobe is affected (Helen Crawford, personal conversation). And placebos are notoriously helpful in relieving pain. (Interestingly enough, they relieve pain at half the rate of the real drug, regardless of the supposed strength of the drug; Evans 1974.) Finally, of course, some lesions to the thalamus and cortex can result in the cessation of pain experiences, even though the peripheral neurons continue to operate normally; and stimulating the medial periaqueductal gray region, tectum, or thalamus directly gives us a painful experience (Davis et al. 1995; Keay et al. 1994).

There is in fact a poor correlation between nociception and pain perception (Wall 1989b, Wall & McMahon 1985). At least, the relationship between stimulating the A-δ and C-fibers and actually feeling or reporting a pain is not at all straightforward. Several tribal rituals give vivid illustrations of the dissociation. In parts of India, for instance, men chosen to represent the gods have steel hooks inserted under the muscles of their back. They then swing above the crowds, suspended on these hooks by ropes, blessing children and crops. They exhibit no pain (Kosambi 1967). For an example closer to home: about 40% of all ER patients reported feeling no pain at the time of injury; 40% more report greater pain than one would expect, leaving only 20% of all ER visitors having pains appropriate to their injuries (Melzack et al. 1982).

Facts such as these have led the International Association for the Study of Pain (IASP) subcommittee on classification to conclude that, "Pain is always subjective. . . . Many people report pain in the absence of tissue damage or any pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. [Pain] . . . is always a psychological state" (IASP 1986, p. 217). The IASP subcommittee clearly thinks that the connections between actual tissue damage, or some other injury, and our sensation of pain is so weak that it is better to discount nociception entirely in their definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, *or described in terms of such damage*" (p. 217, emphasis mine).

Some take this perspective a bit too far and write as though just about any psychological event or any area of cortex has the potential of influencing the perception of pain, what Melzack calls a "neuromatrix" (Melzack 1990; 1991; 1992; see also discussion in Canavero 1994). However, though there are lots of feedback loops and other sorts of pain connections, not every area in the brain is sensitive to pain information. Imaging studies of pains clearly show that phasic pains are keyed to increased activity in anterior cingulate, frontal cortex, thalamus, and primary and secondary somatosensory cortex; and that chronic pains are correlated with increased activity in cingulate and frontal cortex, as well as sometimes with insular cortex, hypothalamus, and periaqueductal gray (see discussion and references in Apkarian 1995). Rat studies suggest that, in addition to the structures discussed above, areas of the limbic system are also involved (Mao et al. 1993). Functional images of human brains indicate that homologous areas are involved in us as well (Apkarian 1995). The higher centers of pain are indeed *centers,* and they work to influence, dampen, enhance, eliminate, and create our sensations and behaviors connected to pain.

In sum, though the data and the discussion in the target articles are quite impressive, it is premature to consider neural activity in the nociceptors or the dorsal horn to be indications of pain. Perhaps it would be best to think of the nociceptors, the dorsal horn, connections to thalamus, cortex and so on, all as aspects or components of a larger pain system. These components work to take pressure, temperature, and chemical readings of our surface (and interior) and to use this information to track what is happening to our tissues. The A-δ cells and the C-fibers do this, as does the spinothalamic tract, but so does its connections to cortex. Neither damaged tissue, particular neural reactions in limited areas of our CNS, our experience of pain, our emotional reactions to pain, nor our bodily behaviors can be identified with pain processing. Bits and pieces of them all are required for pain.

NOTE

1. DICKENSON (sect. 4.4, para. 2) admits that "we need more information on . . . supraspinal analgesia in animal models of persistent pain," and **BLUMBERG et al.** (sect. 6, para. 5) forthrightly says that "one has to consider the possibility of so-called psychogenic pain mechanisms."

Is learning involved in plasticity in nociceptive regulation?

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Abstract: Plastic changes in spinal cord function like neuronal wind-up and increased receptive field are too short-lived to explain chronic pain without structural changes. It is possible that learning could be a mechanism for longlasting changes in nociceptive regulation. A learning process localized to the spinal cord has been shown to be important for the development of tolerance to the analgetic effect of ethanol, suggesting that nociceptive control systems may be changed by learning. Long term potentiation (LTP) is regarded as a useful model of learning and memory. LTP-like changes have been observed in *in vitro* preparations from the spinal cord and in spinal cord field potentials. Recently a long term increase in spinal A-β and C-fibre evoked responses after painful stimulation has been observed. **[CODERRE & KATZ, DICKENSON, WIESENFELD-HALLIN et al.]**

A unique property of the central nervous system (CNS) is the ability to learn. In their discussion of mechanisms of plasticity or of development of tolerance to drugs, neither **CODERRE & KATZ, DICKENSON,** nor **WIESENFELD-HALLIN et al.** discuss the possible involvement of learning or the similarity between plasticity in nociceptive systems and memory processes. In explaining how functional changes can induce chronic pain without any tissue damage, it is a problem that changes such as wind-up, expansion of receptive fields, changes in response thresholds, and increases in spontaneous cell firing are rather short-lived. As a substrate for states with chronic pain we should look for mechanisms that can cause longlasting changes in function without any gross structural changes. Learning could satisfy these requirements.

In fact, some support exists for the hypothesis that processes similar to learning may be involved in plasticity in CNS systems regulating nociception. Jørgensen et al. (1985; 1986; Jørgensen & Hole 1984) studied mechanisms involved in the development of tolerance to the analgetic effect of ethanol, and found, somewhat

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to their surprise, that the important factor determining whether tolerance developed or not, was a learning factor. Tolerance to the analgetic effect as measured with the tail-flick test in rats developed in a week if the rats were tested once a day after administration of the drug. No tolerance was observed if ethanol was given without testing, or if testing was performed before drug administration (Jørgensen & Hole 1984). These learned changes in the tail-flick reflex were observed also when the reflex was separated from supraspinal control by transection of the spinal cord. Triggering the reflex in the presence of ethanol was necessary for the changes to take place (Jørgensen et al. 1985). The learned tolerance showed cross tolerance to morphine and clonidine (Jørgensen et al. 1986).

Thus it seems that the function of CNS neuronal systems that are involved in regulation of nociception can be considerably changed by mechanisms that can be best described in terms of learning, probably a "simple" type of learning that can take place in a rather simple control system, for instance in a spinal reflex like the tail-flick reflex.

Long term potentiation (LTP), first described in the hippocampus by Bliss and Lømo (1973), has been widely used as an experimental model for studying the synaptic basis of learning and memory (Bliss & Collingridge 1993). If LTP could be shown to exist in the nociceptive systems in the spinal cord, this would be important for our theoretical understanding of longlasting plasticity; and even more important, methods for studying the details of the mechanisms involved could be developed.

Some indications of LTP-like phenomena in the spinal cord exist, based on *in vitro* techniques or field potentials. Randic et al. (1993) made *in vitro* intracellular recordings in slices from the dorsal horn and reported LTP in 45%, long term depression in 41%, and no change in 14% of the neurons, for 20 min to 1 hr. Pockett and Figurov (1993) studied ventral horn field potentials in twelve transverse slices. After conditioning stimuli they observed an increase in the field potential in three slices, a decrease in four, and no change in five slices, observed for 2 hours. Liu and Sandkühler (1995) also measured field potential changes in the dorsal horn in nine intact urethane anesthetized rats, after tetanic stimulation. They observed an increase in the field potential in all nine rats. Lozier and Kendig (1995) showed LTP-like changes in slow ventral root potentials in a neonatal rat spinal cord preparation after tetanic stimulation. The changes were observed for 1 hr or more.

The studies published so far on LTP-like changes in the spinal cord have either used secondary measures of neuronal responses or *in vitro* preparations for substantia gelatinosa neuron recordings. A neuron of particular interest in nociceptive transmission and processing is the wide dynamic range (WDR) neuron in the dorsal horn, receiving both nociceptive and non-nociceptive input from the periphery, as well as local and descending modulatory input. In order to study LTP and be able to relate the findings to pain, it would be of great importance to record from these neurons in intact animals, and to study possible LTP after peripheral painful stimulation. Recently we have been able to demonstrate a long term increase in spinal A-β and C-fibre evoked responses after painful peripheral stimulation, recording extracellular single unit activity of WDR neurons in intact anesthetized rats (Svendsen et al. 1997). A great increase in the excitation of the neurons could be observed for the total 6 hrs the experiment lasted, after a short-lived stimulation that induced intense pain under surgical anesthesia. This technique seems promising as a tool in studying longlasting pain induced functional changes that may be related to chronic pain.

Central excitation and inhibitory mechanisms and neuroplasticity are also manifested in trigeminal nociceptive pathways

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Abstract: Central sensitization and related neurochemical mechanisms are also induced in V nociceptive pathways after craniofacial injury or inflammation. Their characteristics raise additional possibilities that may explain some of the phenomena outlined by **CODERRE & KATZ, DICKENSON,** and **WIESENFELD-HALLIN et al.** They also underscore the need for therapeutic approaches to reduce nociceptive inputs to the CNS or their neuroplastic effects which can potentially enhance post-traumatic pain.

The focus of **CODERRE & KATZ, DICKENSON,** and **WIESENFELD-HALLIN et al.** is on peripheral and central neural mechanisms and plasticity related to the modulation of spinal nociceptive processes. In view of the common occurrence of acute and chronic pain manifested in the craniofacial region, including intraoral and musculoskeletal tissues, and the mechanisms postulated in these papers, we think it would be instructive to outline briefly the evidence bearing on these proposals from analogous studies in trigeminal (V) nociceptive pathways.

Stimulation of craniofacial tissues such as the temporomandibular joint (TMJ) by the small-fibre excitant and inflammatory irritant mustard oil results in an inflammatory response in these tissues and a sustained (20–30 min) but reversible increase in jaw-opening and closing muscle activity. The latency and time course of this reflex effect on jaw muscles are comparable to the temporal features of the mustard oil-induced increased excitability (e.g., mechanoreceptive field expansion) of nociceptive (WDR, NS) neurons in V subnucleus caudalis. This is the V analogue of the spinal dorsal horn, which has been shown to be the site of brainstem interneurones involved in this reflex pathway, as well as of projection neurones contributing to ascending somatosensory pathways (e.g., Sessle 1996; Yu et al. 1993; 1994; 1996). These and related findings suggest that "central sensitization" processes at the level of subnucleus caudalis may be involved in the mustard oil-evoked effects and that small-fibre afferent input may be important in at least the initiation of V central sensitization. Moreover, in accordance with some of the concepts reviewed by **CODERRE & KATZ** (e.g., sect. 2.3) and **DICKENSON** (sect. 1), these V changes reflect a central neuroplasticity that can be explained by a "strengthening" or unmasking of some of the convergent afferent inputs that are particularly extensive in V caudalis nociceptive neurones; these features have been implicated in the referral of pain as well as hyperalgesia that can occur after injury or inflammation of craniofacial tissues (see Sessle 1996). Of further significance (especially to the discussion of referred pain by CODERRE & KATZ, sect. 3) are data suggesting that not only are the deep input properties of caudalis nociceptive neurones particularly expressive of such neuroplasticity, but deep inputs may be more effective than cutaneous inputs in inducing neuroplastic changes (Yu et al. 1993); these findings may explain the greater sensory disturbances that have been reported in pain conditions involving deep tissues than those involving cutaneous tissues.

Comparable neuroplastic changes can also be induced by mustard oil application to the tooth pulp. It is interesting to note that these particular changes may be associated with the rapid unmasking of tactile afferent inputs to caudalis neurones that before the mustard oil application had been classified as NS neurones, that is, they acquired WDR neurone-like properties (Kwan et al. 1997). These reversible changes in the receptive field properties of nociceptive neurones, which can also be induced by the application of the $GABA_A$ antagonist bicuculline to the surface of subnucleus caudalis (see below), thus raising another potential substrate of allodynia in addition to those outlined in the three target

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articles. Such pulp afferent-induced central changes could also explain the referred pain following dental injury that **CODERRE & KATZ** describe (sect. 3.2, para. 5). With respect to their description (sect. 4.4) of pulp deafferentation-induced pain, pulp deafferentation-induced V brainstem neuroplasticity paradoxically appears restricted mainly to low-threshold mechanoreceptive neurones, not nociceptive neurones, and is reversible (see Sessle 1996).

The "central sensitization" processes expressed in V nociceptive pathways may involve NMDA receptor mechanisms since the mustard oil-evoked increase in jaw muscle activity and the expansion of the neuronal mechanoreceptive field can be reduced by systemic or intracerebral application of the NMDA antagonist MK-801 in a dose-dependent manner (Yu et al. 1996). A role for NMDA mechanisms in central V nociceptive processing is supported by other V neuropharmacological and immunohistochemical data (see Sessle 1996) and by analogous findings in spinal dorsal horn that are outlined in the three articles. It is also of interest that the local application of MK-801 to TMJ tissues can block the mustard oil-evoked jaw muscle activity (Yu et al. 1996). These findings are consistent with data indicating that NMDA receptors may be located in peripheral tissues (for review, see Erdö 1991) and appear to be the first to document that NMDA antagonists may act peripherally to reduce a nociceptive reflex. Although the detailed mechanisms underlying such a peripheral action remain to be clarified, these findings do raise other potential approaches (e.g., peripherally applied NMDA antagonists) for inducing pre-emptive analgesia in addition to those outlined by **CODERRE & KATZ** (sect. 5) and **DICKENSON** (sect. 4.3).

Several other factors involved in the central sensitization process in the spinal nociceptive system have been outlined by these three target articles. One of these involves endogenous opioids. Central opioids have also been shown to be important modulators of V nociceptive processing (see Sessle 1996). Indeed, central opioids may be recruited to limit the duration and extent of central sensitization evoked by nociceptive barrages entering the CNS: once the jaw muscle and caudalis neuronal excitability increases induced by deep tissue injection (e.g., into TMJ) of mustard oil have dissipated (see above), the changes can be "rekindled" in a dose-dependent manner by administration of the opioid antagonist naloxone (Sessle 1996; Yu et al. 1994). The finding that naloxone administration in animals receiving the TMJ injection of vehicle (mineral oil) does not induce a recurrence of the increased muscle activity indicates that the increased activity is dependent on the previous occurrence of mustard oil-induced effects. Preliminary data (Tambeli et al., unpublished) that the specific mu opioid receptor antagonist CTOP replicates these effects of naloxone suggest that a central mu-receptor opioid mechanism is triggered by the mustard oil-evoked afferent input and limits the increase in muscle activity and associated central sensitization. Our findings appear to be consistent with the concept of opioid recruitment mentioned by **DICKENSON** (sect. 7.1) and by **WIESENFELD-HALLIN et al.** (sect. 4) but may also have relevance to the opioid insensitivity noted in these two articles since it is conceivable that central opioid dysfunction could result from prolonged opioid release induced by a sustained afferent barrage. Peripherally acting opioids such as those noted by DICKENSON (sect. 4.3) do not appear to be involved in these particular effects since the peripherally acting opioid antagonist methylnaloxone does not block the mustard oil-evoked changes (Yu et al. 1994).

Other neurochemical modulators have also been discussed in these three target articles; **WIESENFELD-HALLIN et al.** (sect. 3) especially emphasize the potential role of GABA mechanisms in central inhibitory mechanisms, dysfunction of which may lead to pain phenomena. In the V system, it is interesting in this light that the excrutiatingly painful condition of V neuralgia has allodynia-like features in that it can be triggered by a light tactile perioral stimulus and controlled by the $GABA_B$ agonist baclofen which also affects central inhibition in V brainstem neurones (Fromm 1991). Furthermore, we have shown, as noted above, that local application to caudalis of the $GABA_A$ antagonist bicuculline can result in a marked increase in excitability of caudalis nociceptive neurones and also in the acquisition of a tactile receptive field by NS neurones (Chiang et al. 1996). This raises another possible process, in this case related to $GABA_A$ mechanisms, that may contribute to allodynia if there is dysfunction of central inhibitory mechanisms.

Role of capsaicin-sensitive afferent nerves in initiation and maintenance of pathological pain

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Abstract: This commentary provides experimental data in support of the critical role of capsaicin-sensitive primary afferent fibers in the initiation and maintenance of pathological pain. The demonstration of capsaicin-induced, centrally-evoked cutaneous hyperalgesia, and of neuroplastic changes elicited by the degeneration of C-fiber primary afferent terminals following peripheral nerve damage, indicates a significant contribution of capsaicin-sensitive sensory ganglion neurons in the development of pathological pain conditions. **[CODERRE & KATZ]**

In their target article, **CODERRE & KATZ** put forward the hypothesis that both peripheral and central neural mechanisms contribute significantly to pathological pain. The present commentary provides experimental data in support of a critical role of capsaicin-sensitive primary afferent fibers in the initiation and maintenance of pathological pain. This particular class of neurons is a morphologically and neurochemically well-defined population of primary sensory neurons with a unique dual functional trait. They are involved in the transmission of nociceptive impulses evoked by noxious mechanical, thermal, and chemical stimuli, they mediate somatic and visceral reflexes ("afferent function"), and, through the release of sensory neuropeptides from their peripheral endings, they participate in local regulatory functions of the innervated tissues ("efferent" or "local regulatory" function; Holzer 1991; Jancsó 1968; Jancsó et al. 1977; Lembeck 1983; Maggi & Meli 1988; Szolcsányi 1984). The available experimental evidence indicates that this particular class of afferent neurons may be involved in both the initiation and maintenance of painful conditions.

It has long been known that application of capsaicin to the human skin produces marked mechanical and thermal hyperalgesia (Szolcsányi 1977; Tóth-Kása et al. 1986). Similarly, intradermal injection of capsaicin has been shown to produce cutaneous hyperalgesia; the findings indicated that central sensitization may be responsible for mechanical allodynia after capsaicin (Simone et al. 1991). Animal studies clearly demonstrate that central mechanisms are critically implicated in the initiation of mechanical hyperalgesia. There is experimental evidence that mechanical hyperalgesia can also be elicited merely by stimulation of the central terminations of capsaicin-sensitive primary afferents. Injection of minute amounts of capsaicin into the subarachnoid space brings about a characteristic sequence of vascular and behavioral responses in the rat (Gamse et al. 1984; Jancsó 1981). Intracisternal injection of capsaicin in rats anesthetized with ether elicited an immediate, short-lived cutaneous vasodilatation (i.e., chemically evoked dorsal root vasodilatation) and, after the anesthesia wore off, protective wiping movements. Following this acute excitatory phase, a characteristic mechanical hyepralgesia developed: light touching of the skin or even the hairs evoked vigorous protective reflex movements. It was interesting to note that during this period, which lasts up to 30 min, the areas inner-

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vated by afferent nerves related to the affected medullary and spinal dorsal horn areas proved completely insensitive to noxious chemical irritants, including capsaicin and zingerone (Jancsó 1981; unpublished observations).

These findings strongly suggest that capsaicin-sensitive afferents are essential in the initiation but not in the maintenance of mechanical hyperalgesia. In addition, the fact that the mechanical hyperalgesia produced by intracisternal capsaicin is associated with a deprivation of nociceptive afferent input to the dorsal horn neurons, is in line with the suggestion by **CODERRE & KATZ** that once hyperalgesia is established, it does not need to be maintained by inputs from the periphery (sect. 2.3, para. 2). Further, neurohistological findings indicated an early degeneration of spinal and medullary primary afferent terminals (Jancsó 1981) similar to that seen in peripheral nerve endings upon exposure to capsaicin at concentrations which causes the release of neuropeptide(s) from them (Király et al. 1991).

It may accordingly be proposed that central sensitization is produced by the release of sensory neuron-derived mediator(s) from peptidergic capsaicin-sensitive afferents. This is supported by electrophysiological findings that the sensitization of spinal dorsal horn cells is critically dependent on substance P released from capsaicin-sensitive primary afferent terminals (Dray et al. 1994). Although further studies are needed to clarify this point, the finding that intracisternal injection of capsaicin is associated with an immediate marked cutaneous vasodilatation may indicate that substance P and/or calcitonin gene-related peptide is likely to be involved (Chahl 1988).

The possible morphological changes which may ensue after peripheral nerve damage in the central terminations of nociceptive primary afferent fibers were not addressed by **CODERRE & KATZ.** However, such changes have been shown to occur and capsaicin-sensitive afferents may also be significantly implicated in the development of pain induced by peripheral nerve damage.

Recent findings indicate that peripheral nerve injuries result in a progressive, delayed transganglionic degeneration of C-fiber capsaicin-sensitive primary afferent fibers (Jancsó 1992; Jancsó & Ambrus 1994; Jancsó & Lawson 1990). This may involve the initial release of sensory neuropeptides and thereby contribute to the development of sensory disturbances which follow peripheral nerve damage. It has been suggested that substantial C-fiber afferent deafferentation creates favorable circumstances for structural neuroplastic changes to occur, resulting in a reorganization of spinal dorsal horn neuronal connections (Jancsó 1992). Recent findings lend support to this assumption. It has been shown that after both perineural treatment with capsaicin or peripheral nerve section, which result in massive transganglionic degeneration of C-fiber primary afferent terminals (Jancsó 1992; Jancsó & Ambrus 1994; Jancsó & Lawson 1990), extensive sprouting of presumed thick primary afferents occurs within the substantia gelatinosa, which is normally devoid of myelinated afferent terminals (Mannion et al. 1996; Woolf et al. 1995). These profound structural neuroplastic changes are most probably initiated by degenerative changes in capsaicin-sensitive afferents and, by altering the connectivity of dorsal horn neurons, may contribute significantly to the development of pathological pain after nerve injuries (Jancsó 1992; Woolf et al. 1995).

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Sex differences in pain: And now for something completely different

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Abstract: The belief that women report more somatic complaints than men is not new. Many centuries B.C., the Egyptians and the Greeks already made an association between female pains and *hysteria,* which is Greek for "wandering womb." Despite the commonly held belief that women are more sensitive to pain than men, the issue of sex differences in pain has received little attention from the scientific community in general. It is the merit of **BERKLEY** to draw our attention to this large gap in our scientific knowledge.

> Alas, our frailty is the cause, not we. For such as we are made of, such we be.
>
> *William Shakespeare, Twelfth Night*

As is convincingly shown in **BERKLEY**'s target article, the human literature on sex differences in pain is equivocal, possibly as a consequence of the myriad factors that are operative. Indeed, for nearly every study reporting a sex difference, one can find another reporting none. Consider the following two striking examples. In two controlled studies (Bush et al. 1993 and Feine et al. 1991; both cited by Berkley) on sex differences in response to experimental heat pain, the authors came to opposing conclusions. Although the experimental procedures used in the two studies were very similar (and both groups have extensive experience with psychophysical testing procedures), Feine et al. found that women are more sensitive to experimental pain than men, whereas Bush et al. found no sex differences. A second example concerns the effectiveness of spinal cord stimulation (SCS) in the relief of chronic nonmalignant pain. Whereas North (1991) found a significantly better therapeutic result of SCS in female patients, Kupers et al. (1994) found that men responded better than women.

This large variability in results should warn us against reacting with too much enthusiasm whenever a new sex difference is put forward. For example, in a recent study, Gear et al. (1996) found that kappa-opioids produce significantly greater analgesia in women than in men. In view of the above-mentioned inconsistency in the results on sex-related differences in pain derived from different laboratories, this finding should be interpreted with caution and be replicated in other independent studies.

Although in **BERKLEY**'s review not much attention was paid to animal studies on sex differences, here we find the same inconsistency as in the human literature. For instance, some studies failed to show gender-related baseline differences in hot plate and tail-flick tests and after intraperitonial injection of acetic acid; but other studies showed gender-related differences in the formalin test. Another example: whereas some studies reported that female rats are more susceptible to the development of neuropathic pain after nerve constriction, others showed that after dorsal root section, male rats were more susceptible to the deafferentation pain syndrome.

Despite the enormous variability of gender differences in pain in both clinical and experimental pain studies, the only constants seem to be:

1. *Clinical pain syndromes:* there are significantly more studies showing that women report a higher incidence of endogenous pain compared to men than there are studies showing the opposite.

2. *Experimentally induced pain:* studies either show that women rate experimentally applied stimuli as more painful or no differences are found between the sexes. Very rarely, has it been found that men gave significantly higher ratings than women. It is probably this positive "bias" that explains why it may be worthwhile to switch from induction to deduction.

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In the second part of her paper, **BERKLEY** starts from a number of established sex differences, all exclusively in the biological area. From this she deduces that these differences should also lead to differences in pain experience. I have two remarks on the line of reasoning that is followed in the second part of the target article.

First, the existence of biological differences between men and women does not necessarily mean that these differences are also functionally involved in (a still to be empirically established) sex difference in pain sensation. For example, **BERKLEY** argues that the fact that there are sex differences in (temporal features of) sex hormones may be a factor in why men and women differ in their pain sensation. Although this may seem an attractive hypothesis, the question remains whether these differences in sex hormones also have a functional meaning with respect to the issue of gender related differences in pain sensation?

In a recent study by Cicero and colleagues (1996), the role of sex steroids in gender differences in the antinociceptive activity of morphine was investigated. The results of this study showed that male rats were more sensitive to the antinociceptive effects of morphine than females, males showing at least twice as much antinociceptive effect from morphine. This was a consistent finding in the three antinociceptive assays that were used and over the different dose range of morphine. No gender-related baseline differences in pain responsiveness were found in any of the three tests. Since no gender-related differences were found in serum levels of morphine, these data seem to suggest that the central nervous system of male rats has an enhanced sensitivity to morphine. From the data so far, it is tempting to hypothesize that the observed differences are due to gender-related differences in sex hormones. However, the authors went on to study the effect of castration on the animals' subsequent responsiveness to morphine. They found no effect whatsoever. This seems to suggest that the acute effects of sex steroids are not the basis of the observed gender differences in opioid responsiveness. As suggested by the authors, a possible explanation for these results might be that it is the effect of steroids during critical periods in the development that causes long-term organizational effects on the central nervous system. This is an attractive hypothesis that could be further tested in adult animals that were castrated perinatally.

A second criticism of **BERKLEY**'s review of possible etiological factors in the explanation of presumed sex differences in pain is that she seems to ignore the possible role of cognitive psychological factors in gender-related differences in pain sensation. Pain is not just a sensation but also has important emotional and cognitive components.

According to modern cognitive-psychological theories of emotion, there are two interacting components in emotions: peripheral physiological arousal on the one hand and cognitions associated with the arousal on the other. If a physiological component is present without the cognitive component, clues will be searched for in the environment to label the emotions. In youngsters, these clues are often provided by the parents. There may be important differences with respect to the cognitive labels provided to children of different sexes. Consider a child that complains to its parents of a vague abdominal discomfort that it cannot describe verbally. The parents will try to offer the child a cognitive label for the physiological distress it experiences. They can tell the child that what it feels is pain or they can give another cognitive label to it, say hunger. It might well be that parents use different labels depending on whether they are dealing with a boy or a girl. Despite the progress that has been made during the last decades, we are still plagued with strong stereotypes on how boys and girls should behave and what they should feel or not feel. Boys are expected to be heroic and manly and not to complain too much after minor injuries. Hence it might well be that boys and girls get different clues from their environment about how to label their physiological arousal. As a consequence, girls may develop a greater tendency to label some vague physiological states as painful. This cognitive appraisal may be of less importance when there is a very obvious causal factor (for instance, when a child falls from its bicycle it will be clear from the circumstances that the child is crying because it feels pain), but it may be of great importance in cases where the obvious environmental clues are more equivocal.

In conclusion, the issue of gender-related differences in pain is far from solved. What has become clear from **BERKLEY**'s review of the relevant literature is that the issue is a very complicated one, probably because so many factors influence pain and its expression. So are there genuine sex differences, one is tempted to ask? I think the answer KAREN BERKLEY gives us is comparable to the one that Molière gave in one of his plays when a "doctor" was asked whether women were more difficult to cure than men:

> Monsieur, c'est une grande et subtile question entre les doctes, de savoir si les femmes sont aussi faciles à guérir que les hommes. Je vous pris d'écouter ceci, s'il vous plaît. Les uns disent que non, les autres disent que oui; et moi je dis que oui et non. (Molière, *Le médecin malgré lui*)

Is there a sex difference in the balance of pain excitatory and pain inhibitory processes?

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Abstract: According to **BERKLEY**'s review, women have a higher risk of suffering from pain than men. If this is true, there should be more frequent and more intense activity both in the pain excitatory system and in the pain inhibitory system of women than of men. Consequently, it remains unclear whether the overall effect at the end is more pain or less pain in women. This conclusion fits the weak sex differences observed for experimental and clinical pain as shown by BERKLEY's review of the literature.

It was a great scientific delight to read **BERKLEY**'s comprehensive and thought-provoking review on "sex differences in pain." Clearly, the time is past when a mere description of the facts on sex differences in pain is sufficient. We have enough facts. We need theory for new insights. Consequently, it was wise to look for sex differences in pain from both an inductive and a deductive perspective.

It is always risky to start a deductive analysis from somewhat arbitrarily chosen hypotheses and observations because it is impossible to include all factors which may be relevant. One might ask why **BERKLEY** has chosen these particular factors and omitted others of potentially equal relevance. Yet, her approach can succeed only if one takes the risk of omitting important factors. Otherwise, one would look extensively rather than intensively at reality without ever considering all relevant factors.

Although I understand the necessity of a somewhat imbalanced perspective, I feel the need to add one argument. The pain system is a homeostatic one. Accordingly, excitatory activity is often balanced out by inhibitory activity on both physiological and psychological levels of processing of pain signals. Perhaps surprisingly, more pain at the beginning can result in less pain at the end. Examples are (1) the adaptation-level effect by which an individual perceives pain after a preceding strong noxious stimulus as being less intense than after a preceding weak one (Rollman 1979) and (2) "diffuse noxious inhibitory controls" which are responsible for the phenomenon that a strong sustained pain weakens other phasic pains in a heterotopic fashion (Willer et al. 1984). It is also of interest in this context that the reduction of pain by an analgesic can dampen the endogenous pain control systems and can potentially contribute to more pain in the long run (Le Bars et al. 1992).

Clearly, not all excitatory activity is balanced out by inhibitory activity, a fact that leads to all kinds of pathological pain conditions.

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Nevertheless, even if it is true that there are more factors that predispose women than men to suffer from pain at the beginning, the biological consequence at the end is unclear. Do women end up with a preponderance of pain excitatory processes or with more powerful pain inhibitory systems because of their continuous activation? This likely depends upon a variety of factors and cannot be answered from a deductive perspective but at best from an inductive perspective. Therefore, both perspectives are clearly needed for future research.

Considering the fact that the pain system is homeostatic, including both excitatory and inhibitory activities, it is not surprising that, despite sex differences in certain parts of the pain system, the overall effect of activities in the whole system point to only minor sex differences in pain.

The requirements of a major biological hypothesis

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Abstract: Abundant pathophysiological and clinical evidence suggests that the algogenic code responsible for cardiac pain is not based on "specific" mechanisms (MCMAHON). Recent evidence, however, has led various authors to postulate that some degree of specificity might be involved in visceral pain arising from other sources, but a "spatio-temporal" intensity pattern is still the most plausible hypothesis for the genesis of visceral pain.

The stimulating and well-conceived article by MCMAHON analyzes some conspicuous differences between the sensibilities of cutaneous and visceral tissues and concludes that the encoding of visceral nociceptive events is likely to occur by an "intensity" rather than a "specific" mechanism and that this could be the key difference in viscerosensory and somatosensory processing. I too have been suggesting for some time that the "specific" mechanism seems quite inappropriate to explain visceral nociception (Malliani 1982). However, I would also not take for granted the absolutely specific nature of the somatic algogenic node. There are some phenomena, readily perceptible with the naked eye, that represent an almost insurmountable barrier for certain hypotheses, even when they are based on sophisticated details. For example, how can a giraffe remove its foot from a fire quickly enough to avoid burning if the alarm message can reach its brain only through specific but slow mail (Malliani 1995)? It is obvious that some kind of "pattern," in addition to a hardware connection, seems necessary in an appropriate alarm system; however, I am content to leave this puzzle to the researchers directly involved in this specific area.

Regarding visceral nociception, I have a few comments on the target article by MCMAHON. In general, a major biological hypothesis – such as affirming or denying the existence of a peripheral neural channel specifically transmitting the algogenic code responsible for visceral pain – should not be a mere generalization from a few experimental findings but a much more articulated synthesis. MCMAHON's position seems instead largely based on recent (and surely appreciable) experimental data on the urinary bladder and internal reproductive organs as well as the phenomenon of recruitment of "silent" afferents by sensitization. A broader view seems to be called for.

Any general view of visceral pain should carefully examine what we have learnt about cardiac pain. Indeed, the complexity of the multifarious notions about cardiac pain over the years has no equivalent in any other area of visceral pain: all this attention is probably based on the traditional conviction that pain was the most alarming message from the jeopardized heart, signaling the danger of impending death.

To stress the complexity involved here I would like to recall a few basic observations on cardiac pain that might be crucial for any general conclusions to be drawn.

(1) The study of the impulse activity of single afferent sympathetic fibers innervating the heart and in particular the ventricles has never demonstrated the existence of high threshold sensory endings responsive exclusively to abnormal events, such as ischemia (Casati et al. 1979; Lombardi et al. 1981; Malliani 1982; Malliani et al. 1973), or to chemical substances such as bradykinin (Lombardi et al. 1981) or adenosine (Gnecchi-Ruscone et al. 1995). Conversely, when afferent fibers were studied in the presence of normal hemodynamic conditions, all displayed spontaneous impulse activity and clear responsiveness to normal hemodynamic events; they hence had the characteristics of low-threshold polymodal receptors.

High-threshold mechanosensitive afferents have recently been described in spinal projections and receptor endings located in the urinary bladder (Habler et al. 1990) and the esophagus of the American opossum (Sengupta et al. 1990). This finding could be of paramount importance. However, anesthesia and acute surgery critically modify smooth muscle tone of viscera and hence the natural threshold of a mechanosensitive apparatus might remain impossible to determine with current techniques. In addition, it is difficult to assign an important biological function to signalling extreme bladder distension in animals that need not respect social rules for micturition. On the other hand, the esophagus is a peculiar organ exposed to many possible injuries; hence it might develop a sensitivity to pain more similar to that of somatic rather than visceral structures.

(2) Concerning the crucial role of inflammation, it should be recalled that myocarditis is a painless clinical event. For all viscera, the stimuli that are more likely to produce pain seem to correspond to the category of stimuli that normally elicit reflex responses. For example, contractions or distensions of intestinal walls can give rise to pain, but these very events are also the ones that normally produce reflexes and that are in turn modulated by reflexes. Conversely, burning of the intestinal wall seems to produce no pain (see Malliani et al. 1989). And ulcerative endocarditis can destroy cardiac valves in the absence of pain.

We have, during the years, reiterated (Malliani 1982; 1986; 1995; Malliani et al. 1989) our firm position that the "specific" mechanism seems incapable of interpreting cardiac pain. This position was strongly reinforced by experiments on conscious animals (Malliani et al. 1989; Malliani 1995), during which it was clearly demonstrated that after full recovery from surgery a massive excitation of the cardiac sensory neural substratum, generated by intracoronary injections of bradykinin, produced strong excitatory reflexes in the absence of any signs of pain. Hence the "intensity" mechanism alone is also insufficient to explain the cardiac algogenic code. In contrast, pain can be elicited with a strong but more localized stimulus (such as distension of coronary wall). When the animals had not yet recovered, however, from surgery, similar bradykinin injections did elicit signs of pain.

In clinics, countless observations indicate that no hemodynamic or electrocardiographic variable can predict whether or not anginal pain per se is present.

We have thus advanced the hypothesis that a "spatio-temporal pattern" might explain the onset and, at the same time, the elusiveness of the link between myocardial ischemia and pain (Malliani et al. 1989; Malliani 1986; 1995). This pattern would be characterized by an extremely intensive but spatially restricted activation of sensory endings, impinging upon the centers. Such a heterogeneous abnormal code would be difficult to blunt by central mechanisms. The phenomenon of sensitization might well contribute to this heterogeneous pattern. An intense spatio-temporal characterization has also been proposed by McMahon and Koltzenburg (1990).

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Experimental pain models and clinical chronic pain: Is plasticity enough to link them?

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Abstract: The central hyperexcitability observed in animal models supports a pathophysiological explanation for chronic human pain. Novel information on cholecystokinin (CCK) upregulation offers a rationale for reduced opioid response in neuropathic pain. However, the basic information provided by scientists should not lead clinicians to equate experimental models to chronic human conditions. Clinicians should provide careful reports and attempt to classify pathophysiologically clinical conditions that have so far been grouped generically. **[BLUMBERG et al.; CODERRE & KATZ; DICKENSON; WIESENFELD-HALLIN et al.]**

1. Peripheral and central hyperexcitability as models for clinical pain. The thorough review of central hyperexcitability following cutaneous hyperalgesia by **CODERRE & KATZ** is superb. Buoyed by CODERRE & KATZ's insightful observations, one can forgive them for lumping together referred and phantom pain (phantom pain has nothing to do with misreferral; it is properly referred to something gone). The broad field of cutaneous hyperalgesia and related pathophysiological mechanisms is explored with the available experimental models in humans and animals. However, for the clinician exposed routinely to pain patients it is striking how animal models differ from chronic clinical pain. No experimental model exists in which, after a minor soft tissue injury, stepwise expansion of symptoms and signs develops, occasionally extending far from the original injury, as happens in chronic regional pain syndrome type I (CRPS). CRPS type I is relevant because hyperalgesia is a major symptom and anyone dealing with this syndrome tries to use one or other of the available theories of peripheral and central sensitization to explain it (Jänig & Stanton-Hicks 1996).

It is common clinical experience that most painful physical or chemical injuries heal over time. Thus, the full body of experimental evidence pointing to initial and ongoing central sensitization, always present following injury, has to be interpreted in light of this direct clinical observation. Central hyperexcitability in animals following injury is unlikely to be the only mechanism underlying persistent human pain states associated with hyperalgesia or allodynia following a cutaneous injury. In addition, CRPS type I patients quite commonly exhibit broad areas of negative sensory symptoms; to the best of our knowledge, no experimental model of cutaneous injury suggests the presence of negative sensory symptoms. The same applies to the temporal pattern and the expanding evolution of CRPS type I.

CODERRE & KATZ's paper is very tempting for a clinician: it provides pathophysiological explanations for the most puzzling chronic pain conditions seen in the clinic. Yet, to avoid fooling ourselves as clinicians and fooling scientists by uncritically transferring experimental observations to the clinic, we must question the correspondence between experimental pain and clinical pain. Indeed, chronic pain in humans following acute tissue injury and neuropathy is fortunately a rare exception. Rheumatoid arthritis or a soft tissue trauma provoking severe inflammation and pain in patients almost never leads to chronic pain in the absence of persistent injury. Acute nerve injury in humans can cause chronic and severe pain, however this happens so rarely that nerves are routinely biopsied for diagnostic needs without complications. It is natural to wonder whether the complex reorganisation of spinal neuron activity and their receptive fields, as well as the plasticity of more rostral neural networks in response to cutaneous experimental injury in animals, are relevant to chronic clinical pain. If they are, why is chronic pain in humans so different from experimental animal pain?

One hypothesis could be that although tissue and behavioural responses to acute pain are identical in animals and humans, humans are genetically more protected than animals against chronic pain. Genetic differences in predisposition to chronic pain behaviour have been reported (Devor & Raber 1990). Thus, human genetic idiosyncrasy in chronic pain is a possible though unlikely event, since rats and monkeys should share similar responses to injury but both differ profoundly from humans.

An alternative hypothesis could be that mental control over sensory experience protects most human patients affected by acute injury from developing chronic pain, while mind control may not be equally potent in animals. The corollary of this hypothesis is that mental dysfunction in the presence of tissue or nerve injury could predispose some humans to developing chronic pain. Clinical experience teaches us that this happens; psychiatrists know that somatoform pain syndromes exist and that pain can be generated or maintained by dysfunction of the brain. In addition, the mind could also be responsible for striking improvement or cure.

2. Complex regional pain syndromes. These considerations lead us to **BLUMBERG et al.**'s target article about one of the most controversial syndromes known to pain experts (Ochoa 1995; Jänig & Stanton-Hicks 1996). Two cases will be discussed. The first patient had sequelae and complications following hand aponeurectomy. Symptoms and signs indicate inflammation (hot and swollen hand with limited joint motion), and pain is increased by faster heart beat. Yet this condition is defined as reflex sympathetic dystrophy (RSD) and pulsating pain, that is, the orthostatic component is judged to be a patognomonic symptom. The second patient had partial nerve injury; the pain was relieved, for six months at least, by two nonplacebo-controlled stellate ganglion blocks. This is considered evidence for sympathetic system-dependent pain. The possibility that the pain was relieved by mental activity (fear of having further injections in the neck, or placebo response) is not considered.

The International Association for the Study of Pain (IASP) published a reappraisal of RSD (Jänig & Stanton-Hicks 1996). The main message of that book, in which **BLUMBERG** co-authored the third chapter, is to propose a new name for the clinical conditions formerly defined as RSD, causalgia, sympathetically maintained pain, and so on. The new definition proposed by IASP was specifically intended to avoid misinterpretation of any cause/effect link between sympathetic signs and involvement of the sympathetic nervous system in generating or maintaining the painful state. Indeed the new terms proposed (CRPS type I and II) are intentionally descriptive only. The second message of the IASP reappraisal was to require a careful placebo control of any sympatholitic treatment to avoid false positive interpretation of the outcome of therapy. [See also Spanos: "Hypnotic Behavior: A Social-Psychological Interpretation of Amnesia, Analgesia, and 'Trance Logic'" *BBS* 19(3) 1986.]

3. Neuropathic pain. It is proposed by **WIESENFELD-HALLIN et al.** that the biochemical theory of up-regulation of endogenous anti-opioid substances, such as cholecystokinin (CCK) in neuropathic pain. Their proposal is based on cited observations that peripheral and central neuropathic pain does not respond to opioid therapy. The authors fail to acknowledge that opioid treatment has been reported to be successful in different neuropathic pain conditions by others (Portenoy & Foley 1986). To construe a complex comprehensive hypothesis about neuropathic pain without considering divergent reports seems simplistic.

4. Opioids in neuropathic pain. More properly, in our opinion, **DICKENSON** discriminates different neuropathic conditions of which some may still respond to opioids whereas others do so much less or not at all. Loss of primary nociceptive afferents and their presynaptic receptors seems to be the major difference. In our experience, pain from some peripheral polyneuropathy, ischemic, and inflammatory multineuropathy does indeed respond well to opioids, whereas deafferentation and traumatic spinal injury pain respond less well (although occasionally they do). Whereas direct intrathecal opioid injection has already been applied to circumvent poor response to systemic administration, a stronger rationale may now modify multiple treatment. The dual therapy

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proposed by DICKENSON is certainly an attractive therapeutical opportunity worth testing.

5. Conclusion. It is mandatory nowadays for clinicians to provide highly accurate clinical descriptions to scientists by applying rigorous sensory examination, quantitative testing, pharmacological tests, and scales to quantify patients' performance and pain ratings. Care should be taken to avoid confusion related to verbal communication of abnormal positive sensory phenomena, discriminating between dysesthesiae and allodynia. More important, there will not be much progress in pain research if clinicians do not provide scientists with information on possible mental influences on pain syndromes. This can only be tested by psychological evaluation and proper placebo controls for any treatment; critical long-term follow up is also needed.

Clinicians must be cautious in considering the complex pathophysiological explanations proposed by scientists operating on standardised animal models. The time has also come for clinicians to avoid generic terms such as "neuropathic" pain; pathophysiological classification should at least be attempted. This is particularly true for nerve injuries, which should also be separated according to site (axon, ganglion, root, etc.) and cause (metabolic, toxic, traumatic, etc.). As long as neuropathic conditions such as postherpetic neuralgia, polyneuropathy, and RSD are lumped together, scientists can make little use of clinical reports.

On the other hand, although it is understandable that scientists are attracted by the chance of providing explanations and therapeutical opportunities for clinical conditions, they must remain critical toward experimental models. Nerve section and ligature are painful experimental neuropathies; they cannot be taken as general models for all kinds of peripheral neuropathic pain, and particularly not for "neuropathic symptom complex" with multiple aetiologies such as RSD or causalgia (or CRPS I and II).

Visceral pain and gender differences in pain

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Abstract: My commentary on MCMAHON addresses the fact that only peripheral data have been considered for explaining differential sensibility in somato- and viscerosensory systems. This fails to take it into account that central processing for visceral and somatic inputs is now known to depend on different functional pathways. My commentary on BERKLEY points out that the hypothalamus-pituitary axis is more responsive to stress in females than in males.

Structural features in central processing of somatic and visceral inputs. MCMAHON has done much to show that subtle differences in the peripheral properties of somato- and viscerosensory systems may be enough to explain the differences in sensibilities between cutaneous and visceral tissues. Although it is clear that some such differences exist, it is not obvious that they alone can account for the differential sensibility. MCMAHON has not taken into account recent evidence obtained at central levels, either spinal or supraspinal, that would go against a hypothesis based exclusively on peripheral observations. This new evidence has shown that visceral and somatic inputs are processed in different central structures (Menétrey 1995), forcing us to consider alternatives to hypotheses based exclusively on peripheral observations.

Observations at the spinal level have shown that somatic and visceral afferents project to different areas. Visceral afferents project to Lamina 1 of the dorsal horn, Lamina 10 and the dorsal gray commissure (DGC), as well as to intermediolateral columns, especially the sacral parasympathetic nucleus (SPN). Somatic afferents project to Laminae 1 and 2 and to the deep dorsal horn (mainly Laminae 4 to 6). Such a difference in spinal terminal areas is so obvious that they must clearly have a major functional role which remains to be explored. Visceral afferents also have quite dense supraspinal targets through vagal afferents to both the paratrigeminal nucleus and the nucleus of the solitary tract.

Observations on the ascending spinal pathways have stressed the multiplicity of direct spinal connections relaying inputs to supraspinal levels. Not only is there a multiplicity of tracts but also a diversity in origins, as demonstrated so far in the rat. Pathways thought to be involved mainly in relaying visceroceptive inputs (i.e., the lateral spinoreticular, spinosolitary, spinopontomesencephalic, spinohypothalamic, and spinoamygdalo tracts) not only differ among themselves in terms of cells of origin, none are organized in a way that resembles the spinothalamic and medial spinoreticular tracts which are believed to be involved largely in somatosensory processing. Cells in either the DGC or SPN are important sources for ascending fibers belonging to only some of the tracts involved in visceral challenging (Menétrey et al. 1992).

Observations at supraspinal levels have started to identify nuclei or subregions processing viscero- or somatosensory inputs at various levels of the brain. Recent publications using the evoked expression of immediate early genes have shown that visceronociceptive and somatonociceptive inputs may drive certain supraspinal structures differentially, as is the case with spinal structures. The nucleus of the solitary tract is effectively driven by viscero- but not somatonociceptive inputs; the lateral parabrachial area would contain different subareas more responsive to either visceral or somatic pain. The lateral caudal medulla would be implicated in processing both types of inputs but only briefly after the onset of stimulation.

Taken together, these functional distinctions provide evidence for the existence of different pathways and structures in the differential processing of somatic and visceral inputs. They also support Theobald's (1941) referred pain hypothesis that viscerosomatic interactions could appear at supraspinal levels after visceral and somatic inputs have been conducted rostrally by anatomically separated sensory pathways.

Pain and the gender differences in hypothalamus-pituitary axis. The target article of BERKLEY provides an impressive review of data on sex differences in pain from both clinical and experimental sources and offers interesting hypotheses to explain them. As stated, sex differences in pain do exist but, like other differences, are statistical, not absolute. Among the various factors presented here that could affect differential reactions in response to pain we should also consider gender differences in the functioning of the hypothalamus-pituitary axis; there is higher responsiveness in females than in males in terms of growth hormone, prolactin, ACTH, and corticosterone release.

Associative learning and pain? Why stop there?

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Abstract: It is argued by BERKLEY that there are theoretical reasons why sex differences in pain may result from specific learning processes. I argue that Berkley has not gone far enough in pursuing this suggestion, and that the evidence that learning is a major determinant of pain behaviour is substantial. Moreover, sex differences in pain may represent only a special case of individual differences in pain resulting from learning processes.

The second deductive argument presented by BERKLEY in support of the suggestion that sex differences in pain exist represents the welcome introduction of learning processes as a determinant of pain behaviours. Nevertheless, BERKLEY's argument is somewhat narrow, and neglects the relatively straightforward point that pain is not a physical sign that can be directly measured, in the same way that blood pressure, for example, can be. What is assessed in the case of pain is pain behaviour, whether it be

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medication request or pain report. Given this, we must accept that the relevant behaviours are subject to the same learning processes as other behaviours.

If we accept this, then it becomes apparent that social learning, modelling, operant conditioning, and classical conditioning may all represent learning processes which serve to determine the nature of pain responses in any given individual. [See also Turkkan: "Classical Conditioning" *BBS* 12(1) 1989; Ader & Cohen: "CNS–Immune System Interactions" *BBS* 8(3) 1985; Spanos: "Hypnotic Behavior" *BBS* 9(3) 1986; Rachlin: "Pain and Behavior" *BBS* 18(1) 1985.] Certainly there is empirical support for this position: Faucett et al. (1994), for example, describe sex and race differences in postoperative pain report with reference to a social learning model of pain behaviour. A similar suggestion is made by Baker and Kirsch (1991) concerning measures of pain tolerance. In the case of chronic pain, the role of learning has been promoted as a major determinant of behaviour since Fordyce proposed an operant conditioning model of chronic pain behaviour (Fordyce et al. 1968). More recently (Flor et al. 1990), observational learning has also been proposed as a factor in the development of pain behaviours in chronic pain patients.

What is proposed by **BERKLEY** (sect. 3.1) is that associative learning may result in painful episodes, or possibly vulnerability to pain, cued by "*time* alone" (her emphasis). This does not account, however, for the variety of learning processes and situations which may determine an individual's pain tolerance or vulnerability. This is to some extent related to Wittgentstein's (1958) suggestion that injury results, in infants, in an instinctive pattern of behaviours which we recognise as signifying pain. Over time the infant learns to substitute certain more complex behaviours for these primitive, reactive behaviours: pain reports, medication requests, and so on are merely expressions of pain which have been substituted for more primitive, instinctive expressions. This process of substitution, however, constitutes a learning process (more probably a number of learning processes). Individual differences in pain may be a consequence of this. Although this argument has been characterised developmentally, it is likely that the same processes act, albeit with less vigour, throughout the lifespan of the individual. This is certainly supported by operant conditioning models of chronic pain in adults (Flor et al. 1990; Fordyce et al. 1968).

Referring specifically to the role of sex differences in pain, Kuczmierczyk and Edwards (1989) argue that familial pain models of appropriate pain behavior are related to the subsequent development of pain in offspring (premenstrual symptomatology), possibly as a result of vicarious learning. So if a variety of learning processes determine the quantity and quality (i.e., type) of pain behaviour in individuals, might uniformities in these learning processes, and subsequent behaviors, result in reliable sex differences in pain? This is difficult to test, if we accept that male and female infants are treated in distinct but relatively uniform ways when injured, then we might expect corresponding differences in pain behaviours. These differences would be culture-specific, but this would simply provide further support for the arguments presented above, with related processes acting at different scales (i.e., individual and group). Although empirical data on children are scarce, there is abundant evidence that adult men and women are treated quite differently, as in Bond and Pilowski's (1966) report of significant sex differences in pain medication administered by ward staff.

Physiological antagonism between endogenous CCK and opioid: Clinical perspectives in the management of pain

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Abstract: Numerous mediators are involved in both the control and the transmission of nociceptive messages, and several lines of research have been developed in the management of pain. Complete enkephalin-degrading enzyme inhibitors, which produce naloxone-reversible analgesia in all tests where morphine has been found to be active, remains the most promising way. CCK compounds, especially the CCK_B antagonists also may be interesting drugs. Indeed, they are able to strongly potentiate the antinociceptive effects of the opioids. **[DICKENSON, WIESENFELD-HALLIN et al.]**

WIESENFELD-HALLIN et al. and **DICKENSON** report the different possibilities for therapy in specific pain states such as injury to peripheral or central nervous systems, which are often associated with persistent pain resistant to opioids. As described in both articles, nerve injury induces complex changes in the level of neuropeptides. Thus, an increase in the expression of the mRNA coding for CCK was observed after peripheral axotomy in rat, which could be associated with an increase in the release of CCK from terminals of primary afferents, as suggested by WIESENFELD-HALLIN et al. and DICKENSON. CCK could be one of the neuropeptides involved in the development of neuropathic pain syndrome and could antagonizes the analgesic effects of opioids either released endogenously or applied exogenously. The occurrence of regulatory mechanisms between CCK and opioid systems is now well established (review in Roques & Noble 1996). Thus, it has been shown that the activation of CCK_B receptors by a selective CCK_B agonist reduces the antinociceptive effects induced by endogenous enkephalins protected by RB101, a complete inhibitor of enkephalin catabolism (Fournié-Zaluski et al. 1992); this is supported by the results with selective CCK_B antagonists, blocking the negative feedback control achieved by endogenous CCK, which strongly potentiates the antinociceptive effects of RB101 (Valverde et al. 1994).

The repeated administration of morphine produces serious side effects, including the development of antinociceptive tolerance, and physical and psychological dependence, which are mainly related to the activation of μ opioid receptors, as noted by **DICKENSON.** Indeed, a severe degree of opiate dependence is developed after chronic administration of μ agonists, contrasting with the moderate dependence produced by δ agonists and the even milder effect induced by κ agonists (Cowan et al. 1988). These results have recently been confirmed by Matthes et al. (1996). Thus, mice with a deletion of the gene encoding the μ opioid receptor did not present any sign of naloxone-precipitated withdrawal after chronic morphine administration. Furthermore, repeated injection of morphine failed to induce place-conditioned preference in these mutant mice. Peripheral administration of RB101 induces strong, dose-dependent, and naloxone-reversible antinociceptive responses on the same assays where classical opiates, such as morphine, have been reported to be effective (hot plate, writhing, tail flick, tail electric stimulation, paw pressure, and formalin tests). Endogenous enkephalins in these tests act on μ and/or δ opioid binding sites, depending on the nociceptive stimuli used (Noble et al. 1992). Nevertheless a moderate degree or a lack of tolerance and physical dependence is observed after chronic treatment with mixed inhibitors of enkephalin catabolism (review in Roques et al. 1993). This result can be explained by a more specific stimulation of the opioid-binding sites by the tonically released endogenous opioids, thus minimizing the receptor desensitization or down-regulation that usually occurs after the

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general stimulation of opioid receptors by exogenously administered agonists. Moreover, chronic morphine induces a hypersensitivity of noradrenaline-containing neurons in the locus coeruleus; this is considered to be one of the main causes of the withdrawal syndrome (Aghajanian 1978). It is interesting to note that electrophysiological studies suggest that there is little or no tonic release of endogenous opioids in this brain region under basal conditions (Williams et al. 1987). This is probably one of the major reasons why chronic treatment with peptidase inhibitors induces a lower degree of physical dependence than that observed after chronic administration of exogenous opioid agonists. Indeed, it has been clearly demonstrated that the locus coeruleus is a critical structure in the development and expression of physical opiate dependence (Maldonado et al. 1992).

The goal of discovering orally active analgesics with a potency similar to that of morphine but devoid of major side effects has now been achieved with mixed NEP/APN inhibitors, although these compounds have yet to be evaluated in clinical trials. The selective CCK-B antagonists may also be interesting drugs in the management of pain, as noted by **WIESENFELD-HALLIN et al.** and **DICKENSON.** Indeed, even if they do not induce antinociceptive responses alone, they are able to strongly potentiate the antinociceptive effects of exogenous and endogenous opioids with possible interesting clinical implications, especially in specific pain states which are often resistant to opioids. Thus, it has been demonstrated that a combination of opioids and selective CCK_B antagonists enhances morphine antiallodynic efficacy (Nichols et al. 1995) and suppresses the development of autonomy behavior in a model of neuropathic pain in rat (Xu et al. 1994a); it also effectively relieved the allodynia-like symptom in spinally injured rats (Xu et al. 1994b). CCK_B antagonists were more effective in potentiating the antinociceptive responses induced by endogenous enkephalins than those produced by morphine administration. Indeed, the antinociception observed after the association of the CCK_B antagonist PD-134,308 and RB101 was 800% higher than that observed with RB101 given alone (Valverde et al. 1994). These CCK compounds could also have some potential clinical interest in potentiating other opiate-mediated pharmacological responses. Thus, CCK_B antagonists have been reported to facilitate the antidepressant-like responses induced by endogenous enkephalins in the conditioned immobilisation and forced swimming tests, as well as their alleviatory effects on naloxone-precipitated morphine withdrawal syndrome (review in Roques & Noble 1996).

NOTE
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Are intrinsic inhibitory systems activated or inhibited in pathological pain states?

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Abstract: Neuroplastic changes in the inhibitory systems contribute to pathological pains such as hyperalgesia. Activation or inhibition of the intrinsic inhibitory systems may depend on the pathophysiology which induces a sustained pain state. The mechanisms of hyperalgesia, opioid insensitivity following nerve injury, and opioid tolerance may be related to common neuroplastic changes. **[WIESENFELD-HALLIN et al.]**

Acute thermal or mechanical stimuli or irritants applied to the skin or the viscera of animals evoke well-defined, pain-related behaviors that have formed the basis of the investigation of the behavioral components of the response to noxious stimulus. It has been widely accepted that a number of inhibitory spinal systems, some with cell bodies intrinsic to the spinal cord and some originating from supraspinal sources, can reduce afferent-evoked excitation. The excitatory effects of large afferents is under inhibitory amino acid GABAergic and glycinergic modulatory controls. Interneurons containing peptides such as enkephalin, or bulbospinal pathways containing monamines are activated by afferent input and exert a modulatory influence on the release of C-fiber peptides and produce a postsynaptical hyperpolarization of projection neurons. This is not always the case, however, in the sustained pain state. Recent studies have focused on possible changes in the role of GABA in pain transmission in the spinal cord when acute pain becomes chronic pain.

WIESENFELD-HALLIN et al. describe one of the mechanisms for pain-related behaviors following injury to the peripheral nerve section and spinal cord ischemia: dysfunction of the spinal GABAergic inhibition. However, the role of the GABAergic system in pathological pain seems to depend on the pathophysiology of the pain model. Chronic inflammatory arthritis causes an increase in spinal GABA levels and in the number of GABA-immunoreactive cells in laminae I–III (Castro-Lopes et al. 1992), leading to the suggestion that GABAergic interneurons are activated and participate in the modulation of the hyperalgesic state. Unchanged $GABA_A$ receptor binding and a reduction of $GABA_B$ binding (down-regulation) in the superficial dorsal horn have also been reported (Castro-Lopes et al. 1995). In contrast, a reduction in sensory input by nerve transection produces an ipsilateral reduction in GABA level and in the number of GABA-immunoreactive cells in the spinal cord (Castro-Lopes et al. 1993).

Satoh and Omote (1996) have recently reported that intrathecally administered bicuculline enhances hyperalgesia in rats with peripheral mononeuropathy produced by loose ligation around the sciatic nerve; increased GABA level in the ipsilateral spinal dorsal horn has also been observed. These findings that sustained noxious input induced by nerve injury might lead to release of GABA, resulting in the activation of inhibitory pain modulation. The idea that GABA and glycine might act as co-transmitters in the spinal cord has recently been supported by ultrastructural studies (Mitchell et al. 1993). Although the functional significance of such a co-transmission is still unclear, peripheral nerve injury might induce the release of both GABA and glycine, resulting in activation of inhibitory systems.

Is the monoaminergic descending inhibitory system activated or inhibited in the pathological pain state? It has been reported that peripheral neurectomy and polyarthritis are associated with marked increases in 5-HT, noradrenaline, and dopamine concentrations in the spinal cord (Colado et al. 1994; Godefroy et al. 1987), indicating the activation of monoaminergic descending system. Recently, Satoh and Omote (1996) found that the levels of monoamines involved 5-HT; noradrenaline increased bilaterally in the dorsal horn of the lumbar spinal cord in rats with peripheral mononeuropathy. They also showed that the intrathecally administered 5-HT antagonist methysergide and alpha-2 adrenergic antagonist yohimbine enhanced the hyperalgesia seen in this model. These observations indicate the descending bulbospinal serotonergic and noradrenergic inhibitory systems are activated in peripheral mononeuropathy. The action of the other intrinsic inhibitory systems such as the cholinergic system should also be investigated in the pathological pain state in further studies.

WIESENFELD-HALLIN et al. also review the pharmacological basis of the opiate insensitivity following injury to the peripheral and central nerve systems. Although the reasons for the loss of morphine activity in nerve injured animals are not clearly known, neuroplastic changes which underlie the development of neuropathic pain may result in a reduction of the antinociceptive effects of opiates. WIESENFELD-HALLIN et al. describe possible mechanisms in the target article, including changes in levels of spinal neuropeptides such as endogenous antiopioid substance cholecystokinin (CCK), which mainly diminish opioid action. The authors suggest that reduced opioid sensitivity might depend only in part on down-regulation of opioid receptors. In inflammation, however, the presynaptic opioid receptors produced in the cell bodies

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of C-fibers in the dorsal root ganglion and transported both centrally and peripherally, become functional.

Thus, the sensitivity of opioids in pathologic pain also seems to depend on the pathophysiology of the pain models. More important, the basis of interactions between mechanisms of thermal hyperalgesia, opioid insensitivity following nerve injury, and morphine tolerance may be related to common neural substrates and site of actions (Mao et al. 1995). Hyperalgesia or allodynia following nerve injury results from neuroplastic changes, including activation of NMDA receptors, increases in intracellular Ca^{2+} concentration, and subsequent intracellular activation of PKC and/or NO (Kawamata & Omote 1996; Mao et al. 1993). Some or all of these biochemical steps are capable of leading to the reduced opioid antinociception through decreased efficacy of the opioid receptor-channel complex, uncoupling of G-protein with the opioid receptor, and/or changes in opioid receptor-associated second messenger systems (Mao et al. 1995).

Neuroplastic changes involving activation or inhibition of intrinsic inhibitory systems contribute to the formation of pathological pain such as hyperalgesia. As indicated by **WIESENFELD-HALLIN et al.,** an understanding of the mechanisms of the pathological pain should lead to new strategies for treatment.

Sympathetically maintained pain: Confusing classification, ill-defined diagnostic criteria, and puzzling pathophysiology

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Abstract: Recent studies indicate a role of the sympathetic nervous system in acute and chronic pain. However, the terminology of the clinical sympathetically maintained pain (SMP) syndromes continues to be confusing and the criteria for diagnosis of SMP are being refined. (**BLUMBERG et al.**) Despite significant progress in recent years, the mechanisms of the interaction between the sympathetic and sensory systems in SMP remain puzzling.

Traditionally, the sympathetic nervous system (SNS) has been considered as the involuntary system that controls diverse, but vital, peripheral functions. More recent studies have indicated that the SNS is not only involved in the adaptive reaction to pain, but also plays a part in the pathophysiology of pain and hyperalgesia. The mechanisms of the interactions between the sympathetic and sensory systems, however, continue to puzzle investigators in this field.

In their target article **BLUMBERG et al.** highlight the varying presentations of patients who have a sympathetic component to their pain (sects. 2 and 3). They suggest that these patients can be characterized as having reflex sympathetic dystrophy (RSD), sympathetically maintained pain (SMP), and causalgia on the basis of the clinical picture. Although such classifications may lead to improved treatment of these chronic pain syndromes, the new definitions proposed by the authors are confusing. BLUMBERG et al. imply that in all 3 groups of patients the SNS may be involved, but only one of these groups is termed to have SMP. Historically, the terms reflex sympathetic dystrophy and causalgia have been used for a wide variety of clinical pain states. The role of the sympathetic nervous system in some of these pain syndromes is unclear. Hence the International Association for the Study of Pain's task force on taxonomy has recently recommended the term CRPS: complex regional pain syndrome (Merskey & Bogduk 1994). The *sine qua non* of CRPS is the presence of regional pain and sensory changes following a noxious event in association with edema and changes in skin color, temperature, and sudomotor activity. The pain is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event. The diagnosis is made after exclusion of other conditions that could account for the degree of pain and dysfunction. CRPS type I (RSD) CRPS type II (causalgia) are differentiated based on the absence or presence of a known nerve injury. In certain patients with CRPS, pain depends on sympathetic activity in the affected areas. That aspect of the pain which is relieved by blockade of the sympathetic efferent function has been termed *sympathetically maintained pain.* In contrast, the pain that persists after sympathetic blockade is called *sympathetically independent pain* (SIP) (Campbell 1992). In patients with CRPS, SMP often coexists with SIP and the relative contributions of SMP and SIP may vary between patients. It is important to understand that the SMP/SIP terminology is an operational definition that is useful from a clinical perspective, since treatment is accordingly influenced.

In our clinical experience, patients with causalgia or RSD often present with almost identical clinical pictures, and only a subset of the patients have SMP. Thus, a classification based merely on clinical presentations might not help in predicting treatment strategies. We agree with **BLUMBERG et al.** that the clinical features of patients who respond to sympathetic blocks varies tremendously. They argue that part of this variability is due to the difficulty in defining a complete sympathetic block (sect. 3.3.3). However, the criteria for defining the adequacy of a sympathetic block have been documented (Malmqvist 1992; Raja et al. 1996). We propose that an important reason for the variability in the clinical presentation is the fact, that SMP is often only a component of the chronic pain syndrome, but seldom the only component (few patients have complete pain relief with sympathetic blockade). Realizing that multiple mechanisms might play a role in the maintenance of these chronic pain syndromes, will be an important step forward in designing a more meaningful classification in the future.

Additional tests that help to identify functional mechanisms of SMP are needed. The authors propose the ischemia test, which has reliably predicted the response to sympathetic blockade (sect. 3.3.1). Other tests to characterize SMP include hyperalgesia to cooling stimuli, pain relief associated with a phentolamine infusion and with topically applied clonidine, and the response to provocative testing with intradermal administration of adrenergic agonists (Wesselmann & Raja 1997). Kurvers et al. (1995) observed disturbances in total skin blood flow that varied with the stage of RSD. They suggest that assessment of this parameter might provide an additional criterion to monitor RSD.

There is controversy regarding whether SMP is due to alterations in sympatho-neural discharge and whether the interactions between the sympathetic and sensory systems are direct or indirect. **BLUMBERG et al.** hypothesize that the pathophysiology of RSD may involve an indirect sympathetic-sensory coupling that results from an abnormal pattern in sympathetic vasoconstrictor neurons (sect. 6). Studies on the cutaneous, microcirculatory vasoconstrictive response suggest that the vascular abnormalities in RSD is the result of autonomic denervation rather than increased sympathoneural discharge (Arnold et al. 1993; Kurvers et al. 1994; 1995). Sympathetic dysfunction is postulated to develop as a result of increased sensitivity to catecholamines consequent to sympathetic denervation. A similar hypothesis has been proposed based on measurements of circulating catecholamines in the unaffected and affected limbs of patients with RSD (Drummond 1991).

Substantial progress has been made in defining the role of the SNS in pain behavior in animal models. Further investigations of SMP states in humans are needed to develop better therapeutic strategies.

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Sympathetic nervous system and pain: Phenomenological diversity

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Abstract: This commentary on **BLUMBERG et al.** addresses complications associated with diagnostic testing for sympathetic dependence of pain that can lead to inappropriate positive and negative conclusions. In addition, it is suggested that their "ischemic" test be conceived as a test of the effect of local vascular pressure and that the two types of sensory disorders presented may differ primarily in the degree of sensitization of central pain pathways. Detailed reports with functionally-oriented testing like that done by BLUMBERG are essential for an understanding the pathophysiological mechanisms.

Introduction. The clinical reappraisal by **BLUMBERG et al.** of the involvement of the sympathetic nervous system in pain illuminates some phenomenological and functional differences in sensory, motor, and vascular processes that occur in the patient population. In that article, the investigators propose a conceptual framework for two syndromes plus a third that is a combination of the two; they also describe specific diagnostic methods for differentiation between the syndromes. These concepts and methods can help us to understand the neurological and neurovascular origins of these disorders, but it is important to acknowledge that there is little consensus among investigators regarding the characteristics that typify a particular syndrome or regarding the number of related syndromes with sympathetic involvement.

Detailed clinical evaluations like **BLUMBERG**'s serve an extremely important function in helping to identify the diverse phenomena that are found in the clinic and in the development of clinical tests of the underlying pathophysiological processes. Only with work utilizing knowledge of basic mechanisms can we develop an adequate understanding of these complex disorders.

Basic science studies of sympathetic/sensory functions have revealed an increasing number and diversity of sympathetic/sensory interactions that can occur at different sites, some of which are noted below. Many of the newer discoveries are not discussed in the short target article or in clinical articles by others, as their relevance to human syndromes is largely unknown.

In this commentary, I will critique and expand on some of the issues raised by **BLUMBERG et al.**; I will also suggest alternative descriptors and review additional findings that may help to identify mechanisms through which the sympathetic system influences pain.

Diagnostic categories. **BLUMBERG et al.** propose the use of three diagnostic categories: (1) reflex sympathetic dystrophy (RSD); (2) sympathetically maintained pain (SMP); and (3) RSD/SMP or "causalgia." Their case reports illustrate distinct differences within the set of sympathetically dependent sensory/motor disorders. The categories they propose are preferable to the historical use of the single category of RSD and are also potentially more meaningful in terms of mechanisms than the recently adopted term Complex Regional Pain Syndrome (CRPS; Stanton-Hicks et al. 1995). However, other case reports could be presented to challenge the notion that there are only three different categories of pain relating to sympathetic function, and that is the reason for adoption of the CRPS label.

It seems most useful scientifically that well-defined, functionally identifiable descriptors of sensory and motor phenomena be developed, as **BLUMBERG et al.** have done. If the phenomena are accurately described and adequately tested, then clinicians and scientists can begin to examine mechanisms in a more productive manner, and an understanding of mechanisms will make it easier to develop methods for prevention and treatment.

From the phenomena illustrated by **BLUMBERG,** one might propose the following functional descriptors:

1. Sympathetically maintained conditions, including deep pain, superficial pain, mechanical allodynia, cold allodynia, edema, postural tremor, and high (or low) skin temperature or sympathetically independent conditions.
2. Pain dependent on local vascular pressure or pain independent of local vascular pressure.

An elaboration of the meanings of these descriptors is given below, together with a listing of complications associated with clinical bases for adoption of the descriptors.

Sympathetically maintained conditions. This descriptor simply means that the condition (e.g., deep pain or cold allodynia) is maintained by or is dependent on sympathetic postganglionic neurons. Diagnostic testing can be accomplished by anesthetic ganglion block or by depletion of transmitter by guanethidine (but see below). As **BLUMBERG** emphasizes, it is essential that the efficacy of the procedure be unequivocally determined before one concludes that a condition is sympathetically *independent.* It is also essential that a conclusion of sympathetic dependence be made only after adequate placebo testing (see below). Reports regarding sympathetic dependence or independence should also state whether the determination is based on *immediate* results or on *long-term* results, or both.

One methodological issue mentioned but not emphasized by **BLUMBERG** is the necessity for adequate placebo testing. Remarkably effective, long lasting pain relief is produced by pharmacologically inert procedures (e.g. saline infusion) in many patients having persistent pain (Fine et al. 1994; Verdugo & Ochoa 1993). Because the pain relief in response to a placebo infusion or injection typically develops only after a latency of 30–60 minutes, adequate placebo testing requires a long procedure.

Complications associated with diagnostic testing for sympathetic dependence include the following.

1. Animal studies have shown that inflammatory processes can be dependent on the *presence* of sympathetic terminals, even in the absence of *activity* in the sympathetic efferent fibers (Coderre et al. 1991); therefore pain related to inflammation may be sympathetically dependent but not attenuated by transient sympathetic blocks. Clinical methods for diagnosing such a condition without irreversible ablation of postganglionic efferents have not been developed.
2. Animal studies have shown that both sympathetic efferent and somatic afferent neurons express different quantities of neurologically active peptides as a consequence of axonal injury (Hyatt-Sachs et al. 1993; Levine et al. 1993) or inflammation (Woolf 1996); therefore, sympathetic and sensory functions are state dependent and may differ significantly over time and with changes in extraneural conditions.
3. Regional guanethidine infusion may activate primary afferents and thereby produce sensitization of central pain pathways. This sensitization may mask the benefit of a subsequent reduction in afferent activity due to transmitter depletion.
4. Sympathetic actions on afferents in the dorsal root ganglia have been shown to induce afferent activity in nerve-injured animals (Chung et al. 1993; 1996; Michaelis et al. 1996); however, diagnostic regional blocks with guanethidine will not affect sympathetic actions that take place in the dorsal root ganglia. Thus, a false conclusion of sympathetic independence may be reached with guanethidine testing.
5. Anesthetic ganglionic blocks also suppress incoming activity from visceral afferents. The suppression of visceral afferent activity might lead to an unjustified conclusion that pain is sympathetically dependent when it is actually a referred pain of visceral origin (Kramis et al. 1996).

Pain dependent on local vascular pressure. Two cases are presented by **BLUMBERG et al.**: in one, the deep pain is relieved both by elevating the hand and by vascular occlusion, described as producing local "ischemia." The diagnostic procedure of transient arterial occlusion is a simple test with useful functional implications. I suggest, however, that this not be described as an "ischemic" test but rather as a test of dependence on local vascular pressure. It is highly unlikely that tonically active nociceptors are silenced by a couple minutes of ischemia; it is more likely that

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nociceptor activity is immediately reduced by a decrease in local capillary pressure or capillary distension. This interpretation is consistent with the fact that distal exsanguination is part of the diagnostic procedure; if the pain relief was induced by ischemia, exsanguination would not be necessary.

The pain in BLUMBERG's case report 1 was found to be relieved by sympathetic block as well as by elevation and arterial occlusion. I suggest, therefore, that in this and similar cases, the symptoms be described as including *both* sympathetically maintained pain *and* pain dependent on local vascular pressure. This would convey accurately the facts that the pain was dependent on both sympathetic efferent activity and local vascular pressure. It is conceivable that two separate phenomena contributed to this patient's pain, one related to sympathetic activity and one related to vascular pressure, and an understanding of the pathophysiology might best be accomplished by acknowledging the existence of both, not just the vascular dependence.

Other issues. BLUMBERG emphasizes that sympathetically maintained pain (SMP) occurs mostly in nerve-injured individuals. Reports from others also suggest that SMP is most common after nerve injury, however, there are many examples in the literature of pain relieved by sympathetic block in the absence of detectable nerve injury (e.g., Price et al. 1989). BLUMBERG's case 1 was apparently not nerve-injured, and the pain was relieved by sympathetic block, so it may be functionally misleading to conclude that SMP occurs only after nerve injury.

BLUMBERG stresses that SMP is most commonly reported as "superficial" pain, whereas the pain associated with his RSD category is most commonly a "deep" pain. One possible explanation for the difference, when both conditions are precipitated by an injury to or pathology of deep somatic tissues as in his examples, is the following. The difference in the locus of perceived pain may be determined by the degree of sensitization of central pain pathways. Activity of deep somatic nociceptors that is sufficient to produce sensitization of spinal dorsal horn neurons would tend to make the neurons hyper-responsive to input from cutaneous mechanoreceptors that converge onto the same neurons (Gillette et al. 1994; Roberts 1986). Therefore, tactile stimuli may activate spinal nociceptive neurons and produce pain – this sensory abnormality may be the predominant sensory experience.

The cutaneous hypothesia and the deep pain reported in case 1 were both relieved by sympathetic block. The relief of hypoesthesia in such cases could be regarded as indicative of a supratentorial (i.e., psychogenic) origin for the hypoesthesia. However, the improvement in hypoesthesia that accompanies pain relief is more simply explained by the fact that pain attenuates tactile sensibility in humans (Apkarian et al. 1994).

Sex differences in pain do exist: The role of biological and psychosocial factors

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Abstract: The evidence favoring sex differences in pain seems compelling (BERKLEY). This commentary considers the role of such factors as anxiety, somatosensory amplification, and coping style in accounting for the differential response to pain in the laboratory and clinic, and emphasizes the need to base evaluation and treatment upon individual reports rather than gender-based stereotypes.

BERKLEY doesn't really seem to want to leave the reader with the impression that "the most striking overall feature of sex differences in reported pain experiences is the apparent lack of them" (sect. 4, para. 3). Indeed, she devotes more than half her article to a deductive analysis of biological differences which ought to lead to a sex imbalance, adds a detailed table which lists nearly 40 painful disorders with female prevalence (including many that are chronic, difficult to treat, and of unestablished etiology) compared to 15 with male prevalence, and provides a review of laboratory studies, most of which show lower pain thresholds and tolerance levels and higher pain ratings for women than for men.

I am also led to conclude that, in general, there are "powerful sex differences in the operation of pain mechanisms" (Abstract, p. 1). The important question is not "whether" but "why?" Consideration of the literature indicates that both biological and psychosocial factors are critical in understanding differential performance in the laboratory and differential presentation in the clinic. BERKLEY carefully reviews many of these. I would like to emphasize some and mention several more.

One is anxiety, for which there are marked sex differences in both humans and animals (Rollman 1995). BERKLEY cites the finding by Lautenbacher and Rollman (1993) that there are sizable sex effects for pain threshold, tolerance, and perceived magnitude when subjects are tested with electrocutaneous stimuli but not when more familiar and less threatening thermal stimuli are used. Elsewhere (Rollman 1995), I describe a study in which subjects reported, on a ten-point scale, the intensity of the stimuli at their pain tolerance. Women's tolerance for electrical stimuli was at a point they themselves described as 5 on the scale (moderate), whereas men went to nearly 7. For cold and pressure, the ratings were higher and the sex differences were much smaller. In other experiments, women predicted that they would have lower tolerance than men and exhibited greater pre-testing state anxiety.

Some of these differences may relate to biological factors. Anxiety in humans is influenced by two alleles of a gene encoding a transporter for serotonin (Lesch et al. 1996). Enkephalin-deficient mice are more anxious than those which are genetically sound and exhibit marked differences from controls in supraspinal responses to noxious stimuli (Konig et al. 1996). Patients suffering from temporomandibular disorders (a syndrome in which most patients are women) show markedly enhanced release of cortisol in a social stress paradigm (Jones et al. 1997). Estrogen binding at receptors on the corticotrophin releasing hormone (CRH) gene link the hypothalamic-pituitary-adrenal response to stress and female sex hormones (Vamvakopoulos & Chrousos 1993). Patients with fibromyalgia (another disorder in which most patients are women) show weakened degrees of pain inhibition when tested in a diffuse noxious inhibitory control (DNIC) paradigm (Lautenbacher & Rollman 1997). Findings such as these point to possible mechanisms underlying sex differences in the laboratory and the clinic, but they do not fully explain which biological factors are responsible for the onset of pain disorders and which for their augmentation and maintenance.

Other experimental differences, as well as some of the differential prevalence and incidence of clinical pain problems, seem to be due to sex-related affective and cognitive variables which contribute to the evaluation of ambiguous bodily information and the decision to seek medical intervention. Anxiety, monitoring of physical sensations, symptom attribution, and coping are related in fibromyalgia (McDermid & Rollman 1996). Somatosensory amplification is much stronger in women than in men, predicts the propensity to seek medical care, and is correlated with hypochondriacal symptomatology (Barsky & Wyshak 1990). Females are reported to carry on culturally-specific patterns of pain response longer than males (Rollman 1997). Women report higher levels of catastrophizing ideation when describing thoughts or feelings related to pain (Sullivan et al. 1995).

The variables presented in this commentary, as well as the much longer list supplied by BERKLEY, raise difficult issues about sex differences in pain. They do not distinguish definitively between pain experience and pain expression. They do not indicate which individual characteristics are immutable and which can be modified by pharmacological and psychological interventions.

There may be a temptation on the part of both the healthcare system and society at large to blame women for heightened pain sensitivity or responsiveness, even though many of the affective and cognitive factors as well as the sensory ones have increasingly

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understood genetic bases. The suggestion that there are sex differences in pain response should not provoke differential evaluation of pain reports based upon sex. This would be wrong and unethical. Pain patients, regardless of sex, need to be evaluated as individuals. Only they are able to describe their suffering; medical personnel must act independently of sex in alleviating their distress.

Central inhibitory dysfunctions in neuropathic pain: What is the relationship between basic science and clinical practice?

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Abstract: The possible dysfunction of γ aminobutyric acid (GABA) and opioid inhibitory mechanisms following central and peripheral nervous system injury is an important and potentially useful finding. However, effective clinical application must take into account the specific characteristics of the models used in the studies and the relationship of these models to specific clinical conditions. **[DICKENSON; WIESENFELD-HALLIN et al.]**

WIESENFELD-HALLIN et al. provide an excellent review of studies which appear to indicate the possible dysfunction of γ aminobutyric acid (GABA) and opioid inhibitory mechanisms following central and peripheral nervous system injury. Both of these mechanisms may have a central role in the development and maintenance of neuropathic pain syndromes. The insights in this review reflect the thorough and extensive research that has been conducted by WIESENFELD-HALLIN et al. in this area.

The information contained in this target article is important for several reasons. First, the findings in the review regarding GABAergic dysfunction have direct and immediate application for the management of neuropathic pain. Particularly in the field of pain following spinal cord injury, the findings of this group provide the most comprehensive and systematic evaluation of the mechanisms of allodynia in this condition and provide important direction for clinical treatment. Secondly, the role of cholecystokinin (CCK) in the loss of opioid sensitivity has important implications which, if addressed, may lead to more effective use of opioids in neuropathic pain and perhaps pain of other origins. Thirdly, the conclusions that are drawn regarding the GABAergic and opioidergic controls that exist at a spinal level have wide ranging ramifications, not only for our understanding of neuropathic pain following central nervous system and peripheral nervous system injury, but of the processing of pain in general.

Although the findings reviewed by **WIESENFELD-HALLIN et al.** are important, several considerations must be taken into account when evaluating their significance and potential application. As presented, there is a strong case for the role of GABAergic mechanisms in the development of pain in the acute phase following ischaemic spinal cord injury. However, the exact role of GABAergic mechanisms in the development of pain following peripheral nerve injury is less clear. As described in the review, there is evidence for cell death following peripheral nerve injury (Sugimoto et al. 1990). However, the changes induced by peripheral nerve damage appear to be partly dependent on the type of injury. The model of peripheral nerve injury used by the authors of this review is the axotomy model. However, as recognised by the authors, this model results in characteristics which are different from other models of peripheral nerve injury that cause a partial injury, such as the chronic constriction injury (CCI) model. For example, completely different results regarding $GABA_B$ receptor binding and dorsal horn levels of GABA are found depending on whether the axotomy (Castro-Lopes et al. 1995; 1993) or CCI (Satoh and Omote 1996; Smith et al. 1994) model is used. Therefore, changes which are demonstrated must be seen as specific to the model used in the study.

The mechanisms of opioidergic controls in the modulation of nociceptive and neuropathic information are also complex. Although the role of CCK in the regulation of opioidergic systems is emphasised in **WIESENFELD-HALLIN et al.**'s article, there are several other mechanisms that have been implicated in changing the responsiveness of the opioid system. They are listed in the target article by **DICKENSON** and include: the effects of morphine 3 glucuronide; increased levels of dynorphin; and activation of the N-methyl D-aspartate (NMDA) receptor. Despite this, the use of CCK antagonists provides an attractive possibility that may be useful in the management of neuropathic pain and opioid tolerance.

The discussion regarding the role of GABAergic dysfunction highlights one of the problems faced by those who are attempting to elucidate the mechanisms of neuropathic pain. This is the danger of seeing neuropathic pain as a single entity. In this article, the impression could be given that the mechanisms underlying peripheral and central neuropathic pain are similar, if not the same. However, as was discussed earlier, even the changes induced by different models of peripheral nerve injury appear to be different. Therefore, the specific characteristics that are particular to an animal model must be noted and recognised as a specific type of neuropathic pain that has relevance to a specific clinical problem. Treatment studies must take this into account if successful clinical application is going to occur.

This complexity in animal models is reflected in the clinical situation. Even without considering the differences between peripheral and central nerve injury, there is a complexity about the nature of neuropathic pain following spinal cord injury. For example, people may experience pain that is situated diffusely below the level of the lesion. This type of pain can be readily distinguished from the segmental band of hypersensitivity and pain located at the level of the lesion. This is presumably the type of pain that is being investigated in the studies reviewed in this article. Furthermore, as indicated by the results in these studies, the characteristics of the pain change over time, suggesting that different mechanisms come into play after a certain amount of time has elapsed. Therefore, it is evident that the mechanisms that underlie neuropathic pain in one specific condition, that is, spinal cord injury, are different, depending on the location of the pain as well as the time elapsed following injury. Therefore, while helpful, the results presented in this review must be seen in the context of a variety of complex underlying mechanisms.

WIESENFELD-HALLIN et al.'s review indicates the advances in knowledge that have been made in basic studies regarding the mechanisms underlying neuropathic pain and opioid tolerance. It is to be hoped that careful and systematic evaluation in the clinical setting of GABAergic agonists and CCK antagonists will lead to corresponding advances in our management of this difficult problem.

Novel peripheral mechanisms of opioid analgesia

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Abstract: **DICKENSON** briefly mentions that peripheral opioid receptors somehow become active following inflammation and that the appearance of endogenous opioid peptides at the injury site may be related to immune cell proliferation. Recent findings elucidate the underlying mechanisms in more detail and provide an incentive for the development of a novel generation of analgesics devoid of typical central opioid side effects.

Introduction. **DICKENSON**'s target article comprehensively reviews current understanding of the influence of injury-induced neuronal plasticity on central mechanisms of opioid analgesia. The

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paper briefly mentions that peripheral opioid receptors somehow become active following inflammation and that the appearance of endogenous opioid peptides at the injury site seems to be related to immune cell proliferation (sect. 4.3). Recent information elucidates the underlying mechanisms in more detail. These novel findings underscore the importance of plastic changes not only in the central but also in the peripheral nervous system.

Peripheral opioid receptors and inflammation. Opioid receptors have been demonstrated on peripheral terminals of thinly myelinated and unmyelinated sensory nerves in rats (Stein 1995) and in humans (Stein et al. 1996). Following the occupation of these neuronal opioid receptors by an agonist, the excitability of the nociceptive input terminal or the propagation of action potentials in attenuated and the peripheral release of excitatory proinflammatory neuropeptides (e.g., substance P) is inhibited. These events may account not only for antinociceptive but also for anti-inflammatory actions of opioids in peripheral tissues (reviewed in Stein 1995).

Analgesic effects of locally administered opioids are not readily detectable in normal tissue but they appear very early (within minutes to hours) after the induction of an inflammatory reaction. This suggests that the synthesis of novel opioid receptors is not required but that opioid receptors already preexist on sensory nerve terminals. In inflamed tissue, opioid agonists have easier access to neuronal opioid receptors because the perineurium (a normally rather impermeable barrier sheath encasing peripheral nerve fibers) is disrupted (Antonijevic et al. 1995). In addition, previously inactive neuronal opioid receptors may undergo changes in the inflammatory milieu and be rendered active (Stein 1995). At later stages of an inflammatory process, the peripherally directed axonal transport of opioid receptors is enhanced, which leads to an increase in the number (upregulation) of opioid receptors on peripheral nerve terminals (Hassan et al. 1993). Together, these factors may account for the dramatically increased efficacy of locally administered opioids in inflamed tissue.

Opioid peptides in peripheral tissue. Endogenous ligands of peripheral opioid receptors, opioid peptoids (endorphin, enkephalin, dynorphin), and their respective mRNAs are present in immune cells infiltrating inflamed tissue of animals (Stein 1995) and humans (Stein et al. 1996). These cells include T- and B-lymphocytes, monocytes, and macrophages. To interact with nociceptive neurons and to produce analgesic effects, the opioid peptides must be released. By activation of their respective receptors on immune cells, exogenous corticotropin releasing factor (CRF) and interleukin-1-beta can cause secretion of the opioid peptides and produce potent antinociceptive effects in inflamed tissue (Schäfer et al. 1994). The most important endogenous stimulus for opioid release appears to be locally produced CRF (Schäfer et al. 1996).

Clinical studies. Many controlled clinical studies have examined the peripheral (local) application of morphine (Stein 1995). The most promising and robust results have come from intra-articular administration. The great majority of these studies have reported analgesic effects of small, systemically inactive doses of morphine, administered into the knee joint of patients undergoing orthopedic surgery. These effects are apparently mediated by opioid receptors in the joint (Stein et al. 1996) and they are long lasting, possibly due to opioid anti-inflammatory actions (reviewed in Stein 1995).

Endogenous opioid peptides were also detected in human peripheral inflamed tissue (synovia) (Stein et al. 1996) and these peptides exert potent tonic pain control (Stein et al. 1993). However, these opioid peptides do not interfere with exogenous agonists since intra-articular morphine has equally potent analgesic effects in patients with and without opioid-containing synovitis (Stein et al. 1996). This is surprising because, in the central nervous system, the prolonged elevation of endogenous opioids can lead to a downregulation of opioid receptors and to tolerance, that is, to a decreased effect of exogenous opioid analgesics. Thus, the development of opioid tolerance may be different in the central versus peripheral nervous systems (Stein et al. 1996). This would be extremely interesting for the treatment of chronic inflammatory pain by peripherally selective opioid agonists.

Conclusions. The recognition of peripherally mediated opioid analgesia provides an opportunity for the development of novel analgesic drugs that produce no central side effects (respiratory depression, dependence, addiction, dysphoria, nausea, sedation). The fact that peripheral opioid effects are more pronounced in inflamed tissue may prove advantageous considering that most painful conditions are associated with inflammation (e.g., postoperative pain, cancer, arthritis, trauma, burns). Indeed, several pharmaceutical companies have recently developed opioid compounds that do not cross the blood-brain barrier with promising results in preclinical testing (Giardina et al. 1995).

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Sex differences in descending pain modulatory pathways may clarify sex differences in pain

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Abstract: This commentary addresses the strength of the comparative approach to the study of sex differences in pain. Animal studies can focus our attention on mechanisms of sex differences in these clinical sex differences. Important sex differences are seen in descending pain modulation, thereby providing an explanation for the observation of sex differences in pain perception. **[BERKLEY]**

BERKLEY presents an impressive and important synthesis of the literature on sex differences in pain perception in human subjects with respect to experimentally induced, phasic noxious stimuli and clinical pains of endogenous origin. There are several points on which I wish to comment.

As **BERKLEY** points out, there are numerous reports examining sex differences in the response to widely disparate noxious stimuli in humans. The author is struck, however, by the inconsistencies in the experimental literature, with sex differences being more prevalent for noxious stimuli sharing certain characteristics (pressure and thermal stimuli) and influenced by a wide variety of extra-experimental factors (e.g., hormonal, health-related, motivational, nutritive). My interpretation of the same body of literature is that sex differences in pain perception must be particularly robust, if they are seen so frequently, despite the large number of potentially influencing factors. When sex differences *are* seen, women invariably report greater pain than men; the *direction* of sex differences does not appear to be in question. Preliminary findings from my own laboratory using male and female athletes support this general trend in the literature with respect to noxious thermal and cold stimuli. In fact, when integrating these findings with other findings regarding sex differences in oither sensory modalities and overall body awareness (e.g., Fucci & Petrosino 1983), it is not surprising that females demonstrate a greater discriminability for noxious stimuli.

I believe the strength of the inductive approach to the literature is in identifying the factors that must be controlled in future experiments investigating this question. Given the sheer number of factors that influence pain sensitivity in both males and females, our current experimental designs may not be powerful enough to uncover sex differences in pain perception consistently. Until the experimental literature is in complete agreement on these issues, however, I agree with **BERKLEY**'s admonition to practitioners to refrain from making hasty judgments regarding the clinical applicability of any one study which suggests that males and females might necessitate differential pain management.

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In addition to the deductive approach to understanding sex differences in pain that BERKLEY recommends, I think a strong case can be made for the comparative approach as well. By studying animals, we can get a better understanding of mechanisms underlying sex differences by being able to reproduce them more consistently. Granted that, as in the human literature, a multitude of factors influence the presence of sex differences in pain perception in any one experimental situation (such as stimulus characteristics, time of day, age of subjects), but the removal of social factors seems to allow for a more consistent demonstration of sex differences in pain perception. As in the human literature, when differences *are* seen, female rodents exhibit greater pain sensitivity (as evidenced by lower thresholds to thermal and electrical noxious stimuli) than males (e.g., Kavaliers & Innes 1990; Romero & Bodnar 1986).

Furthermore, striking sex differences in pain modulation in animal subjects can help us re-evaluate our view of sex differences in chronic pain conditions and experimental pain by focusing on the descending component of the pain pathway. Demonstrating pain behavior (including pain report in humans) depends not only on activation of the ascending portion of the pain pathway from peripheral nociceptor to CNS, but also on descending modulation of such incoming pain signals from the brain as first proposed over 30 years ago by Melzack and Wall (1965). Subsequent and ongoing research efforts have identified the experimental factors capable of eliciting this endogenous analgesia (e.g., electrical stimulation, pharmacological intervention, and environmental stress) and they have elucidated the neuronal pathways and neurochemical mediators involved.

Recent research on descending endogenous pain inhibitory circuitry has identified important quantitative and qualitative sex differences in the magnitude of analgesic responses and the neurochemical mediation of such analgesia (e.g., Mogil et al. 1993; Romero & Bodnar 1986). Again, when magnitudinal sex differences are seen, females mount less of an analgesic response than males do, providing an alternate route of explanation of sex differences in clinical pain conditions. When studying the table summarizing sex prevalence in painful disorders provided (Table 1) by **BERKLEY,** it is apparent that not only do more females suffer from chronic pain conditions, but females are over-represented among patients that suffer from fibromyalgia and irritable bowel syndrome, disorders for which identifying a common underlying pathology has been elusive. As BERKLEY points out, the study of sex differences in opioid and nonopioid analgesia pathways is relevant to understanding sex differences in the anesthetic and analgesic properties of drugs. However, sex differences in these systems may be more basic to the understanding of sex differences in the prevalence of chronic pain syndromes. One way to understand sex differences in chronic pain is to look to sex differences in descending pain modulatory circuitry that may normally inhibit these pain messages from reaching the brain. Perhaps a tonically active pain inhibition mechanism that normally acts to inhibit nociceptive information from the joints or gut is disturbed in patients suffering from these syndromes.

Finally, in studying animal models of sex differences in pain and analgesia, it is possible to consider the entire life span of the organism in understanding the ontogeny of such sex differences. When we use the deductive approach, we must also realize that the early life experiences of males and females are different with respect to the hormonal milieu; hormonal influences early in life are capable of inducing permanent changes in nervous system structure and function. These different hormonal environments have recently been shown to affect the existence of sex differences in pain and analgesia in adulthood (Sternberg et al. 1995).

Why can't a woman be more like a man?

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Abstract: BERKLEY's line of reasoning about sex and pain experience suggests a completely different perspective on sex differences in human experimental, clinical, and epidemiological pain research. Although physiological mechanisms may place women at greater risk for pain, women may have found ways to dampen the effect of these mechanisms. Nevertheless, it is a challenge to extrapolate physiological mechanisms in human phenomena from outcomes observed in animal models.

Few pain researchers have been concerned with the difficult task of considering the underlying mechanisms that might contribute to similarities or differences in pain experience on the basis of sex. BERKLEY argues that there are ample biological sex differences to suggest powerful differences in the physiological mechanism of pain transmission, despite the apparently small sex differences that exist in experimental and endogenous pain research. On the one hand, women are clearly biologically different from men and could have substantially different pain experiences; on the other, women seem more similar to than different from men in their pain reports on actual pain experiences. If BERKLEY's arguments about sex differences in the physiological mechanisms of pain transmission are borne out in future research then a radical conceptual shift will indeed be necessary in our efforts to understand the relationships between sex and pain experience. The question changes from "Why do women and men differ in their experiences of pain?" to "How do women dampen the effect of powerful sex differences in physiological pain mechanisms to achieve only small sex difference in their actual pain experience?" Women may know something about pain management that may have useful implications for management of chronic pain.

What do we know about women and pain so far? The most intriguing aspect of reported sex differences in experimental pain are the consistency of the direction of the differences when they occur (approximately half of all existing studies find no difference); lower pain threshold, higher pain ratings, and lower pain tolerance for women. These differences occur in the more rigorous studies and are more often present when the noxious stimulus is electric shock or pressure (Lautenbacher & Rollman 1993). Although there are substantial differences between an experimental and clinical pain context, these sex differences in experimental pain suggest that women may detect endogenous pains sooner than men (i.e., may report pain earlier), and that women may be less willing to ignore and endure such pain (i.e., may seek ways to manage pain earlier).

A number of epidemiological and clinical sample studies have examined sex differences in coping behaviours (Dawson & Adams 1987; Stone & Neal 1984; Verbrugge 1985). Some studies find no sex differences (e.g., Keefe et al. 1991), whereas others find differences related to various strategies. The most compelling sex differences in coping strategies are women's greater likelihood to report using more coping strategies regardless of the specific type of strategy, and women's frequent use of social support strategies. Furthermore, women report more health care utilization for pain, as well as for other health problems. It is possible that women attend to pain more readily and that women manage pain more aggressively than men.

Why would women deal more aggressively with pain than men? As BERKLEY suggests, women may be biologically biased toward an increased risk of exposure to acute, episodic, and recurrent menstrual pain for a substantial proportion of their life. Approximately 60% of women aged 18 to 50 years experience menstrual pain, and of this group, 80% report moderate, severe, or unbearable pain (Taylor & Curran 1985). Unlike many other endogenous pains, menstrual pain does have enough predictability and controllability to facilitate detection and early intervention.

Women also assume more multiple role responsibilities than do

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men, and may have more complex concerns about managing the interference of pain in the activities and responsibilities of daily life (Unruh 1996). Early detection of pain and aggressive management would reduce the interference of pain. Women's early response to pain could improve women's recovery from acute and chronic pain. It could also contribute to the longer life span experienced by women.

Further! If there are sex differences in physiological mechanisms that increase women's exposure to pain, then there may also be counteractive physiological mechanisms to modify this effect, especially when counteractive mechanisms are combined with early and aggressive pain management strategies. And sex differences in physiological pain mechanisms may produce differences in the response of women and men to analgesic regimens (see Berkley 1996; Burns et al. 1989; Gear et al. 1996).

But! The difficulty with BERKLEY's deductive line of analysis are the limitations of animal models for understanding human physiology. Although the physiology of other animals may have parallels in the physiology of the human, psychosocial factors in humans can exert a powerful counterbalance on physiological mechanisms.

Unfortunately, the interaction of psychosocial factors and physiological mechanisms in human pain experience is difficult to control and manipulate in a research context. Outcomes that occur in an experimental context may also occur differently outside of the laboratory setting in a clinical setting.

Does BERKLEY's discussion have further research implications? BERKLEY's discussion about physiological mechanisms should raise questions about the relationship between sex and response to analgesics. This issue is pressing since there is evidence of inadequate pharmacological management of pain particularly for women (but sometimes men) (e.g., Bond & Pilowsky 1966; Calderone 1990; Cleeland et al. 1994; Faherty & Grier 1984).

Why can't a woman be more like a man? Women and men differ in brain chemistry, metabolism, physical structures, and hormonal cycles. Social, cultural, and sometimes religious influences shape and control roles and responsibilities in different ways for women and men. Nevertheless, finding small sex differences in pain experiences when larger differences might be expected, suggests that there are circumstances when women and men are not so different after all!

Sympathetic component of neuropathic pain: Animal models and clinical diagnosis

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Abstract: Although clinical studies and animal models seem to establish an important role for the sympathetic nervous system in many forms of neuropathic and inflammatory pain, there is an ongoing debate on the classification of pain syndromes with sympathetic components. The confusion originates from several sources: failure to acknowledge that the pathomechanism of chronic pain can change during the progress of the disease, which is now strongly underlined by experimental data from suitable animal models. Neuropathic pain is a vaguely defined collection of pain syndromes which includes painful conditions with diverse and largely unknown patho-mechanisms. Clinical diagnosis is difficult and well designed, placebo controlled sympathectomy is rarely performed. **[BLUMBERG et al.]**

Animal data suggest that sympathectomy will affect pain behaviour differently in well established peripheral nerve injury models (Desmeules et al. 1995; Kim et al. 1993; Kinnman & Levine 1995; Shir & Seltzer 1991). Chung's group has reported that post-injury sympathectomy alleviates mechanical allodynia in their spinal nerve ligation model (Kim & Chung 1991). In the same model both mechanical and thermal hypersensitivity was abolished by surgical sympathectomy (Kinnman & Levine 1995). However, the picture is more complicated as in the model using loose ligation of the sciatic nerve (Bennett & Xie 1988), sympathectomy was effective only during the first 10 days after surgery and affected only thermal hyperalgesia. Desmeules et al. (1995) reported that pre-emptive sympathectomy did not affect mechanical hypersensitivity in the model of partial ligation. However, it was effective when performed several months after nerve injury. On the other hand, Shir & Seltzer (1991) described pre-emptive sympathectomy as analgesic, but found exacerbation of pain when sympathectomy was performed at the same time as sciatic nerve lesion. These data tend to support the involvement of the sympathetic nervous system in neuropathic pain; however, they also emphasise the different level of contribution and time course.

The other important issue revealed by studying animal models was the relative independence of sympathetic symptoms (hot or cold skin) from pain related behaviour. Furthermore, no correlation was found between catecholamine content in the affected limb and skin temperature (Wakisaka et al. 1991). Vasoregulation is not under pure sympathetic control; it is also influenced by primary afferents (see Schott 1994). Peptidergic innervation of vessels is common and axon reflex activity is a strong vasoregulator. This aspect also has to be taken into consideration, when "local sympathetic" symptoms are discussed.

The other possible explanation for the discrepancy between catecholamine content and local symptoms is the development of "supersensitivity" to noradrenaline in the painful area. It is well known now that cutaneous primary afferent fibres develop adrenergic sensitivity (Bossut & Perl 1995; McLachlan et al. 1993; Sato & Perl 1991). Under control conditions noradrenaline does not excite primary afferent fibres. However, adrenergic receptors may exist in primary afferents under normal conditions; their role may be modulation of sensory processing in the periphery. After nerve injury upregulation of adrenergic receptors and/or changes in ion channel, expression may create such a condition when sympathetic modulation is amplified. We found that only sensory fibres which develop spontaneous activity after nerve injury respond to noradrenaline (see Fig. 1). Although this response could be blocked by Rauwolscine, baseline activity remains unchanged. These data suggest modulatory function for the sympathetic system in neuropathic plan. Assuming that abnormal, ectopic activity of primary afferents plays an important role in neuropathic pain, sympathetic blockade may have questionable effects which depend on the level of sympathetic contribution.

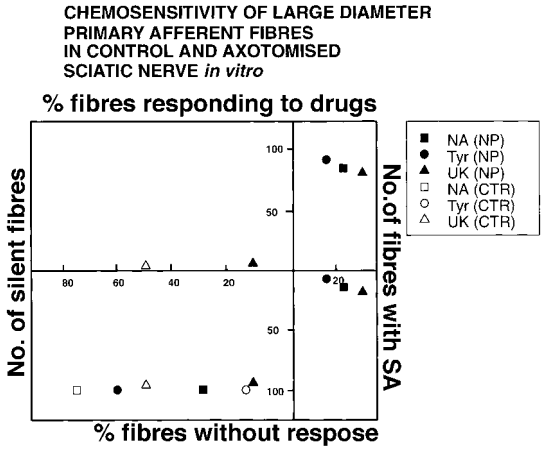


Figure 1 (Urban). Effects of noradrenaline, tyramine, and UK14304 (selective α_2 receptor agonist) on primary afferent fibres from control (ctr) and neuropathic animal (NP) in an *in vitro* model of sciatic axotomy. "Silent fibres" from both control and neuropathic animal were unaffected by either of the drugs, while spontaneously active fibres in the neuropathic animal were overwhelmingly sensitive (for methods see Babbedge et al. 1996).

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The major problem in diagnosing RSD and SMP is the lack of placebo controlled studies. **BLUMBERG et al.** describe a case where sympathetic block (intravenous guanethidine blockade) of the affected limb relieved pain temporarily but repeated block was needed to solve the problem for a long period. During prior treatment, however, only one temporarily successful local anaesthetic block was used. This therapy was not repeated. It accordingly remains inconclusive whether repetition or the nature of the sympatholitic therapy resulted in the success. A placebo controlled study challenges the effectiveness of sympathetic blockade (Verdugo & Ochoa 1994; Verdugo et al. 1994). Ochoa argues convincingly that sympathetic blocks without placebo are irrelevant for the diagnosis of RSD. Furthermore, Dellemijn et al. (1994) reports that "changes in skin temperature following the sympatholytic procedure did not correlate with pain relief."

Recent changes in nomenclature acknowledges the complex nature of RSD (reflex sympathetic distropy) and SMP (sympathetically maintained pain). Complex regional pain syndromes (CRPS; Merskey & Bogduk 1994) reflect more upon the maladaptive imbalance of the sensory, sympathetic, and non-neuronal systems after peripheral injury without overemphasising the role of the sympathetic nervous system.

Sensitization: A mechanism for somatization and subjective health complaints?

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Abstract: The brain seems to be able to generate and uphold sensitization by itself, based on previous experience, or genetic disposition. This seems to be particularly important for muscle pain. There seem to be positive feedback loops where pain produces more pain, and more sensitization. Musculoskeletal pain is the most common pain state. It amounts to almost 50% of all long term sickness absence. But other subjective complaints are also common, and may depend on sensitization. Sensitization has been introduced as an explanation for subjective complaints from the gastrointestinal tract and the brain, like fatigue, tiredness, dizziness, and vertigo. [CODERRE & KATZ]

CODERRE & KATZ provide a very convincing and thorough review of central sensitization as comprised of an initial central sensitization initiated by peripheral pain stimulation. If the initial stimulation is strong enough, the central sensitization may persist in the absence of further sensitization from the peripheral tissue. In this commentary I want to discuss the plausibility of the brain generating and maintaining sensitization by itself – based on previous experience – or genetic disposition.

From a psychoneurobiological point of view, the efferent part of brain-body loops may be the most important clinical aspect. **CODERRE & KATZ** discuss the sympathetic influence on the peripheral tissue, but the central control of the dorsal horn should also be taken into account. It seems reasonably well documented that these mechanisms may form positive feedback loops where pain produces more pain and more sensitization, particularly for muscle pain (Værøy et al. 1988).

However, this may be only the beginning. Positive, self-sustaining feedback loops may well exist also within the central nervous system. This may be particularly important for pain and for other subjective health complaints.

None of the six target articles in this special issue of *BBS* deals with musculoskeletal pain. This is the most common pain state. It is also costly. In Norway, it amounts to almost 50% of sickness absence (Tellnes et al. 1989; Ursin et al. 1993a). Other subjective complaints are from the gastrointestinal tract or the urogenital system, or are "pseudoneurological" complaints, like fatigue, tiredness, dizziness, vertigo, and headaches. When pronounced, the complaints may qualify as a "mental disorder" under the DSM IV criteria for somatization disorder (American Psychiatric Association 1994). However, most cases receiving long term sickness compensation, or permanent disability, do not meet the criteria for any "mental disorder."

In these patients the neurons in feed-forward and positive feedback loops may have developed sensitization. These patients tend to show an abnormal sensitivity to sensory input from muscles, the gastrointestinal tract, and to smell and taste. Sensitization has been suggested as an important neurobiological mechanism in chronic muscle pain (Ursin et al. 1993b), gastrointestinal "functional" complaints (Trimble et al. 1995, Wilhelmsen et al. 1995), multiple chemical sensitivity (Bell et al. 1992), and health complaints to traffic noise (Nivison & Endresen 1993).

Somatization as well as the co-morbid disorders major depression, panic disorder, mania, phobic disorder, irritable bowel, ovarian cysts, and anxiety may all relate to kindling of limbic structures (Bell et al. 1992). Kindling is a sensitization of limbic neurones produced by electrical or chemical stimulation (Antelman 1988). Sensitization of multisensory limbic neurones involved in emotional and vegetative regulation processes may explain the high co-morbidity of the subjective states, and the cross-sensitization from one source of stimuli to another (Bell 1994; Bell et al. 1992).

The neurones in the central nucleus of amygdala may be particularly important. They regulate emotions, arousal, and exploration (Jellestad et al. 1991), and produce corticotrophin-releasing hormone (CRH), but respond with increased production to increased levels of glucocorticoids, rather than the expected decrease (Schulkin et al. 1994). A similar alteration in this axis has been reported for patients with chronic pain and post-traumatic stress disorders (Yehuda et al. 1996). changes in receptor sensitivity and the regulation of CRH and glucocorticoids may be a consequence of the sensitization in self-sustained intracerebral feedback loops.

Finally, the kindling/sensitization hypothesis may offer an explanation for the high correlation between somatization phenomena and reports of exposure to physical, verbal, or sexual abuse (Pribor et al. 1993). Systematic over-reporting and unreliable histories are part of the DSM IV characteristics of somatization patients. The truth value of the statement of misuse may be questioned, but these patients are more sensitive than the rest of the population, and their traumas make them even more vulnerable.

The case of the missing brain: Arguments for a role of brain-to-spinal cord pathways in pain facilitation

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Abstract: This commentary on **CODERRE & KATZ, WIESENFELD-HALLIN et al.,** and **DICKENSON** focuses on: (a) the brain as an under-recognized contributor to pain facilitation at the spinal cord; (b) these brain-to-spinal pathways being activated by learning or by body infection/inflammation; and (c) the resultant spinal release of anti-analgesic neuropeptides, activators of the NMDA-NO cascade, and activators of glia.

The intent of this commentary is not to criticize, for all of the target articles are excellent scholarly contributions to the understanding of pain processing. Our intent, instead, is to bring into focus a few points which were but tangentially broached by **CODERRE & KATZ, WIESENFELD-HALLIN et al.,** and **DICKENSON.** The points can be summarized as follows: (a) Many investigators assume that peripheral signals that induce pain facilitation do so by providing direct input to the spinal cord. However, the brain is an under-recognized contributor to pain facilitation at the level of the spinal

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cord, and the signals may instead go from periphery-to-brain-to-cord. (b) These brain-to-spinal pathways can be activated by learning or by infection/inflammation in the body. And (c) they result in spinal release of anti-analgesic neuropeptides, activators of the NMDA-NO cascade, and activators of glia. Space constraints allow only 16 references to be provided here.

Brain-to-spinal cord circuitry in pain facilitation. It is becoming increasingly apparent that the brain can, via centrifugal pathways, markedly facilitate pain processing at the level of the spinal cord. Perhaps having evolved to serve a recuperative function, these pain facilitatory supraspinal circuits can be activated in response to learned signals for safety, illness signals that arrive at the brain via vagal afferents, or infection/inflammation signals that arrive at the brain via spinal cord afferents (Watkins et al. 1995; Wiertelak et al. 1992). Many of these afferent signals arise from products released by activated immune cells (Bresnihan et al. 1996; Watkins et al. 1995). Indeed, brain-to-spinal cord pathways are now implicated in forms of pain facilitation once assumed to be intraspinal, such as responses to mustard oil (Urban et al. 1996a), carrageenan monoarthritis (Herrero & Cervero 1996), subcutaneous formalin (Wiertelak et al. 1997), and neuropathy (Pertovaara et al. 1996).

While delineation of central facilitatory circuitries is still in its infancy, the nucleus raphe magnus (NRM) has been repeatedly implicated in a variety of pain facilitatory states, including those activated by learned safety signals (Watkins et al. 1997c), subcutaneous formalin (Wiertelak et al. 1997), neuropathy (Pertovaara et al. 1996), and illness (Watkins et al. 1995). Thus the pain facilitatory mechanisms in this medullary area can come under somatosensory or environmental control, supporting previous electrophysiological evidence of pain facilitation from NRM stimulation (Light et al. 1986). It is intriguing to see that studies of learned safety signals (Watkins et al. 1997c) and of the pain facilitatory effects of neurotensin microinjected into the NRM (Urban et al. 1996b) have independently concluded that a dorsal raphe nucleus to NRM to spinal cord pathway is key, with cholecystokinin (CCK) being a critical mediator of pain facilitation at the spinal cord.

Mediation by spinal cord CCK, NMDA-nitric-oxide, and glia. CCK, in fact, is now clearly implicated in a variety of brain-to-spinal cord pain facilitation circuits. Early studies implicated spinal CCK in modulating analgesia from administered opiates and from centrifugal opiate analgesias produced by environmental stimuli. More recently, spinal release of CCK has been implicate in pain facilitatory circuitry activated by learned safety signals (Wiertelak et al. 1992), illness (Watkins et al. 1994), neurotensin injection to NRM (Urban et al. 1996b), subcutaneous formalin (Yamamoto & Nozaki-Taguchi 1996), and neuropathy (Yamamoto & Nozaki-Taguchi 1995). As noted above, most if not all of these phenomena now appear to be mediated by, or at minimum markedly influenced by, brain-to-spinal cord pathways. Whatever the ultimate source of CCK, it is clear that CCK released in spinal cord can both block opiate analgesias and, at higher doses, directly cause hyperalgesia (Urban et al. 1996b). One last item of note regarding CCK is that use of the term "anti-opiate" is likely too restrictive. For anti-analgesia at least, non-opiate analgesias (as inferred by lack of antagonism by high dose naltrexone) produced by epidural GABA-B and 5HT-3 receptor agonists are also abolished by learned safety signals (Watkins et al. 1997b).

Beyond CCK the brain-to-spinal cord pain facilitatory circuits are mediated through activation of the spinal NMDA-nitric oxide cascade. Thus, in these situations, signals from the brain rather than signals directly from the body control activation of these exaggerated pain states. Indeed, the NRM contains spinally projecting neurons that contain substance P, glutamate, and aspartate (Nicholas et al. 1992), key substances in driving NMDA mediated responses. Evidence is accruing that this NRM-to-spinal cord excitatory pathway acts via activation of glia in the spinal cord, resulting in the release of a variety of glial products (e.g., interleukin-1 and nerve growth factor) that are key for the production of hyperalgesia. Interruption of spinal cord glial activation/synthesis can block hyperalgesias induced by either illness or s.c. formalin. A large body of very recent work supports the idea that glia are in fact key links in signal cascades with neurons within the central nervous system (see Watkins et al. 1997a).

Gender differences: Implications for pain management

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Abstract: Despite significant advances in pain research and clinical pain management, little effort has been devoted to exploring whether the same pain treatment strategies are effective for male *and* female patients. Recent studies indicate that sex differences might play a role in the response to noxious events and in the response to analgesic interventions (**BERKLEY**). Further insight into these gender differences will lead to improved pain management for women and men.

In a very thorough and timely review article, **BERKLEY** highlights an important subject: sex differences in pain. Such differences might have important clinical implications for managing patients with acute and chronic pain syndromes (Gear et al. 1996; Unruh 1996).

In most basic science studies and also in clinical research and practice it has usually been assumed that the same concepts can be applied to males and females with respect to pain. The typical subject in pain research has been the male adult rat. It has become apparent, however, that female rodents display differences relative to males on a wide variety of analgesic assays (Beatty & Beatty 1970; Kepler et al. 1989). Similar observations have been confirmed in studies of human pain perception (Feine et al. 1991); women tend to display lower pain detection thresholds and tolerance than men, even when sociocultural factors are taken into account. In addition, the response to analgesic interventions seems to be influenced by gender. For example, female rodents display less morphine analgesia (Baamonde et al. 1989) and less analgesia from the administration of specific mu-, delta-, and kappa-receptor agonists (Kepler et al. 1991). In contrast, in a recent clinical study evaluation the effects of kappa-opioids on pain relief in patients undergoing surgery for removal of their wisdom teeth, females experienced greater analgesic efficacy than males (Gear et al. 1996).

In addition, responses to noxious stimuli as well as responses to analgesic substances depend on the stage of the estrous cycle. During certain estrous stages, proestrus and estrus, rats failed to respond to uterine horn distension (Berkley et al. 1995). In model of cyclophosphamide-induced cystitis (Bon et al. 1996), rats in diestrus exhibited more pronounced signs of pain behavior than rats in estrus. Using a rat model of colonic distension, Sapsed-Byrne et al. (1996) showed that the mean balloon pressure to induce visceromotor responses was significantly lower in rats in proestrus than that in rats in all other stages of the estrous cycle. The response to morphine analgesia varies with the estrous cycle and is attenuated in response to the surge in luteinizing hormone and ovulation (Banerjee et al. 1983; Ratka & Simpkins 1990). Using immunohistochemical techniques, Amandusson et al. (1995) recently demonstrated estrogen receptor-like immunoreactivity in the spinal cord in rats in areas that are involved in the processing of primary afferent nociceptive information, suggesting that the pain modulatory effects of estrogen may be exerted at the spinal level.

We are just beginning to understand the influence of the hormonal milieu on pain and the response to analgesic interventions in females during different reproductive stages. Using the tail flick test, Banerjee et al. (1983) found that rats in the postpartum state showed a marked decrease in sensitivity to morphine. Olofsson et al. (1996) reported in a recent re-evaluation of the

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analgesic efficacy of intravenous morphine in labor pain, that morphine did not significantly reduce the overall labor pain intensity. This is in contrast to the marked efficacy of morphine in other acute pain syndromes, such as post-operative pain after abdominal surgery, which has led to the routine use of patient-controlled-analgesia pumps on surgical wards.

The difficulty we often have as clinicians in managing patients with acute and chronic pain syndromes might be partially due to these sex and chronobiological differences in sensory processing of noxious stimuli as well as differences in responses to analgesic compounds and the variability of their efficacy depending on the hormonal milieu. Future research will have to compare pain perception and pain treatment in males *and* females. In the area of basic science research this will require the development of pain models in female animals in addition to the majority of models that exist so far in male animals (Coyle et al. 1995; Wesselmann et al. 1997). The exploration of the effects of gender and chronobiology on pain opens a new and exciting field for physicians treating patients with acute and chronic pain syndromes, as well as for the basic science and clinical researcher. A better understanding of gender differences in pain is needed, in order to develop improved pain treatment strategies for both men and women.

Central sensitization following intradermal injection of capsaicin

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Abstract: Intradermal capsaicin in humans causes pain, primary hyperalgesia, and secondary mechanical hyperalgesia and allodynia. Parallel changes occur in the responses of primate spinothalamic tract cells and in rat behavior. Neurotransmitters that trigger secondary mechanical hyperalgesia and allodynia include excitatory amino acids and substance P. Secondary mechanical allodynia is actively maintained by central mechanisms. Our group has investigated mechanisms of central sensitization of nociceptive neurons by examining the responses to intradermal injection of capsaicin. These experiments are pertinent to issues raised by CODERRE & KATZ (sect. 2).

1. Effects of intradermal capsaicin injection. Capsaicin injected into the skin of humans causes pain, primary hyperalgesia near the injection site, and secondary mechanical hyperalgesia and allodynia, but not heat hyperalgesia, in the surrounding skin (LaMotte et al. 1991). The pain is immediate and lasts 10–30 minutes. Secondary mechanical hyperalgesia lasts 13–24 h and allodynia 1–6 h. In anesthetized monkeys, capsaicin injections result in an elevated firing rate in wide dynamic range (WDR) spinothalamic tract (STT) cells for over 15 minutes; a lowered threshold for heat responses near but not away from the injection site; and increased responses to innocuous mechanical stimuli applied to skin surrounding the injection site (Dougherty & Willis 1992; Simone et al. 1991). Responses to heat in the area surrounding the injection site are reduced (Sluka et al. 1997). Comparable behavioral changes occur in rats (Sluka & Willis 1997). Paw withdrawal latencies (PWL) to radiant heat applied away from the injection site are unchanged, whereas threshold for paw withdrawal from von Frey filaments is dramatically reduced.

2. Neurotransmitters that initiate central sensitization. Capsaicin injection is thought to initiate central sensitization by activating C nociceptors which release glutamate and substance P in the dorsal horn (see references in Dougherty & Willis 1992). When N-methyl-D-aspartate (NMDA) and substance P are co-released iontophoretically near STT cells, many STT cells show a long-lasting increase in their responses to NMDA and mechanical stimulation of the skin (Dougherty & Willis 1991). Administration of NMDA or NK1 receptor antagonists into the dorsal horn by microdialysis prevents the sensitization of STT cells by capsaicin (Dougherty et al. 1992; 1994).

3. Role of signal transduction pathways. The long duration of the altered pain state following capsaicin injection may reflect the activation of signal transduction pathways. The sensitization of primate STT cells to innocuous mechanical stimuli by intradermal capsaicin injections is blocked by an inhibitor of protein kinase C and mimicked by phorbol ester, suggesting the involvement of protein kinase C (Lin et al. 1996a; Sluka et al. 1997). The sensitization of WDR STT cells is also blocked by inhibitors of guanylyl cyclase and mimicked by 8-bromo-cyclic GMP, which activates guanylyl cyclase (Lin et al. 1997 submitted), suggesting that protein kinase G may also be involved. An inhibitor of protein kinase A also blocks sensitization of STT cells (Sluka et al. 1997). In behavioral experiments on rats, secondary mechanical allodynia following intradermal capsaicin is transiently blocked by inhibitors of G-protein, protein kinase C, protein kinase G, or protein kinase A, suggesting that multiple signal transduction mechanisms are involved (Sluka & Willis 1997). The return of allodynia indicates that it is actively maintained, presumably by activity in central neural circuits, since capsaicin injections produce only a brief (minutes) discharge of C nociceptors (Baumann et al. 1991).

4. Why is there no widespread secondary heat hyperalgesia? Intradermal capsaicin does not produce secondary heat hyperalgesia. LaMotte et al. (1991) propose that capsaicin sensitizes (1) heat-sensitive interneurons by activation of thermal nociceptors and (2) mechanoreceptive dorsal horn interneurons by activation of widely branching chemonociceptors that do not converge on the heat-sensitive interneurons. Mechano- and heat-sensitive interneurons provide separate inputs to wide dynamic range STT cells, with the result that heat thresholds decrease only near the injection site, whereas mechanical allodynia is widely distributed. The STT cells themselves are presumed not to be sensitized. However, after capsaicin injection, primate STT cells are more responsive to iontophoretic application of excitatory amino acids (Dougherty & Willis 1992). Therefore, it is difficult to explain why these neurons do not develop increased responses to heat. Perhaps changes in inhibition are involved. Capsaicin decreases the inhibition of STT cells by iontophoretically released GABA and glycine (Lin et al. 1996b). Changes in inhibition might differentially affect input to STT cells from neural pathways activated by mechanical versus heat stimuli. Specific inhibitory controls might be exerted at a presynaptic level.

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Table 2. Authors' Responses
Distribution of commentators responded to in authors' responses

BERKLEY: Sex differences in pain	MCMAHON: Are there fundamental differences in the peripheral mechanisms of visceral and somatic pain?	DICKENSON: Plasticity: Implications for opioid and other pharmacological interventions in specific pain states
Backonja **Benedetti** **Binik** **Brody** **Clarke** **Ellermeier** **Gijsbers & Niven** **Hardcastle** **Kupers** **Lautenbacher** **Menétrey** **Munafo** **Rollman** **Sternberg** **Unruh** **Wesselmann**	**S. B. McMahon** has elected not to reply to his commentators.	**Backonja** **Benedetti** **Birbaumer & Flor** **Clarke** **Cleland & Gebhart** **Devor** **Gracely** **Han** **Hardcastle** **Hole et al.** **Hu & Sessle** **Marchettini et al.** **Noble et al.** **Omote** **Siddall** **Stein & Schäfer** **Watkins & Maier**

CODERRE & KATZ: Peripheral and central hyperexcitability: Differential signs and symptoms in persistent pain	WIESENFELD-HALLIN, ALDSKOGIUS, GRANT, HAO, HÖKFELT, & XU: Central inhibitory dysfunctions: Mechanisms and clinical implications	BLUMBERG, HOFFMAN, MOHADJER & SCHEREMET: Sympathetic nervous system and pain: A clinical reappraisal
Backonja **Benedetti** **Birnbaumer & Flor** **Clarke** **Cleland & Gebhart** **Devor** **Gracely** **Hardcastle** **Hole et al.** **Hu & Sessle** **Jancsó et al.** **Marchettini et al.** **Ursin** **Watkins & Maier** **Willis**	**Benedetti** **Birnbaumer & Flor** **Clarke** **Han** **Hardcastle** **Hole et al.** **Hu & Sessle** **Marchettini et al.** **Noble et al.** **Omote** **Siddall** **Watkins & Maier**	**Backonja** **Baron & Jänig** **Benedetti** **Clarke** **Elam** **Gracely** **Marchettini et al.** **Raja & Wesselmann** **Roberts**

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Authors' Responses

Female vulnerability to pain and the strength to deal with it

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Abstract: Sex is one of biology's, that is, life's most potent experimental variables. So, are there sex differences in pain? And are these sex differences applicable clinically? The answer to both questions is decidedly yes, of course. But we still have a long way to go. We have much to learn from the study of females, making use of the lifelong changes in their reproductive conditions as experimental variables. We also have much to learn from animals, especially if we apply what we know about their social lives. However, the challenge in all of these studies is not first to look for some mythical neurological entity called pain experience and then to learn how sex modulates it, but rather to seek to understand the rules by which sex influences all of biology's mutually modulatory factors – social, psychological, physiological, cellular, molecular, and genetic – that collectively create the motivating circumstances we designate as pain. It appears almost beyond doubt that on the one hand these factors interact to make women more vulnerable to these circumstances than men, but on the other hand that women have more varied mechanisms for balance. Happily, the details of these sex differences at all levels biological (social to genetic) are now emerging in a rapidly growing body of literature that promises new insights into and applications for the individual person, male or female, in persistent pain.

R1. Introduction

Many authors offered comments on my essay "Sex Differences in Pain": **Backonja, Benedetti, Binik, Brody, Clarke, Ellermeier, Gijsbers & Niven, Hardcastle, Kupers, Lautenbacher, Menétrey, Munafo', Rollman, Sternberg, Unruh,** and **Wesselman.** The issues they raise overlap considerably, and questions brought up by one are sometimes answered by others. I respond here by discussing each issue in turn. The first name listed is that which offered the most pertinent commentary on the issue, followed in alphabetical order by others who also addressed the issue. In addition, commentaries by **Devor, Cleland & Gebhart, Gracely,** and **Ursin** on the issue of central sensitization discussed by **CODERRE & KATZ** are important to arguments here about female vulnerability to pain and are therefore included in that section.

R2. The female as an experimental subject [Gijsbers & Niven, Benedetti, Clarke, Sternberg, and Wesselman]

Gijsbers & Niven state emphatically that "What is needed . . . is a long-term behavioral study of pain in women, which encompasses menstruation, pregnancy, parturition, postnatal menstruation, and menopause." **Sternberg** comments that one must consider "the entire life span," pointing out the need to add prenatal and neonatal considerations of the organizing effects of hormonal milieu. The other commentators emphasize menstrual/estrous influences or pregnancy and parturition.

What underlies these comments is a recognition that changes in the reproductive status of females can be considered natural experimental variables to be exploited experimentally for a better understanding of pain mechanism to the advantage of both sexes. I could not agree more (Berkley 1992; 1993).

R3. Animals as experimental subjects [Sternberg, Brody, Clarke, Gijsbers & Niven, Kupers, Rollman, Unruh and Wesselman]

Sternberg's commentary specifically encourages a comparative approach to understanding sex differences in pain; that is, comparing animals with humans. The effective use by the other seven commentators of a mix of animal and human studies in developing their arguments strengthens hers.

I strongly endorse this important suggestion. A point that both **Sternberg** and **Unruh** make, however, is that one of the supposedly helpful features of using animals such as rats in comparative studies is, as **Sternberg** states, "the removal of social factors." Such a removal would presumably provide better control over other factors. However, all animals are social beings, and thus social factors are omnipresent. Regarding rats, we know that they are nocturnal, huddling animals who live underground in tight tunnels and communicate mainly by odor and touch (Barnett 1963). These social factors are powerful components of the experimental investigation of various physiological processes (Erskine 1989; Pellis et al. 1997), many of them relevant to pain. When scientists isolate rats in individual cages and study them apart from their conspecifics during daylight hours they are removing conspecific social influences, and thus studying their rat subjects in highly unnatural, possibly stressful conditions (i.e., alone with a threatening human and roused from sleep).

Thus, it is indeed important to follow the adage that, "If your subject is a rat, you need to 'think like a rat' " (Becker & Breedlove 1992, p. 5). Doing so might help to develop rat models of cognitive and other social variables that can be used creatively and constructively in studies of various painful pathophysiological conditions (Davis 1996; Berkley et al. 1996; Davis et al. 1997). It is a strength of the comparative approach to pain, to make effective use of what we know about the social lives of our animal subjects.

R4. On separating pain expression from pain behavior: Cognition, learning, stress, response bias, anxiety, and other so-called psychosocial factors [Munafo', Benedetti, Binik, Ellermeier, Gijsbers & Niven, Kupers, Menétrey, Rollman, and Sternberg]

Munafo' states, "What is assessed in the case of pain [experience] is pain behaviour." This straightforward statement succinctly highlights an important point, namely, that

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any interpretation of the significance of any measure of "pain" must take into account all the factors that enter into whatever behavior is being used to assess it. **Munafo'** rightly stresses the importance of learning, arguing that most of the factors that enter into the decision by an individual at any moment to communicate to others by any of a variety of behaviors that an individual is experiencing pain result from a learning history influencing what constellation of personal circumstances comprise "pain" and are appropriate to communicate under the existing situation.

Kupers makes a similar argument in his discussion of cognitive factors, arguing that "boys and girls get different clues from their environment about how [and when] to label their physiological arousal." **Benedetti** stresses that the analysis of sex differences must also take into account the psychological component of pain. **Gijsbers & Niven** concur but add that "situational, temporal, attitudinal, and social factors [which he collectively labels 'psychosocial'] may in themselves be subject to sex differences, which act either to exaggerate or minimise the effects of physiological differences." This point is extended by **Sternberg** and **Menétrey,** who point out that although sex differences in the operation of stress mechanisms and the "hypothalamic-pituitary axis" are likely to play a large role in sex differences in the mechanisms of pain, they are only beginning to be explored. STERNBERG herself is one of several pioneers (Sternberg 1995; **Rollman;** Aloisi et al. 1996; Touchette 1993).

Ellermeier agrees, suggesting that one way to investigate these factors experimentally is to adopt signal detection methodology. This approach allows an investigator to separate "observer sensitivity" from factors collectively called "response bias." Providing a convincing example in his figure, **Ellermeier** goes on to suggest that if this type of analysis were to be retrospectively applied to studies already in the literature, many of the apparent sex differences in them might then be found to have been due entirely to "response bias" and not to "observer sensitivity." In these studies, one might thus have been led to conclude that men are "less willing" to report pain than women, but were not necessarily discriminating (experiencing?) the noxious stimuli differently. **Rollman** argues a similar point, but from another perspective, stressing that sex differences in the many biological, affective, and cognitive features underlying anxiety might "contribute to the evaluation of ambiguous bodily information" so that "somatosensory amplification is much stronger in women" [somatosensory attenuation is much stronger in men?], giving rise to the lessened propensity of men to seek medical care.

These arguments are each well taken, and, as noted by **Binik,** it should be clear from my concluding remarks that I wholeheartedly agree with their collective admonition to consider and to begin to classify all of the many factors that enter into a given individual's "pain behavior" event. On the other hand, all of these arguments (except **Binik**'s) appear to rest on an assumption that there exists some basic immutable biological entity called pain, or pain sensitivity, or pain experience (that may or may not itself possess inherent sex differences) the manifestation of which as pain behavior is modulated by a multifaced array of protean "psychosocial" processes themselves subject to sex differences.

This assumption seems unnecessary and an impediment to our progress in understanding and treating pain. In addition to other problems, it gives rise to such aversive concepts as somatization disorder, somatosensory amplification (or attenuation?), female hyperalgesia (or male hyperalgesia?), pain of psychological origin, response bias, and the like. These terms, some of which may now be temporarily useful in pain care, all serve to encourage a dichotomization of pain into that which is within a normal range and that which is not (pathological), when in fact we all know that a continuum is more appropriate. In other words, we know we can do better.

As we all learned in elementary school, biology is the study of life, encompassing genetics, molecular biology, cellular biology, physiology (the study of groups of cells, i.e., tissues or organs), psychology (the study of individual organisms), and sociology (the highest form of biology, the study of groups of individuals). These various inseparable biological components interact to create within the individual a concept that we have, as a group of individuals, called pain. It is therefore impossible to separate "pain experience" from "pain expression." If we do so, we find ourselves going forever in circles. We only aggravate the problem by trying to designate on the one hand a distinct set of dedicated physiological (or cellular, or molecular, or genetic) mechanisms as the determinant of some sort of basic pain experience or pain sensitivity entity, and, on the other hand, a huge set of "psychosocial" mechanisms that modify pain behaviors.

Sex is one of biology's most potent experimental variables. Sex thereby influences a complex of inseparable and mutually modulatory genetic, molecular, cellular, physiological, psychological, and social factors. In pain research, the enormous challenge is to understand the rules governing these interacting influences and then use what we have learned to reduce suffering.

R5. Increased pain vulnerability in females: The robustness of sex differences in studies of experimentally-delivered noxious stimuli

[Sternberg, Ellermeier, Gijsbers & Niven, Kupers, Rollman, Unruh]

As shown by Fillingham and Maixner (1995), and elaborated in my target article, in about half the studies of responses to experimentally delivered noxious stimuli men rate the painfulness of such stimuli about the same as women, while in the other half men rate the stimuli as less painful than do women. After much discussion of variables that can affect these ratings in either direction, I concluded that, overall, the sex differences were remarkably small. Several commentators took exception to my conclusion (**Gijsbers & Niven, Rollman, Sternberg, Unruh**), arguing that the consistency of the *direction* of differences (i.e., men's pain ratings being lower) should instead be taken to indicate that the differences are in fact "robust" (**Sternberg**). In contrast, other commentators argued that additional considerations, such as response bias (**Ellermeier**) and inconsistencies, particularly in the animal but also in the human literature (**Kupers**), weaken the possibility of sex differences even more than I indicated.

Let me provide three examples of the problem of drawing rational conclusions on this issue.

(1) As reviewed by Fillingham and Maixner (1995), a number of investigators have reported that men rate electrical stimuli as less painful than do women. **Rollman,** however, describes an experiment in which he asked subjects to rate (on a 10-point scale) the pain intensity of

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electrical stimuli at their pain tolerance level. He found that women's tolerance was at a value they themselves described as 5, whereas men's was nearly 7. Thus, one could conclude from the studies cited by Fillingham and Maixner that when stimulus intensity is controlled, women are more sensitive than men. On the other hand, one could argue from **Rollman**'s study that when tolerance ratings are controlled, men are more sensitive than women. In addition, had signal detection methodology been applied, as **Ellermeier** suggests, both of these conclusions might have been different.

(2) In a recent study (Kayser et al. 1996), we found that rat vocalization thresholds to pinching the hindlimb were the same overall in males and females. However, female rats in proestrus and estrus had significantly lower thresholds than those in metestrus and diestrus. Thus, sometimes the females were more sensitive than the males, whereas at other times the males were more sensitive than the females. In addition, we found that thresholds to pinching the base of the tail (an area close to the male rat's scrotum) were always lower in males than females. Furthermore, the same estrous variations occurred in the females. Thus, sometimes males were slightly more sensitive to the base-of-tail pinch than females; other times they were much more sensitive.

(3) In another recent study (Giamberardino et al. 1997), this time using humans, we found that pain thresholds to electrical stimulation of skin and muscles in the arm and leg were about the same for men and women, or, rarely, lower in women than men. Women who regularly suffered from dysmenorrhea, however, had lower arm and leg muscle pain thresholds, particularly perimenstrually, indicating that sometimes, in some circumstances, women were consistently more sensitive than men. On the other hand, we also found that men were so extremely sensitive to stimulation of their abdominal skin and muscle (i.e., a region closer to the scrotum) that they would not permit either male or female investigators to complete the experiment, whereas no such reluctance occurred in any of the women. Thus, for abdominal stimulation, men were consistently more sensitive than the women.

These three examples illustrate why it is impossible to form definitive conclusions regarding the robustness of sex differences in experimental pain sensitivity, much less on their direction.

R6. Increased pain vulnerability in females: Endogenous pains, pleasure, and the relevance of extravisceral structures (vagina, uterus) in women [Brody, Binik]

In contrast to the data from experimental pain studies, it is quite clear from the community-based epidemiological studies of endogenous pain conditions cited in my target article (and earlier by Unruh, 1996) that women suffer from more widespread bodily pains than men, particularly musculoskeletal and visceral. Furthermore, as seen in Table 1 of the target article, there are a great many painful disorders that are more prevalent in women, with ratios sometimes as large as 9:1 (e.g., interstitial cystitis). Only a few painful disorders have a male prevalence. In addition, women regularly encounter painful conditions throughout their lifetime that men do not, such as dysmenorrhea, vulvovaginal disorders, and childbirth (although some might argue that men have their own relatively unique pain-provoking conditions as well; e.g., combat injury, sporting and motorcycle accidents).

In an attempt to understand some of the factors that might contribute to this huge female prevalence of painful musculoskeletal and visceral conditions and more widespread bodily pains (a conclusion with which most of the 14 commentators agreed), I hypothesized that one of many other possible genetic social contributors might be the existence only in women of an additional C-fiber innervated viscus, the vagina. I argued that by means of the well known occurrence of extensive C-fiber divergence along long distances within the spinal cord (Sugiura 1989), women would be more vulnerable to widespread central sensitization initially provoked and then maintained by repeated intense vaginal stimulation.

Brody took exception to this hypothesis, arguing that (a) "vaginas yield far more pleasure than pain" (perhaps only a male could make such a blanket statement, given the many painful vaginal conditions such as vulvodynia in younger woman and vaginal hyperalgesia suffered by most postmenopausal women), (b) vaginal stimulation can produce analgesia and is often pleasurable (certainly true, as also pointed out by **Binik** when discussing the complex mixture of pleasure and pain regularly confronted by sex therapists), and (c) the vagina is "far more resistant to viral invasion than the anus." What **Brody,** but not **Binik,** seems to have missed is my point that whereas men and women have relatively similar visceral organs of digestion (mouth, colon) and elimination (defecation, micturation) and other vital internal C-fiber innervated structures (heart, lungs, liver, blood vessels, etc.), the vaginal canal represents an *additional* visceral structure in women (as does the uterus, see below). It is the addition of this injury-prone and, indeed, under some conditions, highly virus-vulnerable (Marx et al. 1996), C-fiber innervated structure that might contribute, via mechanisms of divergence and central sensitization, to the more widespread pains reported by women and the high female prevalence of painful, primarily musculoskeletal disorders.

R7. Increased pain vulnerability in females: The importance of central sensitization [Devor, Cleland & Gebhart, Gracely, and Ursin]

In their commentaries on **CODERRE & KATZ**'s excellent target article, **Dover, Cleland & Gebhart,** and **Gracely** argue convincingly that the importance of continued peripheral-provoking events in the maintenance of persistent pain suggests that central sensitization might be less important for persistent pain than we now like to think. What is missing from these arguments is a consideration of the origin of the very common chronic and widespread musculoskeletal pain conditions in women (see above), a point made strongly by **Ursin** in his argument for an even greater role of central sensitization, including the brain, than indicated even by CODERRE & KATZ.

This issue is relevant to sex differences in pain, in the following way. It is well known that one characteristic of visceral pain is its referral to parietal structures (e.g., muscles, subcutis, and skin; see **MCMAHON**'s and **CODERRE & KATZ**'s excellent target articles). Recent carefully controlled studies in humans and animals by Giamberardino and colleagues (1993) have shown that visceral pathol-

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ogy, such as passage of a uretal calculosis, produces hyperalgesia mainly in the muscles (and only sometimes in subcutis and skin; i.e., when the visceral pathology is at its peak). This referred hyperalgesia is located primarily in the same segment through which afferent fibers from the pertinent visceral organ enter the spinal cord (called "viscerotomes"; Cousins 1994; Vecchiet et al. 1989). Thus, even though the muscles (or subcutis and skin) themselves evidence no pathology, they are tender. As argued by many, this referred hyperalgesia clearly suggests a centrally generated phenomenon. In addition, Giamberardino's group has shown that the muscle hyperalgesia persists long after the initiating pathophysiology has disappeared. Central sensitization would seem an appropriate mechanism to consider for such persistence. One could argue, however, as do **Devor, Cleland & Gebhart,** and **Gracely,** that the "sensitization" also occurred in the periphery. It would then be input from sensitized peripheral C-fibers that maintained the central sensitization. Therefore, as argued by **Devor,** in order to relieve pain, the most efficient focus would be on developing ways to desensitize the peripheral C-fibers.

However, consider the following findings. In a recent study, Giamberardino et al. (1997) compared muscle and skin pain thresholds (to electrical stimuli) in nondysmenorrheic and dysmenorrheic women in bodily regions located both in uterine viscerotomes (abdomen, left, and right) and other areas (limbs, arm, and leg). We expected that dysmenorrheic women, relative to nondysmenorrheic women, would exhibit muscle hyperalgesia and perhaps skin hyperalgesia in the abdomen, but not the limbs, primarily perimenstrually (i.e., when they were experiencing the strong uterine contractions that give rise to dysmenorrhea; Rapkin et al. 1997). Not too surprisingly, given Giamberardino's earlier studies (1993) showing the persistence of referred muscle hyperalgesia, the dysmenorrheic women in our study exhibited abdominal muscle (but not skin) hyperalgesia not only perimenstrually, but also, to a lesser extent, throughout their entire menstrual cycle (i.e., there was a constant abdominal muscle hyperalgesia in the face of episodic abdominal visceral pain).

Astonishingly, however, the dysmenorrheic women also exhibited muscle hyperalgesia in their arms and legs likewise throughout their menstrual cycle (i.e., there was constant remote, arm and leg muscle hyperalgesia in the face of episodic abdominal visceral pain). These results clearly implicate the importance of central sensitization as part of the mechanisms underlying the widespread muscle hyperalgesia. In other words, the strong episodic uterine contractions, by virtue of the divergence of their C-fiber afferents in the spinal cord, could have produced remote areas of spinal central sensitization, resulting in a widespread muscle hyperalgesia.

The question then arises as to what maintains central sensitization of neurons in spinal segments remote from the initially provoking visceral source. As **Devor, Cleland & Gebhart,** and **Gracely** might argue, it could be that input from sensitized C-fibers innervating the initial provoking viscus maintains it (here, the uterus). On the other hand, a sensitized spinal region can effect parietal structures in those segments (Giamberardino et al. 1993), possibly sensitizing either the peripheral or the central end of the afferents supplying those structures. Afferent input from newly sensitized peripheral afferents (e.g., those from arm and leg muscles) might accordingly contribute to maintaining sensitization of neurons in segments (e.g., those serving arm and leg) that had been initially sensitized by the remote extensions of C-fiber afferents entering the spinal cord much further caudally (e.g., those serving the uterus). If this scenario is correct, then an efficient target for therapy would indeed be central. However, a polytherapeutic approach targeted at both central and peripheral mechanisms would obviously be better (Berkley 1997).

In sum, men do not have a uterus, nor do they have a vagina, both of which are extra visceral female organs subject to episodic intense stimulation or trauma, respectively, and both of which can produce longlasting referred hyperalgesia in muscles as well as in remote regions (Slocum 1984; Murray & Holdcroft 1989; Giamberardino et al. 1997). Thus it may indeed be the case that local and remote central sensitization plays an important role in the maintenance of the many widespread and painful musculoskeletal conditions to which women appear to be more prone.

R8. The strength to deal with it: A conundrum solved (?) [Unruh, Brody, Clarke, Gijsbers & Niven, Lautenbacher]

Most of the commentators agreed with my overall conclusion that men are less vulnerable than women to conditions that both men and women would designate as "pain." What are the mechanisms that create these differences in vulnerability? Much of the previous section dealt with a set of possible physiological processes (additional C-fiber-innervated visceral reproductive structures in women, divergence of C-fiber afferents in the spinal cord, and local and remote central sensitization, including brain), but clearly other processes are at work.

Useful in this context is Wall's (1994) view of the mammalian nervous system (both peripheral and central) as an organ of planning. As Wall sees it, the nervous system is constantly organizing its attached body, for not its current, but its next move. Pain then takes on a different significance – as a motivator. In other words, pain is one of the nervous system's mechanisms for motivating individuals to plan their own care appropriate to the current situation.

For all two-sex mammalian species, a driving force behind "what is appropriate" is its own reproduction (Darwin 1892). For successful reproduction, female mammals must receive sperm from males, preserve its viability, protect the resulting conceptus, and nurture the newborn. For successful reproduction, males must protect the organs that deliver the sperm to females. It is clearly important that any threat to organs of reproduction be dealt with in a manner appropriate to each sex's situation. For females, most of these organs are internal, and thus mechanisms such as those discussed in the previous section for wide dissemination of reproductive-organ-threatening interoceptive inforamtion are entirely appropriate. For males, most of these organs are external, and thus the nervous system's rapid mechanisms for processing exteroceptive information are also entirely appropriate. Both sexes, of course, have mechanisms in place for processing both exteroceptive and interoceptive information (e.g., vulva in females; prostate and testes in males; see also Berkley & Hubscher 1995; Hubscher & Johnson 1996).

What is even more important to the discussion here is how information derived from reproductive organs motivates future action; that is, how that information becomes

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pain. Here all sorts of other processes are at work. These processes range from social/cultural considerations to genetic ones, many discussed above, that together involve the use by the entire nervous system of all accumulated information currently available to it. The net result, evidenced clearly in cross-cultural epidemiological studies reviewed by Unruh (1996) and in my target article, is that men seek less health-care than women and report pains in fewer bodily regions.

At first glance, this situation would seem to place women at a disadvantage relative to men. But further reflection suggests otherwise. **Unruh** states the conundrum clearly: "How do women dampen the effect of powerful sex differences in physiological pain mechanisms to achieve only small sex difference in their actual pain experience?" She then provides a clear answer, which is that women make more aggressive and effective use than men of various coping strategies, health-care utilization, and social support services; she adds that counteractive physiological mechanisms may also exist. **Gijsbers & Niven** provide an excellent example of such processes at work from their own studies, where they found that women in childbirth make use of a "range of behavioural and mental strategies which they have effectively exercised during previously painful experiences" (Niven & Gijsbers 1996). **Lautenbacher** provides an answer similar to **Unruh**'s, stating succinctly that "Perhaps, surprisingly, more pain at the beginning can result in less pain at the end." He remarks that the pain system, like most biological systems, "is a homeostatic one," and points out, as does **Clarke,** that inhibitory and excitatory mechanisms work together at physiological and psychological (and I would add sociological/cultural) levels to balance each other. All of these commentaries provide a strong answer to **Brody,** who objected to what he mistakenly interpreted as my "pathogen model of sex differences in pain" (see my comments above) being "inconsistent with women outliving men by several years."

Unruh's and **Lautenbacher**'s conclusions represent a marvelously creative and useful way of conceptualizing the situation, and I applaud in agreement. If women are indeed more vulnerable to conditions that both men and women have conceptualized as "pain," then by virtue of nature's balancing mechanisms, women will have available to them more biological (i.e., social, individual, physiological, cellular, and genetic) mechanisms for reducing the impact of these conditions. It is then obvious that gaining a better understanding of the details of overall sex differences in pain can be used to great advantage by applying that knoweldge toward improving the health of individuals of either sex.

R9. Pain care [Wesselman, Backonja, Benedetti, Gisjbers & Niven, Munafo', and Sternberg]

Backonja states passionately that "pain can be a sensation or a disorder. A sensation is something we can study in the laboratory dispassionately, but it is quite a different story when we come face to face with a disorder called pain." So, how can we apply what we are beginning to understand about sex differences in pain to the treatment of men and women in pain?

Wesselman provides an excellent review of recent human studies of sex differences in responses to various analgesics and briefly considers emerging evidence in animals on sex differences in endogenous analgesic mechanisms; these are elaborated by **Sternberg. Benedetti** briefly mentions new data suggesting that women may benefit more than men from cognitive/behavioral treatments. While these new data are certainly provocative, I agree completely with the strong statements by **Sternberg, Gijsbers, Munafo',** and **Rollman** that the evaluation and development of treatment protocols for individuals of either sex should focus on the individual's self reports. We are not yet ready, and in fact may never be ready, to dictate different overall pain treatment regimens for females and males. To do so before we have more information could prove harmful to the individuals, and could in the overall delivery of healthcare, lead us back to treatment inequities that we are now so diligently trying to eliminate.

On the other hand, this cautionary note does not mean we should ignore current information, or, worse, discontinue our pursuit of it. Quite the opposite is warranted, as urged in a recent discouraging survey showing that at present, even with governmental pressure to include women in treatment studies, and despite clear emerging evidence in some realms of healthcare that important sex/age differences exist, the issue of gender is not even considered in most studies, and thus gender-neutral treatment recommendations still remain the universal norm (Charney & Morgan 1996).

Five very recent studies, however, provide some optimism.

R9.1. Coronary heart disease. A recent important paper (Douglas & Ginsberg 1996) begins by pointing out that current recommendations for the evaluation of chest pain in women with suspected, but not yet diagnosed, coronary heart disease is based on a model of the disease in men, despite considerable new data indicating important sex differences. The authors then go on to review these new data to arrive at a clear set of recommendations that can be used by attending clinicians when faced with a woman or a man with suspected coronary heart disease. Space does not permit the enumeration of all these differences and recommendations here, but several illustrative examples are as follows:

> 1. Ischemia produces a slightly different pattern of pain in women with known coronary heart disease [than in men]; chest pain while at rest or the presence of other symptoms beyond typical angina during exertion [such as neck and shoulder pain] does not decrease the likelihood of coronary heart disease in women, as it does in men.
>
> 2. The presence of diabetes mellitus is a more powerful predictor of coronary heart disease and its prognosis in women than in men.
>
> 3. Among the elderly, hypertension is a stronger predictor of coronary heart disease in women than in men.
>
> 4. Several researchers have found that a positive exercise test in women is often not followed up with subsequent testing [perhaps because of failure to recognize 1–3 above and other sex differences in signs and symptoms]. . . . Aggressive treatment, including catheterization, of women with positive stress tests is not only clearly indicated but, if anything, may be of greater benefit than similar care in men. (Douglas & Ginsberg 1996)

This exceptional, constructive, and immediately applicable article represents a positive response to Charney and Morgan's (1996) discouraging review and provides a clear example of how best to begin applying what we are beginning to learn about sex differences in pain to the clinic. We must review the emerging literature carefully to assess details of sex differences, use those differences to sensitize us to potentially differential signs and symptoms when diagnosing male and female patients, and apply that knowl-

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edge with great care to avoid inequities when developing treatment protocols for individual men and women.

R9.2. Kappa opioid analgesia. As cited by several of the commentators, a recent article by Gear et al. (1996) has reported that for otherwise healthy and demographically-comparable young women and men undergoing comparable molar tooth extractions, post-operative kappa-opioid analgesics produced larger and longer post-operative pain rating reductions in women than in men. Should this result on a healthy group of young men and women in a specific setting indicate that, when faced with an individual suffering from some persistent pain condition (e.g., bone cancer), kappa-opioids should automatically be the first analgesic prescribed if the individual is a female and some other analgesic if the individual is a male?

Obviously not. Clearly, as discussed in my commentary on Gear et al.'s paper (Berkley 1996), how generalizable these results are to other situations (such as bone cancer) is completely unknown. On the other hand, this important and tantalizing study provides a strong argument for considering kappa-opioid analgesics, particularly in young women patients and particularly when other analgesics prove ineffective. Furthermore, because previous studies on kappa-opioids using only males or failing to assess sex differences had all indicated that these new analgesics were relatively ineffective compared with others in common use, the Gear et al. study also provides a strong argument for addressing sex differences directly in any treatment study. Finally, their study encourages further work to understand the circumstances (and mechanisms) that may create greater effectiveness for kappa-opioids (e.g., see discussion on hormonal involvement in section R9.3) so that these new analgesics may be used more appropriately not only by women, but possibly also by men.

R9.3. Morphine analgesia. As mentioned by **Kupers,** Cicero and colleagues (1996) conducted an important and comprehensive study in rats extending earlier findings by others that morphine antinociception is greater in male than in female rats. What this new study found was that this sex difference was potent in three very different nociceptive assays tested in healthy rats, that is, tail-flick, hot plate, and abdominal constriction tests. They also found that this difference was not due to sex differences in the immediate bioavailability of morphine, because, at the time of peak antinociception, female and male rats had the same peak morphine levels in their sera. This result suggests that the male's increased sensitivity to morphine's antinociceptive properties may be due to an enhanced central nervous system (CNS) sensitivity to morphine, although, as the authors point out, pharmacokinetic studies on morphine remain to be done.

One of the first conclusions following from potent sex differences such as those found above is that the differences depend on sex hormones. Of great importance in this study, therefore, was the fact that two weeks after castration and ovariectomy, when serum levels of all sex hormones were negligible, the rats' responses were identical to those prior to gonadectomy. In support, a recent study on female rats (Gordon & Soliman 1996) showed that, although estrogen and/or progesterone treatment of female rats two weeks following ovariectomy reduced their tail flick and hot plate latencies (i.e., the hormones had antinociceptive effects), there was no increase in brain mu opioid receptor binding. These results suggest that current hormonal status does not underlie sex differences in morphine sensitivity, although, as the authors suggest, they may have an organizational function during development.

Thus, the story unfolding in the animal literature, considerably enhanced by these two studies, suggests that a nonhormonally driven and CNS-derived sex difference exists in the antinociceptive properties of morphine, with males more sensitive than females. However, the issue with regard to kappa-opioid binding is still unfolding. Gear et al. (1996) had found that the analgesic effects do not depend on the women's menstrual stage. Gordon and Soliman (1996), however, found that exogenously administered estrogen and progesterone in ovariectomized rats increased brain kappa-opioid receptor binding. The complex question of hormonal involvement in the mechanisms of analgesia with opioids thus remains to be unraveled.

An important question is how the animal data on morphine relate to humans. This is difficult to answer, not only because little attention has been paid to sex differences clinically (Charney & Morgan 1996), but even more because when morphine is used clinically, it is invariably in cases of pain-associated disease.

It is very well known that morphine affects behavior very differently when used under persistent pain circumstances than when used under pain-free ones. Thus, to Cicero et al.'s (1996) credit, they avoid addressing the issue of morphine's analgesic properties in humans and instead point out possible implications of their findings to the largely anecdotal data suggesting sex differences in substance abuse liability. It is clear, however, that this study calls for further animal research on sex differences in the action of morphine under painful pathophysiological conditions as well as human research on sex differences.

R9.4. Menstrual/estrous stage. It is now becoming apparent that menstrual cyclicity has far ranging consequences in the realm of health-care, with clearcut emerging implications for treatment, prompting urgent calls for research. For example, menstrual stage may be of prognostic importance in surgical treatment for breast cancer (Hrushesky 1996). With regard to pain care, simply knowing that menstrual cyclicity is present, regardless of its basis, hormonal or otherwise, can affect both medically prescribed and self-treatment regimens. For example, for a female with rheumatoid arthritis, knowledge that she will have huge exacerbations perimenstrually and significant ameliorations luteally (Wetherby 1995) would allow her and her doctor to improve her care (e.g., by increasing analgesics just prior to menstruation and scheduling strenuous action-requiring events earlier in her cycle).

It is clear, however, that demonstrations of menstrual or estrous variations must be interpreted carefully before applying them clinically. An important recent two-part study in rats illustrates this point. Holdcroft and colleagues (Holdcroft & Sapsed-Byrne 1996; Sapsed-Byrne et al. 1997) found that thresholds for visceromotor and intracolonic response to colonic distension, but not cardiovascular responses, varied with the rat's estrous cycle. Markedly lower pressures were needed to evoke these responses when the rats were in proestrus than in other stages; in other words, proestrous rats exhibited more abdominal and colonic muscular sensitivity to colonic distension in proestrus than in other stages.

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One interpretation the authors offer is that there may be estrous variations in colonic visceral pain, with pain being greatest in proestrus. However, other interpretations are possible. Another relevant finding in these two studies was that colonic pressures induced by distension did not vary with estrous stage. What this result means is that, during proestrus, smaller fecal boli would trigger defecation.

Proestrus is the reproductive stage in which rats are fertile and most easily aroused by hindquarter tactile stimulation. Thus, it may be that the rat's similarly more sensitive visceromotor and colonic responses to colonic distension during proestrus promote emptying of the colon to facilitate successful fertilization during copulation. Whether there would be an accompanying change in colonic pain is unclear, but seems unlikely. Supporting this interpretation is the finding that cardiovascular responses showed no estrous increases during proestrus. Thus, the clinical relevance of these findings might be more applicable to gastrointestinal motility issues (Wald et al. 1981) than to colonic pain. But, of course, as discussed above in section R9.3, all of these conclusions might change under conditions of colonic pathophysiology (Giamberardino et al. 1997).

R9.5. Sex hormones. It is often a knee-jerk response to assume that any sex or estrous/menstrual stage variations in an entity are due to sex hormones. As discussed in section R9.3 above, this assumption is clearly unwarranted until further study has demonstrated it. Although the issue of sex hormones and pain is an important one, few, if any, human studies have focused on it.

Finally, however, a recent study has directed its full attention on the impact of hormones on a pathophysiological pain condition in humans. In an elegant and well-controlled epidemiological study based on automated pharmacy records of women enrolled in a large health maintenance organization in the northwestern United States, LeResche and colleagues (1997) found that the odds of having temporomandibular disorder pain were increased by approximately 20% and 30%, respectively, in young women who used oral hormone contraceptives and postmenopausal women who used estrogen (or estrogen and progestin) replacement therapies. For the postmenopausal women, these odds increased with increased doses of estrogen. No clearcut increased risk was observed with progestin use.

Although an immediate conclusion from these findings might be that women and their doctors should add an increased risk of temporomandibular pain to their list of cons when weighing the pros and cons of oral contraceptive or estrogen replacement therapy, the authors themselves are rightly very cautious and self-critical in their assessment of the implications of their findings. They make no statements on the clinical applicability of their findings. However, they rightly point out the provocativeness of their findings and provide a long list of future studies to test how generalizable their findings are to other populations and other painful disorders. If their findings do prove generalizable, then understanding the mechanisms that give rise to this increased risk will certainly have a powerful clinical impact.

In sum, these previous five sections not only provide convincing arguments that sex is one of the potent factors underlying pain, they also indicate that progress is well underway toward a better understanding of how to apply the information clinically.

R10. Conclusions [Kupers, Binik, Rollman, and Gijsbers & Niven]

Are sex differences relevant to mechanisms of persistent pain and its treatment? **Kupers,** via Molière, provides a clear answer: "oui et non." I here provide a less clear one: "yes."

Gijsbers & Niven remind us that our conclusions should be based "not on the insignificance of sex differences in behaviour and perception but on their complexity," and that only through further study will we "come to understand the extent to which individual differences in suffering are dependent on generalisable sex differences." **Rollman** states that when it comes to caring for a single human of either sex, we "need to base evaluation and treatment upon individual reports rather than gender-based stereotypes." **Binik** points out that "pain and pleasure researchers have something to learn from each other." I cannot say it any better.

Pains, brains, and opium

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Abstract: In this response, I discuss the roles of the peripheral afferent drive in the maintenance of persistent pain, the concept of preemptive analgesia and the importance of the brain, the detailed involvement of which in pain is far less well understood compared to the events in the spinal cord. A comparison of pain to other sensory modalities is then made together with a discussion of learning and pain. These facets of pain are discussed in the light of treatment strategies for this condition.

R1. Introduction

First and foremost, I wish to say how much I enjoyed and appreciated the comments. One of the great joys of science is communication, and these open and frank views, with their benevolent and constructive comments, illustrate the ways in which advances in a subject can occur via interactions as well as by research. It should also be noted that the comments are from both scientists and clinicians. The remarkable advances in the understanding of pain transmission and control that have arisen over the last decade are in no small part due to dialogue and interactions between these two groups. It is difficult to imagine many other areas of neuroscience where science and clinical medicine are so well integrated. However, we are still using opium and derivatives of the bark of the willow to combat pain – it is perplexing that, given the number of targets that there are for the control of pain,

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the pharmaceutical industry has not developed a single novel analgesic.

R2. Pain starts in the periphery

Where does one start when discussing pain? Logically, where pain starts, and so to the periphery.

A theme that arises in a number of commentaries is the relative role of peripheral activity and central hypersensitivity in setting the level of pain transmission. **Devor, Gracely,** and **Cleland & Gebhart** all raise this point. The issues here are twofold: (1), whether central hypersensitivity can occur in the absence of peripheral activity and (2), the relative importance of peripheral and central activity in the generation of the final sensations.

Because both the above authors and I believe that central hypersensitivity cannot occur in the absence of peripheral activity (see sect. 7.1), the second point I feel is easily handled. As peripheral activity will go nowhere without central transmission and central hypersensitivity needs peripheral activity, the two are intimately linked. Thus blocking either would be effective. Which would be most effective? The actual levels of activity produced by each is one issue. The points made by the three commentators are important ones. Both **Gracely** and I discuss the effects of combination therapy because, as pointed out by **Gracely,** NMDA antagonists would only reduce the sensitized components. Thus, I feel that an NMDA antagonist plus morphine could be the most effective approach to pain control with centrally acting agents, because spinal opioid analgesia, by virtue of the predominant presynaptic actions of opioid receptors in blocking primary afferent transmitter release, would synergize with the postsynaptic reduction in hypersensitivity produced by NMDA blocker (sect. 7.1). The advantage here is that low doses of each could be used and so reduce side-effect liability.

This approach could provide excellent pain relief in situations of tissue damage. A problem is that in neuropathic states, opioids are less effective and there are as yet no studies in humans on the effects of this combination after nerve injury. Here I refer to the commentary of **Backonja,** who agrees with the point I made that morphine needs to be tried in neuropathic pain patients and the dose escalated to a maximum before other approaches are tried. Jadad et al. have shown that some neuropathic pain patients do well on opioids. The commentary of **Marchettini et al.** on the differentiation of neuropathic syndromes and that on the fact that opioids can work in some situations reinforces these points and lends further support to the idea that lumping together all the varieties of nerve damage is counterproductive. Subdivided neuropathic syndromes may reveal certain symptoms that respond to opiates. Note also (sect. 9) that some measures of behaviour in animal models of neuropathic pain respond to morphine whereas others do not. The same point is made by **Siddall,** to whose comments I will return later in the context of inhibitions.

It is also true that blocking the peripheral activity will be equally efficient, as suggested by **Devor, Gracely,** and **Cleland & Gebhart.** I entirely agree with **Cleland & Gebhart** that the basic studies (paras. 7 and 8) suggesting that hyperalgesia persists after nerve block may well be flawed by technical problems. So, since we all agree on this issue, what would be the best approach? I suppose that with, for example, neuropathic pain, an ongoing local anesthetic block is impracticable so the question remains as to how to block persistent peripheral drives. The recent description of unique sodium channels in small diameter peripheral fibres may be a great target (Akopian et al. 1996) but whether selective blockers can be developed is another question. These agents would not influence allodynia.

R3. Stopping pain before it starts

The implications of the degree of peripheral drive for the concept of pre-emptive analgesia are then developed by **Devor, Gracely,** and **Cleland & Gebhart.** The point about the need for relentless block for acute pain management (**Gracely**) is borne out by our study (sect. 7.2) in which the timing of morphine treatment on the formalin response was used. This is illustrated in Figure R1. I agree entirely with the points made by **Cleland & Gebhart** and illustrated in their diagram. I have been using Figure R1 for talks (a case for parallel evolution?) because it makes the same points but also points out that pre-emptive treatments for tissue injury may also pre-empt beneficial evoked inhi-

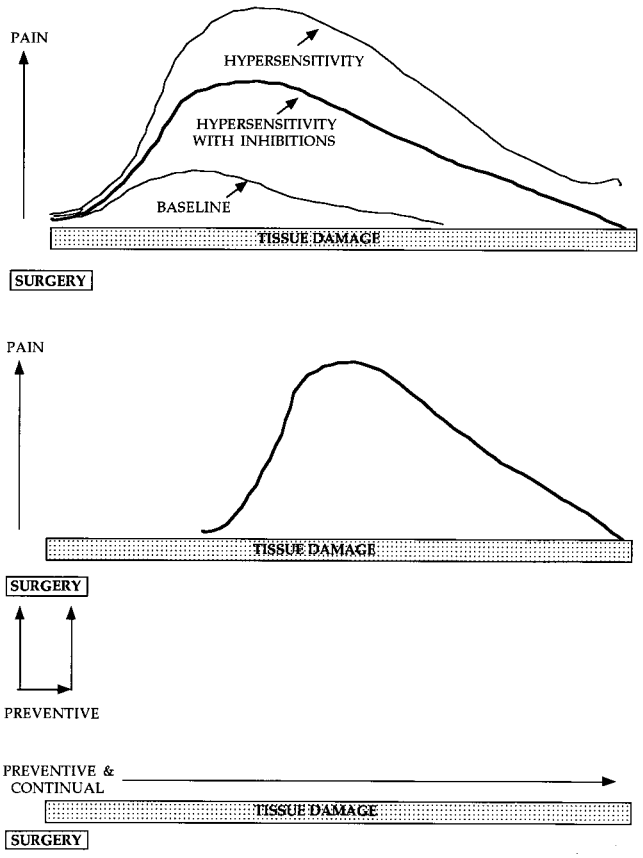


Figure R1. Damage to tissue as a result of surgery (but it could equally apply to inflammation, trauma, or neuropathy) can cause a baseline level of pain transmission that is enhanced by peripheral and central mechanisms of hypersensitivity. The activation of central inhibitory systems will reduce the level of pain transmitted to higher centres. In the second panel, in the presence of continued tissue damage, a short lasting preventive agent (with peripheral or central actions) will only delay the pain that may occur without the compensatory inhibitions, which have also been preempted. The third panel shows how preventive and continued treatment will block all pain until the tissue heals.

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bitions (sect. 7.2). Thus there may be a rebound enhanced pain after a short-lasting pre-emptive treatment wears off. In the longer term, patients may do less well if only a brief pre-emptive block is given. There is some clinical evidence to support this premise, as discussed by McQuay (1994).

R4. Pains and brains

Moving centrally into the spinal cord, I indicated that we understand a reasonable amount about the mechanisms underlying plasticity in this first relay in pain transmission. **Hardcastle** and **Watkins & Maier** are right: the brain should not be missing in any overview of pain. **Hardcastle** quotes my remark on supraspinal analgesia, but I accept fully that we need to know much more about pains in the brains. **Benedetti**'s comments also related to these points because he discusses the anxiogenic actions of the peptide cholecystokinin (CCK). It is interesting to note that CCK causes anxiety and reduces analgesia. I accept the point made by **Watkins & Maier** that the term "anti-opioid" is too restrictive, yet the papers they cite on the wider role of CCK in reducing non-opoid analgesia were published only after my target article.

Han has made many important contributions to the research on CCK and I welcome the additional points that he makes in his commentary, all of which I agree with, but I was unable to mention in my target article because of space constraints. **Noble et al.,** although they entitle their account "Clinical perspectives," discuss pharmacological studies in rodents. I presume that the clinical aspects relate to dependence and tolerance. I take exception to their premise that these are problems with the clinical use of opiates such as morphine. There is really no evidence that tolerance is a major problem, since because increased pain can lead to a need to increase the dose, a condition very different from tolerance. Likewise, a psychological dependence leading to drug-seeking behaviour is a very rare event with clinical use of opioids (see McQuay 1997). The rationale for new opioids does not need to include a problem that not only does not exist but is a myth that has hindered the appropriate use of opiates in the clinical use of pain. It may be possible to cause analgesia via manipulation of endogenous opioids, but, as is clear from several of the target articles and commentaries in this *BBS* issue, an opiate that works in neuropathic states would be more than welcome. In this context, CCK antagonists as adjuncts to morphine might do the trick and NMDA antagonists with an opiate or other combinations as mentioned might be appropriate (sects. 5.2 and 7.1).

In response to pain facilitating brain-to-cord messages in inflammation and illness (**Watkins & Maier**), I would respond that this may well occur but the balance is still tilted toward compensatory inhibitions after inflammation. Although there are peripheral, spinal, and centrifugal contributions to enhancement of pain and hyperalgesia these are held down by inhibition. I still stand by my section 7.3 where I suggested that inhibition is increased in inflammation and reduced in neuropathy. Of this point, more later.

R5. Feelings and pain

The affective side of pain is obviously important and occurs in the brain. Yet, the facts that opioids are rewarding and that noradrenaline and 5HT are intimately linked to mood and anxiety, and CCK to anxiety, may be telling us something about the pharmacological modulation of pain and links between the sensory and affective aspects of pain. It is revealing that CCK is reduced after inflammation (less anxiety?) and thus exogenous opioid analgesia is enhanced. In this situation there is increased descending alpha-2 activity and this increase in noradrenergic transmission could elevate mood and analgesia. By contrast, in neuropathy, CCK is increased (anxiogenesis?) and opioid controls are decreased. Add to these the roles of the endogenous opioids and the anxious enkephalin knockout mouse (**Benedetti**), and a common pattern may emerge in which anxiety and pain go together, and euphoria, anxiolysis, and analgesia go hand in hand, the former in neuropathic states and the latter in inflammation. Pathology in the case of nerve damage disrupts both emotions and sensory control; by contrast, after inflammation, beneficial compensations occur. As shown by **Watkins & Maier,** illness and infections can also impinge upon these systems. So, as discussed above, I am convinced of the importance of the higher centres but it is extremely difficult to investigate some of these events with animal studies due to anaesthesia in electrophysiological studies and problems of interpretation in behavioural approaches. The ability to scan the human brain is most likely to provide the impetus to studies of brains and pains. However, it must not be forgotten that the brain responds, in terms of affective and sensory responses to inputs from the spinal cord. The ability of peripheral and central events to substantially alter ascending messages (by increasing or decreasing them) will have a major impact on what messages arrive in the brain and will alter the affective nature of the stimulus.

The peripheral and spinal events are important in their own right, and one need consider only nonmammalian species. The survival value of the response to a noxious stimulus is ancient in evolutionary terms and occurs in very primitive organisms where it is likely to have little or no affective component (Glanzman 1995; Ghirardi et al. 1995). Understanding the first relays is an essential step toward understanding the higher consequences.

R6. Controlling pains

Whilst nestling in the spinal cord, I wish to comment on **Siddall, Clarke, Hu & Sessle,** and **Omote.** The latter comment really reiterates the points I made in sections 4.4. and 7.3 regarding the role of inhibition, both amino-acid and monoamine mediated, and adds some new data. It is interesting to note the enhanced monoamine systems in neuropathic states, which must be the one example of an increase in inhibitions in neuropathic pain. **Omote** mentions the peripheral actions of opioids in inflammation, a topic I mentioned briefly. **Stein & Schäfer** dilate upon this topic from a field of study created almost single-handedly by Stein. I agree entirely that an opioid devoid of central penetration would be an analgesic in inflammation, but I would add that the degree of analgesia produced by this peripheral effect may not be that high and that the control of inflammatory pain is less of a clinical problem than the control of neuropathic pain where this peripheral action may not be so apparent. However, if there is a mixed pain, inflammatory and neuropathic, or inflammation around a

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damaged nerve, then this tactic may translate to other pain controls.

Hu & Sessle emphasise that trigeminal mechanisms of pain, of critical importance not only for dental pain but for headache, migraine, and trigeminal neuralgia, may share characteristics with many of the spinal events described. I agree with all of **Hu & Sessle**'s points and read with interest their new findings on the importance of NMDA excitations and GABA inhibitions in the final determination of trigeminal output.

Clarke brings together various strands and we appear to be in full agreement with the idea that inhibitions are a major part of the story. The problem with neuropathic pain (and **Siddall** reinforces this point) is that inhibitions may fail. This may be due in part to neuronal dysfunction (GABA) and in part to a number of other factors (see sect. 5 of original article). Thus, if opioid controls are reduced in neuropathic pains, the approach taken is either to reduce excitations (excitability blockers, membrane stabilizers, and anticonvulsants) or to enhance monoamine inhibitions by the use of antidepressants. **Clarke**'s points reinforce my own about the complexity of the descending control systems. However, the number of receptors and the important point made by **Clarke** regarding the opposite effects on motor control means that the chances of producing novel drugs with selective effects on pain is actually quite high.

In addition to the monoamines, GABA could be a target (**Siddall**) and the benzodiazepines may be one way to enhance inhibitions. However, as we have recently argued, their use depends on the state of $GABA_A$ receptor mediated controls. Benzodiazepines enhance GABA function. If, as might well be the case, GABA controls are increased after inflammation, there could be very little increase that benzodiazepines could induce. Furthermore, in neuropathic pains, if, as several of us have mentioned, there is a loss of GABA controls, possibly due to neuronal dysfunction, then there will be no GABA tone to be augmented. Controlled clinical studies on the use of benzodiazepines are needed. We have recently reviewed this area of pain research (Dickenson et al. 1997).

R7. Learning about pain

The final area covered by the commentaries is that of pain and learning. **Birbaumer & Flor** make a number of points, several of them already addressed earlier in this Response. Yes, the higher cortical processing of pain is critical and memories may well be established as a result of painful experiences, as well as compatible processes occurring in other sensory modalities. Not only may tinnitus be a facet of this but we need to consider hallucinations and agnosia as part of a wide spectrum of pathological and drug induced alterations in the processing of sensory events in the world around and within us. I gave the details of combination therapy for pain because of the multiple pharmacology of the systems; I and several others (see sect. R2) feel that there is no central processing without peripheral drive.

The exception to this is central pain. I did not cover this area because almost nothing is known about it. However, it may not be correct to consider pain as simply another sensory modality. As **Hardcastle** in particular points out, there is a major psychological component to pain, and in most people, this is unpleasant. Other sensory modalities, visual and auditory (see **Birbaumer & Flor**), are neutral. These modalities do not elicit a withdrawal reflex either. The survival value of the stimulus is ancient in evolutionary terms and occurs in very primitive organisms, as mentioned earlier. Learning in response to a noxious stimulus can be demonstrated in aplysia, which has only a few hundred neurones, but even here, the events are sufficiently complex (Glanzman 199; Ghiradi et al. 1995).

Hole et al. discuss learning with regard to noxious inputs, but although enhanced responses can occur in response to an intense stimulation, I feel that the role of inhibition in controlling these events is of utmost importance. The four studies **Hole et al.** cite include two in slices where most inhibitions may be severed, a neonatal cord, where inhibitions have not matured and excitations are greater, and an adult anaesthetized rat. Yes, central enhancement of incoming messages could be viewed as a form of learning, but under these circumstances we find almost exactly the same results as Randic. Not all spinal nociceptive neurones are facilitated; a number show reduced responses after peripheral inflammation, indicating compensatory inhibitions (Stanfa et al. 1992). In fact, **Hole et al.** only mention one facet of hippocampal function, long term potentiation (LTP [see also: Shors & Matzel: "Long-term Potentiation" *BBS* 20(3) 1997]). It is clear that in addition to this prolonged potentiation there is also short- and long-term depression and short-term potentiation. The latter is common in the spinal cord and depressive mechanisms are likely to hold the former in check. Again, in the marine mollusc, both short- and long-term potentiation can occur and inhibition controls the extent of potentiation (Fischer & Carew 1993; Ghiradi et al. 1995). As proposed in section 7.3, if these inhibitory mechanisms function normally in the mammalian spinal cord, pain is held in check, a sensible *modus operandi* for a sensory system. In neuropathic pain, where inhibitions may fail, the long-term hyperalgesias and allodynias dominate. It would be pointless to have a system in the spinal cord in which the gain is routinely shifted upward for many days after a brief stimulus.

R8. Conclusions

Pain is a sensation that is handled differently by the central nervous system depending on the nature of the stimulus (affect, reflex-induction, and commonness). The mechanism of peripheral and central sensitization are much more common and widespread than, for example, tinnitus. Most humans experience many acute pain states where either or both of these events are likely to occur (sprained ankles, sunburn, childbirth, dental surgery, etc.). I appreciate the comments of **Birbaumer & Flor** but feel that pain is more than just another sensory event. There are parallels with other sensory events and other forms of learning but pain stands alone as a sensory system. It can be amplified at peripheral and central sites, where the level of transmission is controlled by inhibition and where the net end result is unpleasant. As a result of a series of events at peripheral, spinal, and higher levels, people suffer pain, they do not simply perceive it.

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What exactly is central to the role of central neuroplasticity in persistent pain?

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Abstract: The commentaries on our target article have raised important issues about central neuroplasticity and its role in persistent pain states. Some suggest that central neuroplasticity plays nothing more than a minor role in persistent pain, while others argue that persistent pain depends critically on peripheral inputs for its maintenance. Some stress that persistent pain relies to a large extent on changes in the brain and on centrifugal inputs from brain to spinal cord, whereas others argue that it depends on alterations in inhibitory as well as excitatory systems. We attempt to address each of the commentators' points, while defending our position that central neuroplasticity is critical to pathological persistent pain states.

Whether one calls it central hyperexcitability, sensitization, or neuroplasticity, the critical role of changes in central nervous system (CNS) function in persistent pain have been stressed both in our own target article and in the others in this issue of *BBS*. It is clear from the commentaries that the concept of noxious stimulus- or injury-induced central changes has captured the attention of pain researchers world-wide. What is also clear is that there are many ideas and opinions about the nature of these changes and the extent to which they contribute to the pathophysiology of persistent pain. In an effort to integrate the large amount of material provided in the many insightful commentaries, we would like to draw the reader's attention to specific themes that have arisen, as well as to outline our own view on them. Despite the disparate views, we believe the commentaries have one thing in common. They all ask: What is the principal role of central neuroplasticity in persistent pain? Most agree that central changes play a role in pain processing, but some argue that peripheral pathology is central to its expression, and thus to persistent pain. Others argue that although central changes are key players in pathological pain, a greater emphasis should be placed on changes in the brain and the influence of the brain on spinal cord. Finally, still others point out, as we have, that central changes are important, but that the importance of changes in inhibitory rather than excitatory mechanisms must be stressed.

Determining the relative contribution of central changes and peripheral inputs is critical to answering the question of whether central neuroplasticity contributes to persistent pain. The issues raised in the commentaries can be condensed into four key questions. (1) Does central neuroplasticity exist? (2) If it exists, what role does it play in persistent pain in animal models or human clinical pain? (3) Are peripheral inputs more important than central changes for the expression of persistent pain? (4) Can neuroplasticity exist in the absence of continued or ongoing peripheral inputs? Most of the commentators seem to accept that central neuroplasticity exists. It would be difficult to ignore the growing body of experimental evidence demonstrating several forms of central neuroplasticity including wind-up, dorsal horn neuronal sensitization, and receptive field expansions, as well as hyperexcitable flexion reflexes and nerve injury-induced sprouting and the production of dark neurons in dorsal horn. However, it is possible to argue, as do **Cleland & Gebhart,** that central neuroplasticity plays only an insignificant role in animal and human experimental hyperalgesia models. **Marchettini et al.** add that what occurs in animal experimental models may have little to do with what happens in human cases of chronic clinical pain. Furthermore, it is also possible to argue, as do both **Devor** and **Gracely,** that although central plasticity exists, from a treatment perspective it may be more appropriate to target the peripheral pathology that maintains it rather than the central site where it occurs. On the other hand, there is support from **Jancsó et al.** and from **Willis** to suggest that central sensitization can be maintained in the absence of continued sensory input. **Hu & Sessle** go on to suggest that central sensitization in trigeminal nociceptive pathways may depend on an unmasking or strengthening of convergent inputs.

Cleland & Gebhart have come to a different conclusion based on additional studies and their appreciation of certain critical technical limitations. However, these additional studies do not rule out a role for central neuroplasticity in hyperalgesia. Thus, the studies of Puig and Sorkin (1996), Dubner and Ruda (1992), and Woolf et al. (1992) indicate that peripheral injuries lead to changes in afferent activity, neuromediator release, and structural alterations that are present during both the development and the maintenance of hyperalgesia associated with these injuries. In each of these cases, however, the hyperalgesia-inducing injury is also associated with prolonged peripheral tissue changes. Thus, it is not unreasonable to expect central changes to accompany both phases of the response. It is important to realize that central neuroplasticity and continued inputs from the periphery are not mutually exclusive. However, when ongoing peripheral inputs are present, they obscure our ability to demonstrate that hyperalgesia is in part due to central changes. Even when using so-called direct methods (i.e., preinjury and postinjury block), results can be confounded if the injury is intense enough to produce prolonged peripheral changes. Thus, if intense peripheral inputs outlast a preinjury block then the block is unlikely to produce pre-emptive effects. On the other hand, if an important consequence of central sensitization is to amplify peripheral inputs, then eliminating peripheral inputs with a postinjury block may often eliminate nociceptive responses and hyperalgesia. These results do not rule out central neuroplasticity; they only stress that in many instances pain behaviour requires peripheral input to be fully expressed, a conclusion that we have espoused in our target article. On

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more technical grounds, we find it surprising that **Cleland & Gebhart** accept that effective anesthesia was produced by 50 μl of lidocaine in the study of Dallel et al. (1995) whereas they discount the anesthetic effect with a much larger volume (150 μl) of the longer lasting anesthetic bupivicaine in the study of Coderre et al. (1990). We were also somewhat surprised that a 50% reduction in withdrawal latency, significant at a p-value of <0.01, was deemed only weakly significant in the study of Coderre and Melzack (1985), while a stated nonsignificant trend in the study of McCall et al. (1996) was interpreted as significant by **Cleland & Gebhart.**

Marchettini et al. are more receptive to the concept of central plasticity, but they remain doubtful that it plays a role in persistent human pain states. They correctly point out that there are examples of chronic clinical pain for which there are no experimental animal models. We agree that clinical and experimental pain are not identical, but we maintain that insights into the pathophysiology of clinical pain can be derived from experimental models. Even animal models as simple as the mouse tail-flick test have provided considerable information about the analgesic efficacy of various pharmaceutical compounds. It is true, however, that we are in need of additional animal models of chronic pain with demonstrated validity for human pain conditions. It should be noted that in human experimental trials, phenomena such as wind-up (Price et al. 1994) and hyperexcitability of flexion reflexes (Dahl et al. 1992) have been demonstrated and probably play a role in clinical pain. The fact that many human conditions – e.g., arthritis, soft tissue injury, and procedures such as nerve biopsies – do not lead to chronic pain in the absence of persistent injury is not proof that central plasticity does not exist, but only reinforces the point that there are fortunately other physiological mechanisms at work that undermine its expression and long-term survival. Unfortunately, there are probably other cases where these protective mechanisms are unable to overcome the negative consequences of central neuroplasticity or peripheral sources of pathology.

Marchettini et al. may be right that genetic differences may play a key role in determining who is at risk for developing chronic pain, as has been well articulated by Devor and Raber (1990), and that human cognition can lead to suppression or augmentation of pain perception and can produce variability in human pain behaviour that is less likely or dramatic in animal models. We agree with **Backonja,** who argues that neuropathic pain is an intricate condition that cannot be explained by neuroplasticity alone. A complex interaction between peripheral pathology, CNS changes, and reactive emotive processing must be taken into account.

Both **Devor** and **Gracely** make the point that central neuroplasticity is selective and not striking in intensity and hence that targeting the peripheral pathology would be a more effective treatment. We agree that there has recently been an overemphasis on central mechanisms in the explanation of persistent pain states. However, until recent years there was barely a recognition that central plasticity played any role at all in persistent pain. Over the last several years there has been a growing recognition that central plasticity exists and plays a role in persistent pain. In the introduction of any new idea, there is a tendency to overstate its significance. Throughout the target article we made an effort, as did Gracely et al. (1992), to bring peripheral mechanisms back into the picture and to focus on the interaction between peripheral and central mechanisms of persistent pain. We stress that in some clinical pain states peripheral mechanisms may dominate, whereas central mechanisms may be more important in others. It is true that there has been an explosion in the literature on novel centrally acting agents, such as N-methyl-D-aspartate (NMDA) antagonists for the treatment of persistent pain. Perhaps for many patients such a treatment is neither appropriate nor effective. However, there may also be a group of patients who do not respond when peripheral pathologies are targeted but are responsive to such a central treatment (Backonja et al. 1994; Eide et al. 1994; Kristensen et al. 1992; Nikolajsen et al. 1996). Rather than seeing central treatments as targeting an all-inclusive, final common pathway, it may be more instructive to think of them as alternatives, to be used when agents targeting the peripheral pathology are ineffective. It is for this reason that we must not be too quick to dismiss new treatment possibilities.

Generally, we agree with **Devor** and **Gracely** that in many instances central sensitization is probably not so much pathology as a natural response of the CNS to peripheral pathology. It is clear, however, that CNS neurons are capable, in some instances, of developing pathological characteristics (i.e., epileptic foci). Because neurons involved in pain transmission share neurochemical similarities with those involved in epilepsy, including glutamate activity at NMDA receptors, it is not inconceivable that, as suggested in the commentary by **Backonja,** such central pathologies may contribute to some persistent pain states. Furthermore, as discussed by **Jancsó et al**., peripheral nerve injuries result in progressive structural changes in pain transmission pathways, including transganglionic degeneration of C-fiber primary afferents, sprouting of large fibers into substantia gelatinosa, and a reorganization of spinal dorsal horn neuronal connections, all central changes which could contribute significantly to the development of persistent pain after nerve injury. Also, as described by **Hu & Sessle,** central sensitization that is evident in trigeminal nociceptive pathways may depend on an unmasking or strengthening of convergent inputs. Since neuroplasticity is more effectively induced by noxious deep inputs, **Hu & Sessle** also suggest this may explain why greater sensory disturbances occur after injury to deep tissues than after injury to cutaneous tissues.

The question remains as to whether central sensitization can be sustained in the absence of continued inputs from the periphery. **Gracely** has given evidence of persistent clinical pain states where inputs from the periphery are necessary, and in our target article we have given clinical examples in which it is possible that inputs from the periphery are not necessary to sustain central hyperexcitability. Although **Gracely** does not rule out the possibility, **Cleland & Gebhart** and **Devor** are more skeptical, and **Ursin,** in contrast, supports even the concept of self-sustaining positive feedback loops. **Jancsó et al.** argue that sustained central sensitization is possible, because after intracisternal injection of capsaicin a mechanical hyperalgesia develops in the skin area that becomes completely insensitive to further noxious chemical stimulation. Furthermore, both **Jancsó et al.** and **Willis** point out that capsaicin injection to the skin produces a significant hyperalgesia that is dependent on central sensitization. **Hole et al.** and **Birbaumer & Flor** further support this concept

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and argue that sustained central sensitization could be explained by mechanisms similar to those involved in learning and memory processes.

Hole et al. review the data from their own as well as four independent studies that suggest that phenomena such as long-term potentiation may exist in spinal cord dorsal horn. In relation to the mechanisms triggering sensitization, **Willis** describes how the sensitization of spinothalamic tract neurons induced by intradermal capsaicin is mimicked by excitatory mediators such as glutamate and substance P and blocked by both NMDA and NK1 receptor antagonists, as well as inhibitors of various protein kinases. **Jancsó et al.** also refer to evidence that perineural treatment with capsaicin produces transganglionic degeneration of C-fiber primary afferents and extensive sprouting of large fibers within the substantia gelatinosa, resulting in alterations in connectivity similar to those produced by peripheral nerve sections. This evidence is all quite significant, since, as we point out in our target article, the hyperalgesia produced by capsaicin typically long outlives the duration of its initial afferent barrage.

Devor raises an important question: What is there about the theory of central sensitization that would predict *stamping in* of an ingrown toenail, but not an episiotomy scar? Our model proposes that reactivation of a somatosensory pain memory requires a drive and that this drive may originate in the periphery, DRG, spinal cord, or brain. In the case of amputation, we need to consider whether the loss of normal sensory nerve impulses (deafferentation) that follows amputation in some way plays a role in either the stamping in process, the re-activation stage, or both. We have previously argued that the interruption of afferent input associated with amputation or deafferentation may facilitate the central neural changes that contribute to the formation of pain memories by removing normal inhibitory control mechanisms (Coderre et al. 1993). There are, however, examples of pain memories recurring in the absence of obvious deafferentation, although it is true that the example of postepisiotomy pain raised by **Devor** is not among them. Thus, cardiac pain had been referred to the site of a compression fracture in the upper back (Henry & Montuschi 1978) and pain in response to stimulation of the nasal mucosa may be referred to teeth that had recently been filled (Hutchins & Reynolds 1947; Reynolds & Hutchins 1948). It appears then that deafferentation may not necessarily play a role in the stamping in of a pain.

What about the role of deafferentation in the reactivation of an established pain trace? The most important difference between a phantom ingrown toenail and an episiotomy scar is that the former has no peripheral referent, since the body part has been surgically removed. We need to consider some of the less obvious implications of this fact for the reactivation of a pain trace after amputation. In addition to the loss of afferent input that results from amputation of a body part, there is also a loss of visual, tactile, and proprioceptive information related to the limb; it can no longer be seen, touched, or felt. What is the effect of this loss of information on the perception of a phantom? We would argue that the cortical and subcortical influences that normally inhibit established pain traces may be further reduced by the absence of information from sense modalities that might otherwise confirm or disconfirm the percept (e.g., of a painful ingrown toenail) arising from the periphery. Following amputation, the likelihood of re-activating a pain memory that had a visual component (e.g., ingrown toenail) is increased because the potential inhibitory effect of vision has also been removed. In general, as the number of modalities involved in the pre-amputation pain experience increases (and thus the more sources of potential feedback are removed), so does the probability of re-activating a past pain once the limb has been removed. This could occur because there are fewer senses available to provide a reality-based check (i.e., exert an inhibitory influence) on the perceptual processes generating the phantom (Katz 1993).

Implicit in any discussion of memory is the assumption that the CNS has been changed as a function of prior experience. Although we did not explicitly refer to *learning* in our target article, we agree with **Hole et al., Birbaumer & Flor,** and **Watkins & Maier** that learning processes must underlie expressions of new behaviour. Perhaps the most fascinating example of this in the phantom limb pain literature is *learned paralysis* (Ramachandran 1994), in which the brain has *learned* that an immobile phantom hand cannot be moved. An extremely creative solution is to use mirrors to trick the brain into thinking that the phantom is moving by having the amputee look into a mirror while his contralateral intact hand is positioned to coincide spatially with the felt position of the phantom hand. When the amputee attempts to carry out the same movement with both hands while looking at the phantom (i.e., reflection of the intact hand), the sight of the hand moving determines the ultimate perception, and the amputee feels as if the once paralyzed hand is now moving freely. This experiment highlights the dominant role of vision over other sensory modalities in circumstances involving exteroceptive sensibility. There are other examples of this intermodal integration and perceptual dominace of vision (Katz 1993). Patients undergoing brachial plexus or spinal local anaesthestic blocks and patients with complete brachial plexus avulsions or spinal cord transections all report vivid phantom limbs that are felt to be coincident with the postion of the real limb as determined by sight. However, when a patient's deafferented limb is moved from one position to another with eyes closed, the felt position of the phantom corresponds to the last seen position of the real limb. When patients open their eyes, the phantom is reported to *fuse* with the new position of the real limb as perceived by sight. These examples demonstrate that we are dealing with a perception system that is even more complex than the traditional supraspinal pain signalling system envisioned by **Hardcastle** in her commentary.

There is no doubt, as **Benedetti** argues, that psychological factors play a role in the perception of pain after surgery. It is for this reason that we routinely administer the multidimensional McGill Pain Questionnaire in our studies of pre-emptive analgesia (Katz et al. 1994; Katz et al. 1996a; Katz et al. 1992). We have also administered other measures of psychological and emotional functioning, including anxiety and depression (Kavanagh et al. 1994). Although we and others have found that pre-operative administration of analgesics or local anesthetic agents can pre-empt postoperative pain, we have yet to find any differential effects of these psychological factors on analgesic requirements after surgery. A recent prospective follow-up study of patients who had undergone lateral thoracotomy showed that 52% of patients reported daily or weekly pain of moderate intensity approximately 1.5 years after surgery (Katz et al.

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1996b). The interesting finding was that postoperative pain within 6 hours of surgery was the only significant predictor of long-term pain. In contrast, pre- and postoperative measures of anxiety and depressive symptomology were not predictive, suggesting that these psychological factors did not differentially influence the experience or reporting of pain. While psychological factors are important, too much emphasis on them may blind clinicians and researchers to other potentially significant predictors of longterm pain – in this case, intense postoperative pain.

As noted above, the model we developed in the target article allows for the maintaining drive to originate from brain regions either directly or indirectly involved in the processing of nociceptive information. As we did not emphasize this possibility in the target article, we welcome the commentary by **Watkins & Maier** who bring into focus a novel line of pain research involving brain-to-spinal cord circuitry. Whereas it is well established that noxious peripheral stimulation leads to a sensitization of spinal cord neurons, **Watkins & Maier** introduce the novel concept that centrifugal brain to spinal cord pathways allow descending inputs from brain centers such as the nucleus raphe magnus to facilitate nociceptive processing in spinal cord as well.

Along similar lines, **Benedetti** discusses the role of nociceptive emotional integration in the limbic system and its relation to pathological pain; and **Ursin** raises the possibility of the brain generating and maintaining sensitization in the absence of peripheral input. Elsewhere, we have outlined a mechanism through which cognitive and affective processes associated with higher cortical and limbic centers may alter phantom limb sensations via either brain-to-brain or brain-to-spinal cord circuitry (Katz 1996). As an example of the latter, phantom limb pain intensity may be modulated by higher brain centers involved in cognitive and affective processes via a multisynaptic network of descending inputs that impinges on preganglionic sympathetic neurons in the lateral horn of the spinal cord. These descending inputs would subsequently produce diffuse peripheral autonomic discharge and activation of primary afferent fibers located in stump neuromas. This activity would, in turn, project to spinal cord dorsal horn neurons subserving the amputated limb and to rostral brain structures where the impulses contribute to the perception of pain. Consistent with the learning model outlined by **Birbaumer & Flor** in their commentary, we have proposed (Katz 1993) that through repeated activation, neural circuitry is strengthened among brain regions subserving cognitive, affective, and sensory processes. Hence phantom limb sensations and pain may be triggered by thoughts and feelings in the absence of primary afferent feedback from peripheral structures.

Clarke is right in pointing out that our target article concentrated heavily on excitatory mechanisms rather than inhibitory mechanisms. It is quite true that failure of inhibitory mechanisms could underlie some forms of pathological pain. Indeed, this possibility is discussed in greater detail in the accompanying target articles of **Dickenson** and **Wiesenfel-Hallin et al.** Furthermore, many of the most effective treatments that clinicians use today (opiates, α2-adrenergic agonist and tricyclic antidepressants) are based on the enhancement of inhibitory systems rather than suppression of exictatory systems. These treatments are available today because of the research efforts into inhibitory systems (endogenous opioids, descending control circuits, etc.) in the 1970s and early 1980s. This is precisely why it is necessary to develop a better understanding of the excitatory mechanisms that play a role in persistent pain. The accelerated pace of research into excitatory mechanisms (neuropeptides, excitatory amino acids) in the late 1980s and 1990s promises to deliver novel clinical treatments that will give us additional options to alleviate persistent pain.

To respond to a specific comment from **Clarke** about referred pain: we did not mean to suggest that referred pain relies on tonic inputs from the area of referral but rather that referred pain is influenced by additional inputs from the area of referral. Unless one proposes an axon-reflex-like peripheral response in the referred area, this conclusion is necessary to explain how referred pain sensations can be reduced by local anesthesia of the referred area. In response to **Marchettini et al.,** we wish to point out that we did not intend to equate phantom limb pain with referred pain and that in the final analysis we described phantom limb pain as pain that is projected (not referred) to the amputated region. Last, in response to **Devor**'s stated paradox about Aβ-fiber input producing both increased inputs and counterstimulation-induced decreased inputs: (1) There is no requirement that central sensitization reliably render Aβ-fiber input painful, and (2) counterstimulation is most often produced by heterosegmental sensory input.

No brain, no pain

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Abstract: The theme of my target article was dysfunction of inhibition in the spinal cord as an important factor in the development of chronic pain states. Some commentaries focused on the role of more central mechanisms and the limited usefulness of animal models for understanding mechanisms of human pain. More specific comments concerned the roles of GABA and cholecystokinin in pain control.

The commentaries can divided into broad categories dealing with the following issues:

1. Spinal mechanisms are inadequate to describe the pathophysiology underlying chronic pain because not enough attention has been focused on conditioning and learning (**Birbaumer & Flor, Hole et al., Watkins & Maier**), central effects of infection/inflammation (**Watkins & Maier**), cortical functions, and emotions (**Hardcastle**). Pain facilitating circuits descending from the brain to the spinal cord may have a key role in the organization of

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response to pain. Furthermore, it is unquestionable that mechanisms rostral to the spinal cord are of great importance in pain perception and suffering. However, the emphasis of this review was on spinal mechanisms because a better understanding of these should offer great hope for therapies, with minimal side effects. Of course, pains that involve structures central to the spinal cord, such as thalamic or idiopathic pains, cannot be treated in the same way as pains arising from peripheral or spinal pathology.

2. Animal studies are of limited use in understanding clinical human conditions (**Marchettini et al.**). It is undoubtedly true that human pain and suffering reported verbally cannot be duplicated, for obvious reasons, in animals. However, after careful analysis of animal behavior one can certainly detect abnormalities that might be relevant to the human experience. More specifically, abnormal pain-like behaviors that can be alleviated by drugs (Wiesenfeld-Hallin et al. 1997) and other therapies, such as spinal cord stimulation (Stiller et al. 1996), that are useful in humans for pain relief should be considered as evidence for the relevance of the animal model. In discussing the reduced analgesic effect of opiates reported by some clinicians, but not others, **Marchettini et al.** write that making "comprehensive hypotheses on neuropathic pain without considering divergent reports seems simplistic." However, such reports are considered under section 4.1 (para. 2) in the target article, and even in our own animal studies we have found reduced potency of intrathecal morphine following axotomy, rather than a total lack of effect (Xu & Wiesenfeld-Hallin 1991). If the potency of opiates is indeed reduced in neuropathic pain, physicians need to consider carefully whether "analgesia" after large doses has a large sedative component. The sedative effect of systemic morphine in experimental pain states can be analyzed with careful behavioral techniques (Xu et al. 1992). Furthermore, comprehensive hypothesis about neuropathic pain is proposed, but there is a suggestion that there may be some common mechanisms. As pointed out by **Siddall,** different models of neuropathy (axotomy vs. partial nerve injury) may have very different mechanisms. It has recently been demonstrated that there are considerable differences among various models of partial nerve injury (Kim et al. 1997).

3. A number of neurotransmitter systems are involved in the mediation of chronic pain. The target article concentrates on two systems: γ-amino butyric acid (GABA) and cholecystokinin (CCK). The role of GABA in the mediating of chronic pain states may involve both the GABA-A and GABA-B receptor in both spinal and trigeminal pathways (**Hu & Sessle**). Furthermore, dysfunction of the GABA-ergic system may differ in pain states with varying etiologies (**Omote, Siddall**).

CCK's role as an antianalgesic or antiopioid is now widely accepted, on the basis of pioneering studies from a number of laboratories (**Han, Noble et al., Watkins & Maier**). Although the functional role for such a mechanism from the evolutionary point of view may seem counterintuitive (**Clarke**), there are very interesting hyptheses about a role for CCK as a negative feedback control for endogenous opioids (**Han**). In spite of a great deal of research on the antiopioid action of CCK, however, the precise mechanism of action is not well understood. There is general agreement about an interaction between the CCK and the mu-opioid receptor, but there is divergence of opinion about whether there is also an important interaction between the κ (**Han**) or δ opioid (Benoliel et al. 1991) receptors. An important therapeutical possibility for CCK antagonists would also be to increase the analgesic effect of inhibitors of enkephalin-degrading enzymes, which increase the potency of endogenous opioids (**Noble et al.**). Like all neuroactive substances, CCK has a number of functions in the central and peripheral nervous systems, including being a potent anxiogenic when applied exogenously (**Benedetti**). In fact, highly selective CCK-B antagonists have been found to have a potent anxiolytic action in rodents (Hughes et al. 1990). It is tempting to suggest that clinically useful CCK antagonists could have a double beneficial effect, by reducing the sensory and affective/anxiogenic aspects of pain.

Sympathetic contribution to pain – need for clarification

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Abstract: Certain patients with a possible contribution of the sympathetic system to pain may not fit the definition of complex regional pain syndromes (CRPS), which raises the question of terminology for those patients. To further clarify the relationship between the sympathetic system and pain, apart from the need for placebo studies, there remains an urgent need for a satisfactory definition of the criteria for a complete sympathetic block. It also remains uncertain whether a change in the discharge pattern of sympathetic fibres underlies the changes in sympathetic organ function, often found in patients with CRPS.

R1. Introduction

Our target article received a number of thoughtful and well structured commentaries. It was not possible, nor was it our intention, to clarify all aspects of the relationship between the sympathetic system and pain. The commentaries accordingly show that there is a need to clarify the contribution of the sympathetic system to pain states.

R2. Definition

We were aware of recent changes in nomenclature from the international association for the study of pain regarding the "complex regional pain syndrome" (CRPS) (Merskey & Bogduk 1994). Nevertheless, for one group of patients we found it reasonable at this stage of the discussion to continue using the term "reflex sympathetic dystrophy"

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(RSD), which is CRPS type I, because of its widespread distribution. In the same sense we used the term causalgia, which is now CRPS type II, for a second group of patients of the three we described in the target article. In the new terminology, CRPS type I and type II are differentiated based on the absence or presence of a known nerve lesion. Whether all the pain in these conditions is mediated by some kind of sympathetic-sensory coupling remains uncertain. This is one of the reasons for introducing the term "CRPS," which does not name any sympathetic pain component in these conditions. We agree with the commentary of **Raja & Wesselmann** on this point.

In contrast to the complex clinical picture in RSD and causalgia, there was a third group of patients that, in addition to the related consequences of a partial nerve lesion, suffered from only two main symptoms: spontaneous pain and allodynia. Both were confined to the zone of the lesioned nerve and were relieved by sympatholytic strategies. To describe this group of patients we used the term "sympathetically maintained pain (SMP) syndrome." **Raja & Wesselman** found it confusing that of three groups of patients with involvement of the sympathetic system, only one was described as having SMP. We found it useful to refer to these patients in terms of their major symptom, which is pain mediated by the sympathetic system. Moreover, these patients could not be said to have causalgia, because (except for the occurrence of a nerve lesion) the clinical picture of these patients did not fit that category. **Raja & Wesselmann** unfortunately failed to propose an alternative descriptor for our SMP patients.

Baron & Jänig also pointed to the problem of the defining SMP syndrome as a clinical entity, but they recognised that this group of patients fit neither CRPS I nor CRPS II, since a symptom of both CRPS types is the distal generalization. They instead suggested, for example, that in the case of an affected ulnar nerve, the condition be called ulnar nerve neuralgia with SMP. In other words, with any kind of neuralgia (e.g., peroneal or median nerve) there exists a subgroup of patients who will suffer from sympathetically maintained pain. We concur with this suggestion.

R3. Diagnostic test

We suggested a number of diagnostic tests for the diagnosis of RSD. These included a systematic measurement of skin temperatures (SKT) bilaterally under resting conditions and under controlled whole body warming and cooling. In addition we proposed the so-called "ischemia test" as a new diagnostic tool for RSD/SMP and discussed the problems of sympatholytic strategies with respect to quality control.

In their commentary, **Baron & Jänig** stressed that SKTs in patients with RSD may fluctuate, so laterality differences must be interpreted with care in defining reliable diagnostic criteria for CRPS I. To avoid depending on the actual level of SKT laterality difference we introduced the notion of "systematic laterality difference in SKT" (Blumberg 1991) in which all (five) measured points show either higher or lower SKT values on the affected versus the healthy side. As this condition was frequent in patients with RSD, we suggested the systematic measurement of SKT as a diagnostic tool.

Both **Baron & Jänig** and **Roberts** suggest that the term ischemia test may be somewhat misleading because for most readers it would imply that the ischemia leads to blockade of activity in primary afferent terminals. **Roberts** also mentions that the test should instead be described as a measure of dependence on local vascular pressure. Indeed, activity in primary afferent terminals is not blocked by the short period of ischemia used in this test; it is much more likely that the pain relief is due to changes in local vascular pressure. These are pathophysiological considerations, however, and neither the activity of afferent terminals nor the local vascular pressure can be controlled in the test. On the other side, the test will not work until the ischemia introduced can be seen clinically (as whitening of the skin) and can be controlled by the cuff, which gives rise to suprasystolic pressure. Thus, we would still suggest using the term "ischemia test." Before the test can be recommended, it must be shown that it discriminates between CRPS I patients and other patients with neuropathic pain, as **Baron & Jänig** suggest.

Pain relief from sympathetic blocks may be a placebo effect in our patients, as noted by **Marchettini** and **Benedetti,** because there were no placebo controls. The problem of assessing placebo in sympathetically maintained pain has been discussed extensively by Price et al. (1996). In cases with RSD, any placebo controlled sympathetic block should take into account not only the pain behaviour, but also the edema, which, as seen in our RSD case report, decreased each time following a blockade. Moreover, in view of the acute edema relief that we have found with sympatholytic spinal anesthesia (Blumberg et al. 1994), it is hard to believe that this may be a placebo effect.

In our target article we indicated that for any pathophysiological interpretation of the effect of sympathetic blocks, it should be ascertained whether or not the block was complete. **Raja & Wesselmann** suggest that the criteria for defining the adequacy of a block have already been documented (Malmquist et al. 1992; Raja et al. 1996). However, the criteria reported in these papers do not seem to be sufficient.

First of all, these criteria were all derived from measurements (SKT, skin resistance, etc.) at small areas of both hands and feet. Thus, unblocked areas due to partial blocks (see, for example, Fig. 4B of our target article) may be missed. Second, SKT of 34°C following sympathetic block, as mentioned in the paper of Malmquist et al. (1992), or even lower SKT values, as reported by Raja et al. (1996), indicate that the block was incomplete. In case of complete blocks, the SKT in all blocked areas should come close to body core temperature (see Fig. 4C of our paper), which is approximately 36.5° to 37°C. Finally, sympathetic reflexes should also be investigated under the block (as noted in our paper and by **Elam**) for dermal sympathetic outflow which should also include thermoregulatory reflexes. This was not done in any of the studies of the adequacy of a sympathetic block. We certainly realize that in the clinical setting it will be very difficult to investigate these reflexes.

After all, the criteria for a complete block remain uncertain. Hence, pain states which are independent of the sympathetic system should not be diagnosed if sympatholytic procedures do not relieve the pain, unless the efficacy of the procedure has been unequivocally determined, as noted by **Roberts.** In addition, as was also mentioned by **Roberts,** in case of a nerve lesion one must consider the

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possibility of sympathetic-sensory coupling in dorsal root ganglia (Michaelis et al. 1996). In such a case, regional sympathetic blocks with for example, guanethidine, may give false negative results.

R4. Sympathetic function

As noted by **Elam** and by **Baron & Jänig,** sympathetic effector dysfunction does not necessarily imply altered sympathetic nerve traffic because effector organ function may be affected by nonsympathetic neurons, by nonneuronal factors, and by factors related to denervation with an associated nerve lesion. Contrary to **Raja & Wesselmann**'s suggestion, vascular abnormalities in RSD cannot be related to denervation if such abnormalities (even acute ones) develop in unlesioned areas (see our case report 1). To confirm the change in sympathetic activity, we recommended simultaneously recording sympathetic activity in both the affected and the unaffected sides.

It is interesting to note that such data are presented by **Elam** for three cases with RSD. One of these cases had a cold hand following a minor lesion to a single finger tip; another case had a cold foot following a sciatic nerve lesion; and the last case presented with a warm foot after trauma to the back of the foot. Despite marked sympathetic effector dysfunction, skin sympathetic activity (i.e., the sizes of sympathetic bursts) showed no laterality differences under resting conditions or after sympatho-excitatory stimulations.

Elam concluded that regional autonomic dysfunction does not necessarily indicate a change in the pattern of sympathetic nerve activity. His observations do not seem to allow this conclusion, however. The size of any recorded sympathetic burst may be the result of either the number of impulses of one fibre (i.e., its discharge pattern) or the number of fibres active within the burst. Thus, **Elam**'s recordings cannot rule out the possibility that changes in the firing-frequency of individual sympathetic fibres may be the cause of the laterality differences in sympathetic organ function in his three cases of RSD.

To explain the finding of autonomic dysfunction, one can only cite related phenomena in the lesioned nerve (e.g., loss of fibres) or at the effector organ (e.g., denervation supersensitivity) in cases of partial nerve lesion (as discussed by **Elam**). For the vascular abnormalities of the other two cases, both presenting with edema and one with cold, the other with warm skin, **Elam** offers no pathophysiological explanation. Thus it remains uncertain in his cases how an entire hand can become cold after a lesion of a finger tip, or by what mechanism an entire foot becomes chronically warm after a lesion of the back of the foot, without considering ing sympathetic involvement. Unfortunately, thermoregulatory reflexes have not been investigated in any of these three cases.

R5. Hypothesis

To explain the relationship between (1) pain, (2) microcirculation (as indicated by the orthostatic component), (3) ischemia, and (4) the effect of sympatholytic strategies on the pain (and the edema) in RSD, we hypothesised a vicious circle. Within this circle, persistent nociceptive input from the periphery maintains an altered (sensitized) spinal process; this in turn maintains an abnormal discharge pattern in sympathetic vasoconstrictor neurones, leading to disturbed microcirculation, which activates nociceptive fibres. The circle is started (i.e., caused) by nociceptive input generated by the lesion before the onset of RSD. Thus, contrary to **Backonja**'s interpretation of our hypothesis, we did not suggest that dysfunction of the sympathetic system causes RSD. Moreover, we did include the component of central sensitization. The main aspects of the hypothesis are also in line with the work of **Gracely** (Gracely et al. 1992).

We proposed that the abnormal vasoconstrictor discharge pattern generates the edema by increased vasoconstriction on the postcapillary side compared with the precapillary side. Thus, contrary to the interpretation of **Backonja,** we did not consider sympathetic hyperactivity in RSD. Rather, we suggested that there is an imbalance in the activity of the vasoconstrictor neurones supplying the post- versus the precapillary side. Indeed, as both **Baron & Jänig** and **Clarke** note, this part of our hypothesis does not yet have any experimental support.

Clarke also argues that skin warming cannot take place if such a disregulation of pre- to postcapillary flow is active. However, inside the regions under study in cases with RSD, the behaviour of SKT is mainly mediated by blood flow regulation through the arteriovenous shunts, not by blood flow in the nutritive capillaries. Physiologically, these parts of the vascular bed are regulated separately. Thus, the occurrence of edema with warm – or cold – skin is compatible with our hypothesis.

Our hypothesis also implied that the above imbalance causes increased filtration pressure, which generates the edema and can at the same time activate afferent fibres (e.g., deep nociceptors). As both **Clarke** and **Roberts** note, the orthostatic component of the pain in RSD supports the idea that tissue pressure is an important stimulus in the generation of the pain in this condition. Since increased interstitial pressure and swelling per se do not cause pain, **Baron & Jänig** raise the possibility that in RSD, the cause of the pain is not deep nociceptors activated by this pressure but central changes maintained by afferent input from deep tissue that is normally subthreshold for the central neurones. Such a possibility should certainly be considered.

Baron & Jänig also suggest that our "hydraulic hypothesis" is too simple to account for the edema and its reversal following sympatholytic strategies. Unfortunately, they do not present any other idea about the nature of the edema in RSD, but they reject the idea that the edema is due to release of vasoactive peptides from nociceptive fibres. Thus, as they correctly recommend, more research is needed to clarify the nature of this important symptom of RSD, and its possible sympathetic contribution.

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Letters "a" and "r" appearing before authors' initials refer to target article and response, respectively.

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