Mechanisms of Complex Regional Pain Syndromes

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Some patients who suffer an injury to a peripheral nerve, and some patients who suffer a relatively trivial musculoskeletal injury, develop a bizarre and seemingly unique pain syndrome. In its most florid state this syndrome is characterised by the following:

- Pain
- Hyperalgesia
- Allodynia
- Vasomotor, sudomotor and temperature changes
- Trophic changes in the skin
- Motor impairment
- Osteoporosis.

A further feature is that the symptoms and signs seem disproportionate in severity to the nature of the precipitating injury, and occur in a region considerably larger than the one affected by the original injury. Thus, in the case of a nerve injury, the changes occur outside the territory innervated by the affected nerve. In the case of a musculoskeletal injury, the changes affect anatomical regions beyond that of the injured part. More curiously, the same symptoms can develop after visceral injuries (e.g., myocardial infarction) or central nervous system injury (e.g., stroke) and be manifest in a limb that is remote from the site of injury.

The pain in question is an unpleasant sensory experience but has no unique or singular quality. In some cases it may be burning in quality; in others it may be deep and aching. It may be dyseasthetic; it may be spontaneous or present only when evoked by palpation of the affected part.

Hyperalgesia is an exaggerated or increased response to a stimulus that is normally painful.[1]

Allodynia (meaning foreign energy) is pain evoked by a stimulus that normally does not produce pain.

Vasomotor changes include vasodilation or vasoconstriction manifest respectively as reddening and swelling or cyanosis of the affected part.

Sudomotor changes include excessive sweating or dryness of the affected part.

Temperature changes mean warming or cooling of the affected part.

Trophic changes include keratosis, brittle nails, hair loss and brawny induration of subcutaneous tissues.

Motor impairment includes, muscle spasm and contracture of muscles each of which resist and interfere with voluntary movement.

Osteoporosis means elution of calcium from bones ostensibly because of increased osseous blood flow.

There is debate, confusion and controversy concerning the distinction between hyperalgesia and allodynia. Some regard the two as complementary aspects of the same phenomenon and mechanism, i.e., a shift to the left of the response curve of sensory nerves [2] (Fig. 1). Under these conditions, stimuli of an intensity that normally would be painful are perceived as more painful than usual. This constitutes hyperalgesia. Stimuli of intensities that would normally not be painful become painful. This constitutes allodynia.

This interpretation, however, ignores the essential meaning of allodynia, which is that the stimulus that evokes pain is qualitatively, not quantitatively, different from those that normally evoke pain. The cardinal example is brushing the skin, i.e., a mechanical stimulus that is delivered tangential to the skin surface and which does not involve pressure and deformation of the skin. This type of stimulus never evokes pain under normal conditions, regardless of its magnitude.

Confusion arises when touch perpendicular to the skin surface is used as the stimulus. Touch involves pressure, and pressure of sufficient magnitude can under normal conditions be painful. A shift to the left of the response characteristics of high threshold mechanoreceptors would render them low threshold mechanoreceptors. However, in that event, the nature of the modality involved does not change. Receptors normally capable of being nociceptive are simply rendered more sensitive. In contrast, when strictly defined, allodynia requires a switch in the modality.

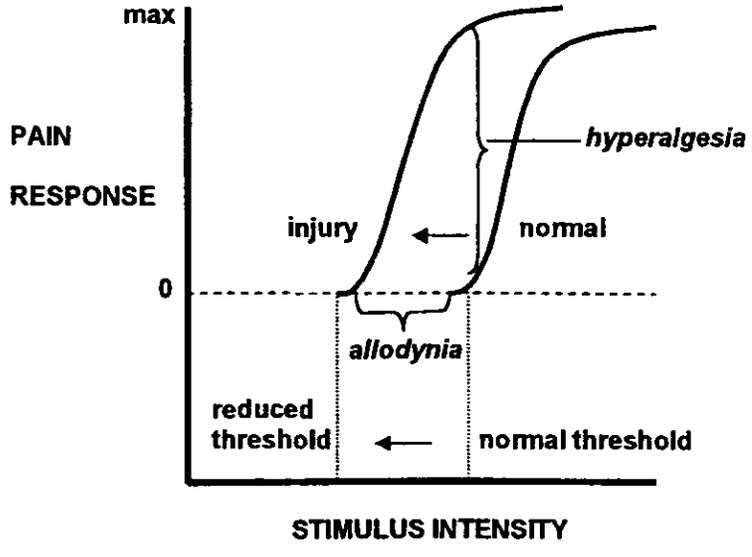

Figure 1. A definition of hyperalgesia and allodynia in terms of a shift to the left of the response curve of a sensory neurone. Under normal conditions the neuron is activated by a stimulus intensity that constitutes a normal threshold for nociception. After injury the response curve shifts to the left. Allodynia is the pain evoked by stimuli of intensity less than normal threshold. Hyperalgesia is the greater response to stimuli of an intensity that normally would be painful.

Mechanisms of Complex Regional Pain Syndromes

For such reasons some authorities[3] have objected to allodynia being defined on the basis of a shift to the left. They prefer hyperalgesia to refer to the increased sensitivity of (normally) nociceptive afferents. On the other hand, Price et al[4] distinguish two types of allodynia. One they describe as low-threshold Aβ allodynia, which is evoked by gentle brushing with a cotton swab. The other they describe as high threshold allodynia, which is evoked not by gentle stimuli but by intense static stimuli, like pressure, that normally are not painful. The latter would be what Campbell[3] refers to as hyperalgesia. Others[5,6] recognise similar distinctions. They consider brushing to be a dynamic (moving) stimulus, and refer to pain evoked by such stimuli as brush-evoked allodynia or dynamic allodynia. Pain evoked by static pressure they refer to as static hyperalgesia.

The danger of misusing the term allodynia lies in the inference that might be drawn. If allodynia is simply a shift to the left of the response curve of otherwise potentially nociceptive afferents, all that is required is a mechanism that lowers the threshold of activation of their pathways. This could readily be achieved by facilitating or disinhibiting their second-order neurones. However, if allodynia requires a change in modality, the mechanism cannot involve simply a lowering of threshold, it must involve a switch, in which non-nociceptive afferents gain access to nociceptive pathways, be that by developing totally new connections, or opening latent or previously suppressed connections.

In the present article, when quoting previous and especially older literature the term *allodynia* is used without further qualification to mean whatever the original author felt it to mean. Otherwise, when considering the mechanisms of this clinical feature, the terms *brush allodynia* and *pressure hyperalgesia*, as defined above, are used.

Historical Perspective

In the past, patients presenting with a constellation of neurologic, vasomotor and trophic features attracted diagnostic labels[7] that:

	Example
Described the region affected	Shoulder-hand syndrome
Described the circumstances of onset	Post-traumatic pain syndrome
	Post-infarctional scelero dystrophy
Reflected one or more of the component features	Post-traumatic spreading neuralgia
	Post-traumatic painful arthrosis
	Chronic traumatic oedema
	Post-traumatic oedema
	Acute atrophy of bone
	Peripheral acute trophoneurosis
	Traumatic angiospasm
	Post-traumatic osteoporosis
	Traumatic vasospasm
	Reflex neurovascular dystrophy
Implied the mechanism	Sympathetic reflex dystrophy

Two terms that arose into most common usage were *causalgia* - meaning burning pain, and *reflex sympathetic dystrophy (RSD)*. The term causalgia was applied to cases in which nerve injury was the precipitating event. RSD was applied to cases in which a nerve injury was not evident.

On clinical grounds, the vasomotor, sudomotor, temperature and trophic changes, were inferred to indicate sympathetic overactivity or underactivity, and it was the presence of these features that distinguished the syndromes from other painful conditions due to nerve injury, musculoskeletal injury, or visceral disease. Classical or archetypical descriptions of the two conditions were developed that grouped the clinical features as injury, neurological features and sympathetic features.

Causalgia

Injury

Partial nerve injury was regarded as the cardinal aetiological factor in causalgia. The most frequently affected nerves were said to be the sciatic, the median, and the brachial plexus.[7] Causalgia was reported to occur in about 2-5% of such nerve injuries.

Neurological Features

In addition to the sensory loss resulting from the primary nerve injury, the patient suffers from pain and other sensory disturbances. The pain is usually burning in quality, intense, continuous, with episodes of more severe pain; and is usually felt distally in the affected limb.[7,8]

The other sensory disturbances are hyperalgesia and allodynia. These terms were used to refer to the phenomenon that the patients found that touching, or even brushing the skin of the affected part to be painful. These features were regarded as due to sensitisation of intact nerve endings in the affected limb by sympathetic activity, rendering them more easily activated by normal and subliminal stimuli. Evidence brought to bear in support of this inference was that:

- sympathetic features were otherwise prominent in the syndrome;
- sensitivity could be abolished by interrupting sympathetic activity by sympathectomy or by sympathetic nerve blocks,[7-10] or by the infusion of guanethidine.[11,12]

Mechanisms of Complex Regional Pain Syndromes

- In patients successfully relieved of their pain and sensitivity, the injection of noradrenaline intradermally immediately reproduced the causalgic symptoms.[13]

Sympathetic Features

The sympathetic features of causalgia were believed to evolve through an early and a late phase.[7] In the early phase, the vascular changes consist of vasodilation and consequent warmth with sweating and redness. Later, the vascular changes consist of vasoconstriction with consequent cooling and cyanosis of the skin. The skin undergoes atrophy and becomes glossy. Hair loss occurs. Initially the subcutaneous tissues are oedematous, but later they stiffen. Similarly, joints swell but later stiffen. In parallel, muscles initially spasm but later atrophy. Bones progressively become demineralised.

An attractive synopsis is that there is an early "angry" phase with vasodilation, warmth, redness, swelling, and spasm, followed by an atrophic phase of vasoconstriction, coldness, cyanosis, induration, stiffness and osteoporosis.

Reflex Sympathetic Dystrophy (RSD)

RSD shares many of the features of causalgia, and differs essentially only in the nature of the precipitating cause.

Injury

The trauma is often trivial. RSD has been reported after simple sprains,[7] dislocation,[7] fracture,[7,14] a crush injury,[7] a surgical procedure,[7,15] and even simple venepuncture.[16] Other causes include spinal injury, cerebrovascular accidents, spinal cord injury, myocardial infarction, diabetic neuropathy, and central nervous system disease such as multiple sclerosis (see Appendix I).

Neurological Features

The cardinal feature of RSD is pain that is continuous and burning in quality and usually felt distally in the affected limb. The pain is accompanied by hyperaesthesia and hyperalgesia.[7,17] The major difference between RSD and causalgia is the lack in RSD, of obvious sensory loss. Otherwise the neurological features of the two conditions are remarkably similar. Indeed, there is no detectable difference in the description of pain given by patients with causalgia and those with RSD.[18]

This lack of difference could be interpreted as suggesting that nerve injury does occur in RSD, but that the injury affects nerves that lack a cutaneous distributions such as muscles nerves and articular nerves, and therefore, escapes clinical detection.

As in causalgia, the neurological features of RSD were believed to be due to facilitation of peripheral nerve endings by sympathetic efferents and noradrenaline, for they could be relieved by sympathetic blockade[7,9,10,19] or intravenous guanethidine.[11,20,21]

Sympathetic Features

The sympathetic features of RSD were grouped into three phases (Table 1).[7] As in causalgia an initial "angry" or "inflammatory" phase was typically followed by a cold, dry, stiff and atrophic phase. The involvement of the sympathetic nervous system in these changes was inferred because sympathetic blocks or guanethidine infusion could reverse the changes, at least in the early phases.[7,9,10,11,20,21,22] The joint stiffness and muscle atrophy seen in the late phase could not be reversed by neural blockade.

Histological studies of the joints of patients with RSD, revealed various degrees of synovial oedema, proliferation of synovial cells and capillaries, fibrosis of the sub-synovium, and some periarticular infiltration by chronic inflammatory cells.[23] Bone scans revealed a predominant localisation of nuclides in the juxta-articular region of bones suggesting a focal increase of blood flow to these areas.[24] This in-

TISSUE	TEMPORAL PHASE		
	EARLY	INTERMEDIATE	LATE
VASCULAR	Warm Dry	Cold Sweating	Cold
SKIN	Red	Cyanotic Glazed	Pale Smooth Glossy
HAIR		Loss	Denuded
NAILS		Brittle Grooved	Brittle Ridged
SUBCUTANEOUS	Edema	Brawny	Atrophy Fat loss
JOINTS	Swollen Tender	Thick Stiff	Fibrosis Ankylosis
MUSCLES	Spasm	Wasting	Atrophy
BONES		Osteoporosis	Atrophy

Table 1. The sympathetic features of reflex sympathetic dystrophy grouped in temporal phases to describe the phases of the conditions. Based on Bonica.[7]

creased blood flow was inferred to be the mechanism of demineralisation seen in RSD.[24]

Thermographic studies showed that affected limbs may be warmer or colder than the unaffected limb but more commonly colder in chronic cases.[25] Temperature asymmetry, however, is not unique to RSD, for it can occur in other pain states, by asymmetries greater than 2°C, and particularly when greater than 3°C are more frequent in RSD than in other disorders.[25] However, although skin temperature in RSD may not be significantly different from that of the uninvolved limb, muscle blood flow and resting blood flow are significantly increased.[26]

Extension

Perhaps the most bizarre feature of RSD is its extension to regions well beyond the initially affected area. Scintigraphic[23,24,27] and neurologic studies have shown that subtle and substantial changes can be detected in the opposite limbs of patients with RSD and there has been one case report of RSD affecting the whole body after surgery for low back pain.[28]

Problems

Many problems befell the continued or wider recognition of causalgia and RSD. Foremost was the definition of liminal cases. Although the classical and archetypical descriptions rendered the recognition of florid cases straightforward, they did not define early or minimal cases. Critics asserted that:

- the label of RSD is quite practitioner dependent, ranging form a hyperalgesic, sweaty, oedematous, cool appendage to simply any surgical outcome that fails to meet the expectation of the operating surgeon.[29]
- of patients labeled as having RSD, perhaps 85% had nothing that even approached RSD, and clearly had other diagnoses such as neuralgias, peripheral vascular disease, and even myofascial pain syndromes.[29]

Otherwise, critics [30-35] have noted that:

- sympathetic features are not consistent,[33,36] skin temperature changes are variable and may be the same, warmer, or cooler on the affected side;[37] therefore, this cannot be a discriminating, diagnostic criterion;[30]
- the cutaneous features of RSD do not necessarily imply abnormal activity of sympathetic nerves;[33] they could be manifestations of normal responses to injury;[30] coldness and cyanosis could be due to hypersensitivity to circulating amines[33,35] and warmth and redness could be due to neuropeptides possibly released antidromically from sensory nerves;[35] trophic changes can be ascribed to disuse[30] or immobilisation;[31]
- abnormal skin temperatures can occur in the absence of any noradrenergic vasomotor innervation;[35]
- pain does not correlate with vasomotor or sudomotor activity, and causalgic pain can occur in the absence of vascular changes;[32,33]
- microneurographic studies have detected no abnormal sympathetic activity in patients with RSD;[32,33,38-41]
- the effect of sympathetic blocks is unpredictable, and does not predict the effect of sympathectomy;[33]
- pain relief after blocks does not correlate with the duration of effect of sympathetic blocks,[11,33,42]
- pain relief after blocks is independent of the thermal effects of blocks;[11,33]
- sympathetic blocks relieve pain even when the causative lesion is proximal to the block;[32]
- pain is relieved by blocking the stellate ganglion with morphine which does not produce block of sympathetic efferents;[32,43]
- intravenous clonidine interrupts sympathetic transmission but has no effect on pain;[33,44]
- the effects of stellate ganglion blocks have never been controlled in any studies of causalgia;[30,33,45] one study found that only 15 out 54 blocks satisfied criteria for an effective block;[46]
- stellate ganglion blocks are not target specific; very little of the injectate reaches the area of the stellate ganglion and much spreads elsewhere;[29]
- when compared to saline controls, intravenous guanethidine or reserpine has no diagnostic or therapeutic efficacy;[47-50]
- saline is just as effective as phentolamine in relieving pain;[51-53]
- investigations of the purported sympathetic and noradrenergic basis of RSD have found decreased, rather than increased, levels of catecholamines in the venous blood of limbs affected by RSD;[30,33,54,55]
- the intra-cutaneous injection of noradrenaline evokes pain in only a minority of patients but few patients remain sensitive to such injections when re-examined 12-16 years later;[56]
- with respect to taxonomy, critics have asked how to classify patients who lack sympathetic features or patients who have the sympathetic features but no pain.[31]

These observations strike at the heart of the traditional, clinical models of causalgia and RSD and their diagnosis. Denied sympathetic blocks and intravenous guanethidine, proponents are left with clinical features of questionable specificity upon which to make the diagnosis.

A Resolution

At a conference held in 1993, proponents of RSD[29,57] agreed that:

- the term (RSD) had lost any clinical or research utility because of wide-

Mechanisms of Complex Regional Pain Syndromes

spread, indiscriminate use, with no diagnostic or descriptive criteria;
- the reflex that is required by the term has never been demonstrated;
- the linkage to the sympathetic nervous system is inconsistent and inconstant;
- the term *dystrophy* is used imprecisely and the features may not be present consistently.

They resolved to create a nomenclature that was based on a descriptive method which was clinically useful but did not imply any particular mechanism.[29] They arrived at the term *complex regional pain syndrome* (CRPS) on the grounds that

Complex: recognised the intellectual and clinical complexity of the symptoms and signs encompassed by this rubric

Regional: described the distribution of the symptoms which is the hallmark of the conditions

Pain: is the sine qua non of the condition.

Syndrome: recognised that the condition was not ascribed to a single aetiology, and represented a cluster of symptoms and signs.

This nomenclature was adopted for the second edition of the taxonomy of the International Association for the Study of Pain.[1]

The condition previously known as RSD was reclassified as CRPS type I. Its diagnostic criteria were to be:[1]

1. The presence of an initiating noxious event, or a cause of immobilisation;
2. Continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event;
3. Evidence, at some time, of oedema or changes in skin flow, or abnormal sudomotor activity in the region of pain;
4. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

The condition previously knows as causalgia was reclassified as CRPS type II. Its diagnostic criteria were to be:[1]

1. The presence of continuing pain, allodynia or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.
2. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.
3. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

These revisions addressed several criticisms that had been raised about RSD and causalgia. The emphasis on "sympathetic" features was reduced. Instead, the emphasis lied on the presence of pain and allodynia or hyperalgesia. Oedema, changes in skin blood flow, or sudomotor activity needed to be present only at some time in the course of the condition. A link to the sympathetic nervous system was not implied [29] and, in particular, there was no implication that the sympathetic nervous system was responsible in any way for the pain.

CRPS	
Type I	**Type II**
SMP	SMP
SID	SID

*Table 2. **The four types of complex regional pain syndrome (CRPS). SMP; sympathetically maintained pain. SID; sympathetically independent pain.***

Indeed, a further dimension was added that did not prejudice the primary diagnosis. It was recognised that the pain of CRPS might be relieved by sympatholytic procedures or it might not. Pain not so relieved was classified as sympathetically independent pain (SID), whereas pain relieved by sympathetic blocks was classified as sympathetically maintained pain (SMP). Whether or not the pain could be relieved by sympathetic blocks was not considered an essential criterion for any condition. It was simply a feature that extended the classification to four basic conditions (Table 2).

Mechanisms

In the past, authorities ventured to explain all the features of CRPS by singular, comprehensive models. These models, however, were essentially heuristic. They linked the various features descriptively into a single disorder, but afforded little or no insight into the specific mechanisms of each

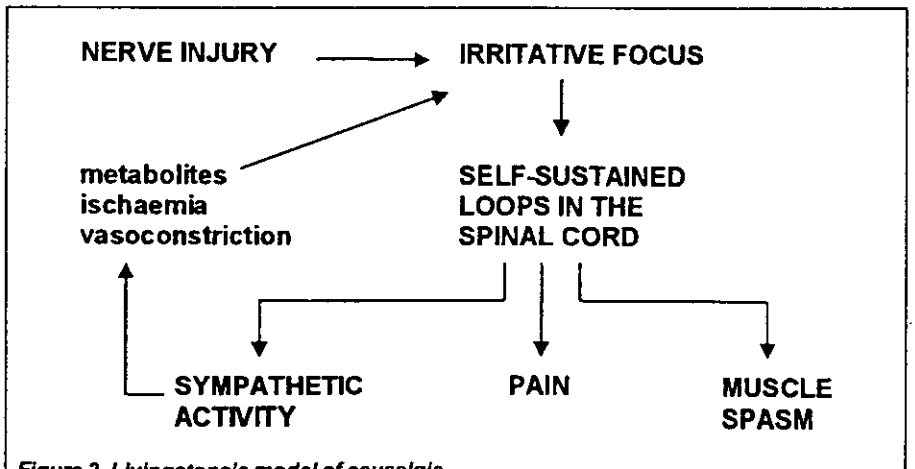

*Figure 2. **Livingstone's model of causalgia.***

feature. One of the earliest models, that of Livingstone,[58] serves just as well today as it did when it was first conceived (Fig. 2). Authors of later models acknowledge that theirs are essentially based on that of Livingstone.[59]

The Livingstone model maintains that nerve injury creates a peripheral "irritative" focus that, in turn, generates "self-sustained loops" in the spinal cord that generate muscle spasm, pain, and sympathetic activity. The latter causes vasoconstriction and ischaemia in the periphery, forming metabolites that are responsible both for the sympathetic features of the condition and maintenance of the irritative focus.

While encapsulating the essential features of CRPS such models do not offer insights into the mechanisms involved. They do not explain the nature of the "irritative focus" or how it generates "self-sustained loops" or what these actually are. Moreover, these models accept that sympathetic activity is an essential part of the condition and mechanisms involved, which modern research has brought into question. Nevertheless, such models have served to direct attention towards individual components of the syndrome in the pursuit of the explicit mechanisms involved.

Brush Allodynia

Of all the features of CRPS, brush-evoked allodynia is the best understood. For allodynia there is a satisfying model supported by experimental evidence both in humans and in laboratory animals.

Brush allodynia is mediated by Aβ fibres. The evidence for this is that:

- the reaction time for this sensation is consistent with the conduction velocity of large myelinated afferents;[4,60-63]
- the pinprick threshold for brush-evoked allodynia is equal to, or nearly equal to, that of low threshold mechanoreceptors in healthy skin;[4,60-63]
- electrical stimulation evokes pain from symptomatic tissues at stimulus intensities that evoke only tactile sensations in normal skin;[4,40,60,63-65]
- brush-evoked allodynia is abolished by nerve blocks at a time when tactile sensations are but other sensations remain unaffected.[5,38,40,62,66]

Brush allodynia also involves central neuronal plasticity. The evidence for this is indirect in humans but direct in laboratory animals.

In humans, the application of capsaicin to skin lowers the threshold for activation of tactile mechanoreceptors in nearby skin unaffected by the capsaicin.[5,60,66-69]

The mechanism of this sensitisation is central for it is evident upon electrical stimulation of peripheral nerves, which bypasses any putatively sensitised peripheral nerve endings.[5,67]

Similar phenomena have been observed in animals, and are associated with expansion of the receptive fields of WDR neurones and lamina I neurones in the dorsal horn.[70-75]

The expansion of receptive fields explains the extension of allodynia to regions beyond the immediate site of injury in CRPS.

Blocking peripheral nerves relieves allodynia in regions beyond the territory of the affected nerve.[65]

Primary nociceptive input initiates and maintains brush allodynia. The evidence for this is circumstantial.

Some studies have shown that nociceptive primary afferents are sensitised to mechanical, thermal, and chemical stimuli in patients with brush allodynia, which implies ongoing activity in these afferents.[6,39] However, others have found no evidence of sensitisation of C fibres or Aδ fibres.[76]

Nevertheless, other studies have shown that blocking afferent input from sources of nociception, either by using local anaesthetic blocks or by compressing nerves, abolishes both spontaneous pain and allodynia.[5,60,65,77]

It would, therefore, seem that ongoing input from primary afferents is essential for the maintenance of allodynia. The implication is that this input triggers central sensitisation. However, the mechanism by which nociceptive input initiates and maintains central sensitisation has not been established. One conjecture is that nociceptive input facilitates second-order neurones through the action of glutamate acting on NMDA receptors, and through the sustained action of substance P and neurokinin A.[60] Neurokinin A has been shown to spread beyond its immediate site of release following noxious stimulation,[78] and may well thereby excite distant neurones, rendering them more sensitive to peripheral input. An alternative conjecture is that central sensitisation could be due to loss of inhibition of second-order neurones resulting from transsynaptic degeneration of inhibitory inter-neurons caused by nociceptive excitotoxicity.[4,60,74,79]

In essence, the mechanism of brush allodynia can be summarised as shown in Figure 3. There is no evidence that

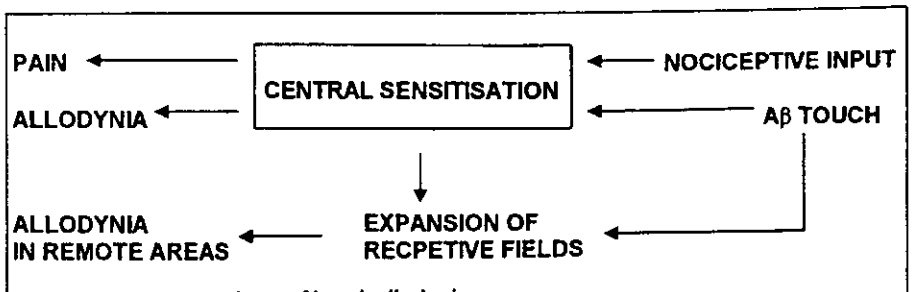

Figure 3. The mechanisms of brush allodynia.

Mechanisms of Complex Regional Pain Syndromes

brush allodynia is sympathetically mediated. Experiments have shown that in patients in whom allodynia is relieved by sympathetic blocks, electrical stimulation of Aβ fibres, and vigorous rubbing of the previously affected skin does not re-evoke allodynia.[80] This argues against peripheral sensitisation. Any role of the sympathetic nervous system must relate only to the sensitisation of primary nociceptive input or to the maintenance of central sensitisation. However, any such role is dependent on the validity of the data concerning sympathetically maintained pain.

Static Hyperalgesia

The available evidence indicates that static, or punctate, hyperalgesia is due to a shift to the left of the response characteristics of nociceptive afferents, due to central sensitisation.

Experimental injury to the skin produces mechanical hyperalgesia in normal volunteers[5,60,66,8] that is mediated by nociceptive afferents [6,39,66,68] that exhibit increased sensitivity.[82-84]

Central sensitisation must be operating because punctate hyperalgesia is not abolished by peripheral blocks of the injured site[68] and outlasts the spontaneous pain induced by capsaicin injury to the skin.[66]

In animal experiments, the extension of hyperalgesia to areas remote from the original site of injury is associated with expansion of the receptive fields of second-order nociceptive neurones.[72,85-87]

The inability of peripheral blocks to relieve static hyperalgesia indicates that the central sensitisation involved differs from that which underlies brush allodynia. Whereas sensitisation to Aβ input requires ongoing peripheral nociceptive activity, sensitisation to nociceptive input seems to be induced by a noxious stimulus but outlasts that stimulus. What is not known is how long that sensitisation lasts: whether it is self-limited or permanent; or whether it is rekindled by periodic nociceptive input in order to appear long-lasting. In animals, features of hyperalgesia resolve spontaneously;[88] therefore, there are no models, at present, of the long-lasting hyperalgesia seen in humans.[86]

Spontaneous Pain

In the past, basic scientists who have sought to explain the pain of CRPS have explored not only the mechanisms of the pain but also its relationship to sympathetic activity. Their investigations, however, predated the doubts that have been cast on the validity of sympathetic blocks and, therefore, the necessity of linking pain to sympathetic activity.

Accurate figures on the prevalence of SMP are hard to find, but some studies suggest that only 45% [89] or as few as 36% [52] or 33% [77] of patients with CRPS have SMP. Even fewer patients have genuine SMP if responses to blocks are discounted for placebo effects.[52] Phentolamine[51-53] and guanethidine[47,48-50] infusions are just as effective as saline infusions and so cannot be regarded as specific tests of sympathetic mediation. The only unchallenged hallmark of sympathetic mediation have been local anaesthetic blocks of the sympathetic trunk. However, a recent study now calls even them into question.

In a cross-over study, Price et al[90] performed stellate ganglion blocks or lumbar sympathetic blocks using either normal saline or local anaesthetic. In terms of immediate pain relief and relief of allodynia and hyperalgesia, the two agents were indistiguishable. Local anaesthetic differed from normal saline only in that it afforded longer-lasting relief. Consequently, the immediate response to sympathetic blocks cannot be held as a diagnostic criterion for sympathetically mediated pain.[90]

Consequently, the significance of sympathetic mediation of pain may have been overestimated in the past, and the pursuit of a sympathetically mediated mechanism of pain applies to only a minority of patients. Nevertheless, the mechanisms that have been proposed serve equally for SIP as they might for SMP.

Review articles have suggested four possible mechanisms of the pain of CRPS. They are ephapses,[90,92] sympathetic afferents,[32,33,90,92] neuromas,[92,93] and ectopic activity in dorsal root ganglia.[88,92,94] Each of these requires an injury to a peripheral nerve and, therefore, serves to explain the pain of CRPS type II. No explanations have been proffered for CRPS type I. However, the pain (and other features) of CRPS type I can be explained if it is assumed that this condition involves occult (i.e., clinically unapparent) nerve injury.

The **ephapse model** requires that, after nerve injury and at the site of injury, connections develop between peripheral axons such that impulses along one are transmitted to the other. The connections could be between sensory afferents such that normal stimuli along the distal segment of an intact and non-nociceptive afferent are communicated to the proximal segment of a nociceptive afferent, resulting in non-noxious stimuli being perceived as painful. The connections could be between efferent sympathetic fibres and nociceptive afferent fibres, such that efferent activity is reflected as nociceptive activity.

Arguments against this model are that:

- such ephapses as do occur after nerve injury are not between the appropriate axons required by the model;[90]
- ephapses between sympathetic and afferent fibres have not been identified;[45,59]
- if ephapses occur between distal non-nociceptive axons and proximal nociceptive axons, the opposite should also occur such that peripheral noxious stimuli would be

perceived as not painful (this has not been observed);[63]
- ephapses take time to develop and, therefore, cannot explain the early onset of pain;[8,65,92]
- local anaesthetic delivered to the putative site of such ephapses does not relieve pain,[92] and
- afferent activity from ephapses is not synchronous with sympathetic activity.[90]

The model of **sympathetic afferents** has been promoted by one author[32,33] largely on the grounds that other models inadequately explain the pain of CRPS. Although the author refers to earlier anatomical literature on the existence of sympathetic afferents, this work has not been corroborated by modern studies; nor is there any convincing physiological evidence of afferent activity in sympathetic nerves in patients with CRPS. Earlier reports that morphine injected around the stellate ganglion relieves the pain of CRPS without affecting vasomotor activity [43] have been contradicted.[94] This model remains only a conjecture available for pursuit if other explanations are less satisfying.

Neuroma-formation is the one proposed mechanism of pain in CRPS that has most often been invoked in the literature on CRPS.[35,45,90-93] However, this does not necessarily argue that it is the most favoured or the best explanation. Rather, it may be only that neuroma formation is the most studied and best understood pathophysiological phenomenon of nerve injury. Therefore, when authorities are called upon to offer explanation for CRPS they gravitate to what is most studied and best understood.

Neuromas occur when peripheral nerves are transected. Within hours of transection, axon sprouts appear from the cut end of the proximal segment. Between two and 30 hours after injury, a small proportion of these axons exhibits spontaneous discharges.[95] With the passage of time a greater proportion of axons discharge spontaneously and become mechanosenstive.[96-100] Moreover, the sprouts are sensitive to circulating adrenaline and noradrenaline, and the excitation of neuromas by amines can be blocked by phentolamine.[91] This latter feature rendered neuromas particularly attractive as a source of SMP.

The neuroma model is attractive in that it provides a pathology consistent with nerve injury and capable of producing spontaneous pain. However, while directly applicable to CRPS type II, it is not applicable to CRPS type I, unless it is acknowledged that in CRPS type I neuromas are formed on deep nerves, and have hitherto been clinically inaccessible. Moreover, the neuroma model predicts that the pain of CRPS would be relieved by blocking the neuroma, but peripheral blocks or neurectomy do not always succeed in relieving the pain of CRPS.[8,32] The neuroma model has also been rejected, at least for SMP, on the grounds that:
- there is no correlation between pain and vasomotor activity;[32]
- sympathetic activity is normal in CRPS;[32,101] and
- substances other than adrenaline and noradrenaline are equally capable of exciting neuromas, including these include acetylcholine, histamine and prostaglandin E.[32]

An adaptation of the neuroma model is the **constriction model.**[102] In experimental animals if ligatures are applied to a peripheral nerve so as to constrict it but not transect any of the axons, the animal develops pain, allodynia and hyperalgesia.[102] At the site of ligature, the axons are compressed by the ligatures and by the oedema that occurs.[103] Distally, axons degenerate. Virtually all the myelinated axons degenerate and nearly all the unmyelinated axons.[103,104] Physiologically, however, myelinated and unmyelinated fibres become spontaneously active, both distal and proximal to the site of injury.[103] The activity of C fibres and Aδ fibres is presumed to be the basis for pain induced by this type of lesion. The source this activity has not been established for certain but one interpretation is that it arises from growth cones from the axons at the site of injury.[103] The injured axons develop an increased number of sodium channels and an increased number of α-adrenergic receptors, which renders them susceptible to spontaneous discharge and to stimulation by amines.[9,91] In effect, the injured axons behave like neuromas, and the condition is sometimes regarded as a neuroma-in-continuity.[91]

The constriction model offers an explanation of CRPS type without requiring frank transection of a nerve, as in the case of neuroma. It can also be adapted to explain CRPS type I. Somatic injuries might fail to injure a peripheral directly but focal swelling of injured tissues surrounding a peripheral might nonetheless constrict it.

Ectopic impulse generation in **dorsal root ganglia**[88, 105,106] is an appealing alternative to the neuroma or constriction models in that it explains why peripheral blocks, in some cases, fail to relieve the pain of CRPS. Unfortunately, this model has barely been explored in experimental animals and not at all in clinical studies. The circumstantial evidence is that:
- after transection of a peripheral nerve, not only do neuromas develop but dorsal root ganglion cells become spontaneously active;[88,105-107]
- dorsal root ganglion cells also become active after constriction of a peripheral nerve;[108]
- the spontaneous activity that develops after nerve constriction is not abolished by transecting the affected nerve proximal to the site of injury or just distal to the dorsal root ganglion, but it is totally abolished if

Mechanisms of Complex Regional Pain Syndromes

the dorsal root is transected proximal to the dorsal root ganglion;[108]
- after nerve injury, dorsal root ganglion cells receive a neo-innervation by sympathetic efferent fibres;[109]
- spontaneously active dorsal root ganglion cells are activated by adrenaline,[88,105] and are suppressed by phentolamine.[109]

The latter phenomena render the dorsal root ganglion model an attractive explanation of SMP. Moreover, the dorsal root ganglion model offers an explanation of pain that is relieved by stellate ganglion blocks but not by regional intravenous blocks of the upper limb.

The model that has attracted the greatest acclaim is that of **Roberts.**[110] Indeed, it was hailed by Bonica as "brilliant".[111] This model proposed that at the time of injury, C fibres activate and sensitise wide dynamic range (WDR) neurones in the spinal cord. These neurones remain senstisied by normal inputs from large diameter afferents whose activity is perceived as painful and is maintained by sympathetic activity. In support of this model, Roberts and colleagues showed in animal experiments that only WDR neurones were activated by sympathetic stimulation,[112] and that such stimulation drove hair afferents and slowly adapting peripheral afferents.[113]

Arguments raised against this model are that:
- there is no correlation between pain and vasomotor activity.[32,33]
- the frequency of stimulation required to activate peripheral receptors by sympathetic stimulation is large and in excess of what is normally encountered in sympathetic nerves.[59]
- sympathetic activity is normal in CRPS.[32,101]
- if WDR neurons were sensitised, sensitivity should be also be evident for other modalities such as heat, but this is not always the case.[64]
- the model requires that the sensitisation of WDR is maintained not by nociceptive input but by input from large diameter afferents. It predicts that sympathetic blocks would eliminate this sensitisation by normalising the activity of large diameter afferents. Were that the case, then stimulating large diameter afferents, electrically or by vigorous rubbing of the skin, should reinstate the pain and allodynia after a sympathetic block. This is not the case.[4,64] Successful sympathetic blocks eliminate hyperalgesia, and protect the patient from re-activation of their pain.[64,80]

Central Mechanisms

Where all the foregoing models fail is in the explanation of CRPS that develops following lesions in the central nervous system (Appendix I), in which there is no peripheral injury, and no basis for the formation of neuromas or the development of spontaneous activity in the dorsal root ganglia. Indeed, the occurrence of CRPS after central lesions has repeatedly been raised as a criticism of all peripheral-based models of the pain of CRPS.[32,33,92] For this reason, several authors have gravitated towards a "central" mechanism for the pain of CRPS, although without elaborating any particulars.[8,92,93] Sunderland[8] introduced the notion of a "turbulence" hypothesis, in which causalgia was caused by disordered activity in the spinal cord induced by retrograde and trans-synaptic degeneration following peripheral nerve injury. Nathan[93] referred to the work of Denny-Brown[114-116] as an explanation of the spread of pain and hypersensitivity.

The studies of Denny-Brown[114-116] revealed that the organisation of the spinal cord and brainstem is far more complex than the peripheral models of CRPS currently admit. In the normal state, segmental nerves ramify over multiple spinal cord segments and elicit both excitatory and inhibitory influences over multiple segments through the dorsolateral tract. Normal sensation involves not simply the response of a single neurone at the level of entry of a peripheral afferent, but a profile of excitatory and inhibitory activity over several segments. Transecting a peripheral nerve results in quite bizarre sensory changes. These changes do not involve ongoing peripheral activity, but occur as a result of loss of peripheral input. They include development of areas of numbness and areas of hyperaesthesia but most strikingly, these areas are not fixed; they change size, and can be made to shrink or enlarge by manipulating the tonic inhibitory functions of the dorsolateral tract either by injections of strychnine or by selectively transecting the tract.[114-116]

These observations indicate that the wiring of the spinal cord is such that simple loss of input from the periphery can result in hyperaesthesia, not because of sensitisation of the dorsal horn, but through loss of inhibition. Others have studied the same phenomenon more explicitly.

Studies in cats have shown that, following peripheral deafferentation, receptive fields of dorsal horn neurons increase[117,118] but the extent of expansion is too great to be accounted for by axon sprouting.[118] Rather, the investigators reasoned that the expansion was due to unmasking of latent synapses, ostensibly through loss of inhibition.[117,118] Furthermore, earlier work by Hillman and Wall[119] had shown that the peripheral receptive fields of low threshold and high threshold receptors overlap extensively, and have different excitatory and inhibitory effects on dorsal horn neurons. More significantly, they showed that these receptive fields and their effects were subject to descending modulation. Blocking descending inhibition increases the activity of dorsal horn cells and increases the sizes of their recep-

tive fields.[119]

Meanwhile, other studies have shown that deafferentation causes spontaneous activity in nociceptive neurons in the dorsal horn or trigeminal nucleus.[120-122] This activity is not driven by peripheral input; indeed it can be exacerbated by spinal anaesthesia. Denied their accustomed peripheral input, these neurones behave as if they have unstable membranes and discharge spontaneously. Moreover, they lack receptors to conventional transmitter substances, and are unreceptive to iontophoretic application of GABA, glycine, glutamate and homocysteine.[120]

Collectively these observations allow for a central model of the pain of CRPS. The pain is not caused by peripheral nociceptive input but either by peripheral deafferentation or by loss of descending inhibition. Thus, the pain of CRPS could be a form of "central" pain, caused, in some cases, by peripheral deafferentation or, in other cases, by central lesions. Such a mechanism is the only one that can account for both peripheral and central causes of CRPS. Allodynia and hyperalgesia occur in company with the pain not because of excitation or facilitation, but as a result of loss of inhibition of surrounding segments.

A Synthesis

Just as peripheral models do not explain the pain suffered by patients with central causes of CRPS, the central model does not explain those cases in which peripheral somatic blocks still relieve their pain. A diplomatic synthesis could be that there is no singular explanation for the pain of CRPS. Rather, it might be that different patients suffer injuries at different sites along a common pathway. As a result, patients may resemble one another clinically, but the mechanisms of their pain are slightly different. Another modification is that perhaps as patients evolve through different phases of their condition, the mechanisms change. Thus, it might be that peripheral mechanisms operate early, but more central mechanisms operate later, when the condition becomes refractory to peripheral interventions.

Sympathetic Features

The so-called sympathetic features of CRPS almost defy explanation. The confounding factors are the variation between and within patients, and selection bias in studies of these patients. For example, Baron and Maier [123] studied only patients with cold limbs, whereas Kurvers et al [124] studied patients with warm limbs.

Traditional descriptions of the phases or stages of CRPS (Table 1) are idealised and have not been corroborated. When tabulated according to duration of symptoms, the "sympathetic" features of CRPS type I do not differ [125]. Early in the course of the condition, a somewhat greater proportion of patients (86%) exhibit oedema, but oedema is present in 55% of patients at 12 months. Osteoporosis on x-ray is uncommon in patients with a history shorter than two months, but is evident in some 40% of patients with a history longer than two months. The incidence of other features such as colour difference, temperature difference, hyperhidrosis, trophic changes in hair or nails, as well as well and neurological features, does not differ with time [125].

When tabulated according to whether the affected limb is warm or cold, the "sympathetic" features do not differ. Oedema occurs somewhat more frequently in patients with warm limbs and a short history; and trophic changes are more common in patients with a cold limb and a longer history. However, the incidence of hyperhidrosis, abnormal nail growth or hair growth, motor features or sensory features does not differ.[124]

Modern evidence clearly discounts sympathetic overactivity as the basis for the "sympathetic" features of CRPS.[123,126] At rest, skin blood flow and skin temperature may be greater, lower, or the same as on the unaffected side,[127] but if patients are acclimatised to a warm environment, they exhibit essentially normal sympathetic reflexes. At most, the evidence suggests that in the early phases of CRPS, vasoconstrictor drive is deficient.[123,126] Moreover, the deficiency lies in the central nervous system and not at spinal or peripheral levels.[126]

Such deficiencies as do occur are selective for certain aspects of vasomotor control. Whereas vasoconstrictor drive may be decreased, sudomotor activity is normal or may be enhanced.[128] Although thermoregulatory skin blood flow may be increased in early CRPS, nutritive skin blood flow is not. Yet both are decreased in later CRPS.[124] These irregularities indicate that mechanisms other than, or in addition to, sympathetic activity affect the vasomotor state of the affected limb, particularly in the later stages of the condition.

Among the mechanisms suggested are:

- hypersensitivity or upregulation of peripheral adrenoreceptors on blood vessels;[33,35,59 123,124,126]
- increased vascular permeability due to inflammatory mediators;[45,129]
- antidromic activity in C-fibres causing vasodilatation.[35,130]

Accordingly, the "sympathetic" features of CRPS may involve a mixture of various mechanisms at different times or at different stages of the condition. Decreased vasoconstriction might complement antidromic or inflammatory vasodilatation, but when vasoconstrictor drive returns it might compete with antidromic or inflammatory vasodilatation, resulting in unstable and variable features.

Regardless of the mechanism of vasomotor disturbances contemporary authorities agree that there is no corre-

Mechanisms of Complex Regional Pain Syndromes

lation between sympathetic dysfunction and pain.[32,33,123,126]

With respect to central causes of CRPS (Appendix I), peripheral mechanisms of the sympathetic features cannot be invoked. The only explanation must be disturbed descending control of sympathetic drive.

Summary

Given the available evidence, Livingstone's model can be elaborated as shown in Figure 4. The model allows for either a peripheral nerve injury to initiate the process, or a central lesion of the nervous system. The model presumes that in CRPS type I an occult nerve injury occurs.

Nerve injury might cause deafferentation and/or neuroma formation, or involve a constriction injury of the nerve. Neuroma formation or constriction injury causes spontaneous activity in C fibres and Aδ fibres, either at the site of injury or in dorsal root ganglion cells. This activity is transmitted to the nervous system where it excites and facili-

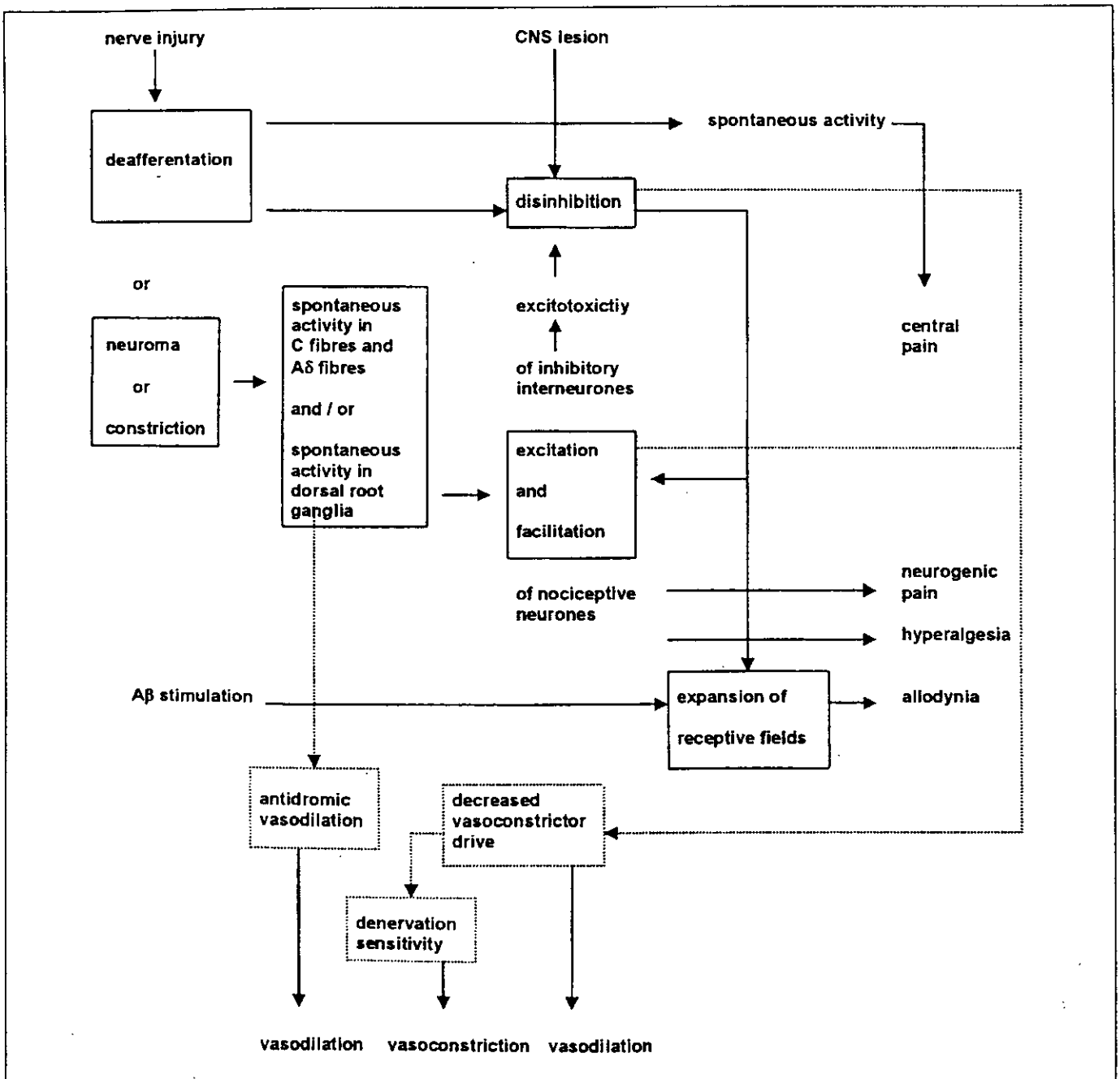

Figure 4. A model of the mechanisms of CRPS.

tates nociceptive neurones in lamina I and in lamina V. That activity is perceived as pain, which by the mechanism involved is neurogenic pain. Facilitation of the central neurons becomes the basis for hyperalgesia, and also causes expansion of the receptive fields of adjacent neurones. The expanded fields capture evoked activity in Aβ fibres which is received by the facilitated neurones, and is perceived as allodynia.

As well, or alternatively, inhibitory interneurones are stimulated by afferent activity and undergo excitotoxicity. Loss of inhibitory interneurones results in disinhibition of nociceptive neurones and in expansion of receptive fields.

On the other hand, additionally or alternatively, deafferentation alone may result in disinhibition of interneurones, and thereby facilitation of nociceptive neurones and expansion of receptive fields. Meanwhile, deafferentation may result in spontaneous activity in nociceptive neurones, thereby causing central pain.

A CNS lesion could evoke the same processes by causing disinhibition directly within the central nervous system. In order to accommodate visceral causes of CRPS, the model must assume that visceral disorders involve an injury to one or more of the nerves of the affected organ, or deafferentation of that organ.

Central to the generation of "sympathetic" features is disinhibition. This could be caused by central lesions or by deafferentation, and results in decreased vasoconstrictor drive, in the first instance. Subsequently, blood vessels develop denervation sensitivity. Meanwhile, in the case of peripheral lesions, spontaneous activity in nociceptive neurones may also cause antidromic vasodilation, which supplements or competes with sympathetically mediated vasodilatation or vasoconstriction.

The model expects and requires no reinforcing effect of sympathetic activity on the processes that generate pain and other features. Such effects require more compelling data on the role of sympathetic nerves in CRPS.

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Mechanisms of Complex Regional Pain Syndromes

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