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Complex regional pain syndrome: Part 1

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Introduction

This section of *Topical Issues in Pain 3* is devoted to conditions that have been largely attributed to pathobiology of the sympathetic nervous system. The previous chapter overviewed the anatomy and basic physiology of the autonomic nervous system. This chapter discusses the cluster of presentations that are classified under the umbrella term complex regional pain syndrome. The chapter describes and discusses their features and some aspects of their mechanisms and manifestations that may be of interest to physiotherapists seeking a broader understanding of the complex multifactorial underpinnings. The following two chapters discuss the pathobiology relating to the known *pain* mechanisms involved in CRPS.

Why is it that some people develop incredibly complex symptom presentations, often after relatively little in the way of injury? Remarkable cases where minor traumas quickly develop dramatic presentations—a simple bang on the elbow is followed by swelling of the hand, marked loss of joint range of motion and intense pain over the whole forearm that soon becomes resistant to all attempts to relieve the pain and which can then develop into an ongoing and devastating problem—are part of the experience of most physiotherapists. Cases of patients who present with quite long term pain and disability that includes observations and/or complaints by the patient of feelings of swelling, temperature changes, blotchy skin, altered sweating, poor skin health etc., are not uncommon and are often attributed to 'sympathetic' mechanisms. Is this true? What do we know about the role of the sympathetic nervous system in producing these states?

Further, can these sometimes awful presentations be prevented from happening in the first place, and once they are established how should we be thinking about their management?

This chapter, and the next two, explores and reviews postulated and known mechanisms relating to pain states where the sympathetic nervous system has been assumed to have a significant role.

It seems logical to assume that the autonomic nervous system, and hence the SNS, has to be involved in some way in all injuries, pathologies and pain states. The SNS, under normal conditions, has been shown to respond to nociceptive activity and to the presence of pain (see previous chapter and also reviews by Vallbo et al 1979, Wallin & Elam 1997). The reasoning is that since tissue damaging events represent a threat to the system's homeostasis and survival, the SNS, whose prime role is to engage defensive mechanisms, is likely to play a role in activating and co-ordinating the body's responses to restore or maintain homeostasis. Unfortunately, this isn't how the bulk of the literature on the role of the sympathetic nervous system in pain states following pathology or injury appears to view the situation.

An important point is that in normal circumstances, while the SNS *responds* to pain, its activity does not significantly excite sensory neurones and *cause* pain. Thus, the 'adaptive' role of sympathetic activity in the presence of pain is focused more on 'recovery physiology' rather than on the production of pain (Michaelis 2000).

Complex regional pain syndrome—new terminology to replace old

The role of the sympathetic nervous system in pain states has been a long held and reasonable assumption. It is based on the belief that sympathetic activity or hyperactivity is in some way involved in symptom generation. This belief is backed up by the clinical finding that sympathetic blocks, or destruction of sympathetic nerves when used in conditions diagnosed as having sympathetically maintained pain (SMP), like 'reflex sympathetic dystrophy' (RSD), are occasionally good at relieving pain as well as symptoms like oedema and sweating that are so often attributed to abnormal SNS behaviour. Further support comes from the finding that in some patients pain associated with neuropathy and RSD can be provoked by injection of adrenaline or noradrenaline or other 'adrenoreceptor agonists' (see Torebjork et al 1995, Wall 1995), whereas in normal people these hormones have no pain producing effect.

However, there is considerable argument surrounding the hypothesised role of the sympathetic system and also great difficulty in classifying patient presentations accurately. For example, many patients who fit into the RSD category do not respond at all to sympathetic blocking and a great many who do respond find that the relief is only temporary (see Chapter 4). Some patients may respond to a sympathetic block early on in the course of their problem, but not later, or vice versa (Torebjork et al 1995, Wall 1995). It seems that some patients can shift from having pain that may be dependent on sympathetic activity to having pain that is not. Some pain mechanisms appear to move and change over time, even though the presenting symptoms may appear stable.

For the past 10 years or so the golden nugget status that the sympathetic system has achieved and held on to has been subjected to quite a strong challenge that has resulted in a revised downward rating (see Chapters 3 & 4.)

In an attempt to clarify the nature of RSD and the role of the sympathetic nervous system in pain states a working party of world experts was set up following an International Association for the Study of Pain 'Special Consensus Workshop' held in Orlando, Florida USA in 1993 (Stanton-Hicks et al 1995). As an example of some of the challenges facing the group, the problems with the term RSD are representative: 'The term RSD is used imprecisely as it refers to changes in soft tissue which may or may not depend upon the sympathetic nervous system, may not be the consequence of a reflex, and may occur later in the disorder' (see Stanton-Hicks et al 1995, p 128). The goals set out in the workshop were to examine the terms RSD, causalgia, sympathetically maintained pain (SMP) and sympathetically independent pain (SIP) and to revise the classifications and definitions for better clinical utility.

One overriding theme was that the continued use of the term 'sympathetic' was unhelpful as it implied a pathological mechanism attributable to the sympathetic system that lacked conclusive evidence and which may have provided a barrier to the consideration of alternative mechanisms or a multiplicity of mechanisms acting in concert.

The group chose to use 'Complex Regional Pain Syndrome' (CRPS) as an overall term: *complex* to denote the varied clinical phenomena in addition to pain (see below); *regional,* since the distribution of symptoms and findings are so general, widespread and beyond the area of the original lesion—often being in the distal part of the extremities and rarely on the trunk and face, but having the potential to spread to other body areas; and *pain* since it was the cardinal symptom and being so disproportionate to the inciting event (Stanton-Hicks et al 1995, Boas 1996).

Within the CRPS designation are two subsets: Types I and II; both depend on the apparent cause and on the presentation—see Box 2.1. Type I corresponds to the 'old' RSD and Type II to 'causalgia.' Essentially the difference between the two is that Type I follows a tissue injury and Type II follows a frank nerve injury. A major departure as a result of this classification is the separation of the previously implied focus on sympathetic elements or mechanisms from the definitions. The result of this is the recognition that virtually any disorder, including CRPS, may have a component of sympathetically maintained pain alongside pains whose mechanisms are quite independent of the system, hence the terms sympathetically maintained pain (SMP) and sympathetically independent pain (SIP) (see Figs 2.1 and 2.2).

A major effect of this new classification is the focus on the presentation's history and the constellation of signs and symptoms, rather than on a presumed mechanism that seems to have unfairly overburdened the sympathetic system with responsibility and ignored other mechanisms that may be more relevant.

An important point for physiotherapy is that mechanistic approaches to pain syndromes like this are not necessarily helpful since they represent an interventionist biomedical paradigm whose object is to recognise a pathobiological mechanism, usually related to a pain mechanism, and then to *directly* alter the mechanism in some way. The recognition that pain is one thing but function and having a life are others too, does not seem to enter the therapeutic equation too easily. Even so, most physiotherapists like to feel comfortable with the problem they are dealing with and the belief here is that knowing about the current state of the art with regard to mechanisms is an important issue.

Box 2.1 Classification: complex regional pain syndrome (CRPS)

CRPS describes a variety of painful conditions that usually follow injury, occur regionally, have a distal predominance of abnormal findings, exceed in both magnitude and duration the expected clinical course of the inciting event, often result in significant impairment of motor function, and show variable progression over time.

CRPS Type I (RSD)

The syndrome follows an initiating noxious event.

1. Spontaneous pain or allodynia/hyperalgesia occurs beyond the territory of a single peripheral nerve(s) and is disproportionate to the inciting event.
2. There is or has been evidence of oedema, skin blood flow abnormality, or abnormal sudomotor activity, in the region of the pain since the inciting event.
3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

CRPS Type II (Causalgia)

This syndrome follows nerve injury. It is similar in all other respects to Type I.

1. Is a more regionally confined presentation about a joint (e.g. ankle, knee, wrist) or area (e.g. face, eye, penis), associated with a noxious event.
2. Spontaneous pain or allodynia/hyperalgesia is usually limited to the area involved but may spread variably distal or proximal to the area, not in the territory of a dermatomal or peripheral nerve distribution.
3. Intermittent and variable oedema, skin blood flow change, temperature change, abnormal sudomotor activity, and motor dysfunction, disproportionate to the inciting event, are present about the area involved.

Sympathetically maintained pain

Pain that is maintained by sympathetic efferent activity or neurochemical or circulating catecholamine action, as determined by pharmacological or sympathetic nerve blockade. SMP may be a feature of several types of pain disorder, and is not an essential component of any one condition. Conditions without any response to sympathetic block are, by contrast, designated as having sympathetic independent pain states (SIP).

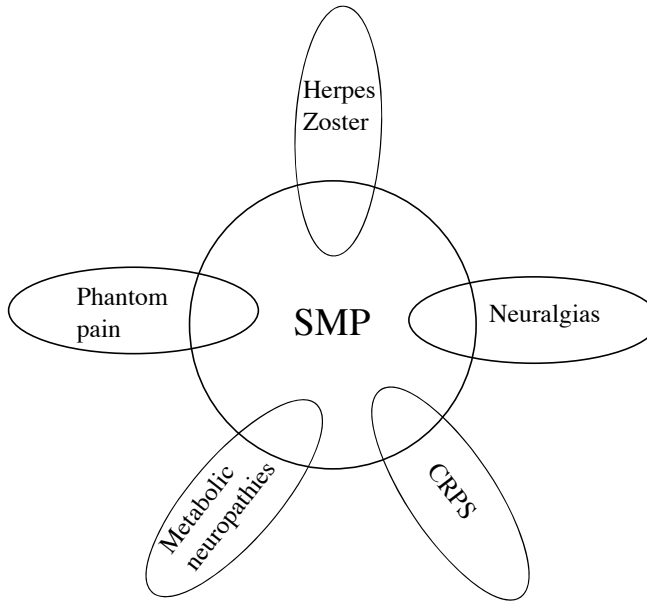

Fig. 2.1 Common pain conditions and the possible contribution of SMP to each.

Adapted from: Boas RA 1996 Complex regional pain syndromes: symptoms, signs, and differential diagnosis. In: Janig W, Stanton-Hicks M (eds) Reflex Sympathetic Dystrophy: a reappraisal. Progress in Pain Research and Management Vol. 6. IASP Press, Seattle 79–92

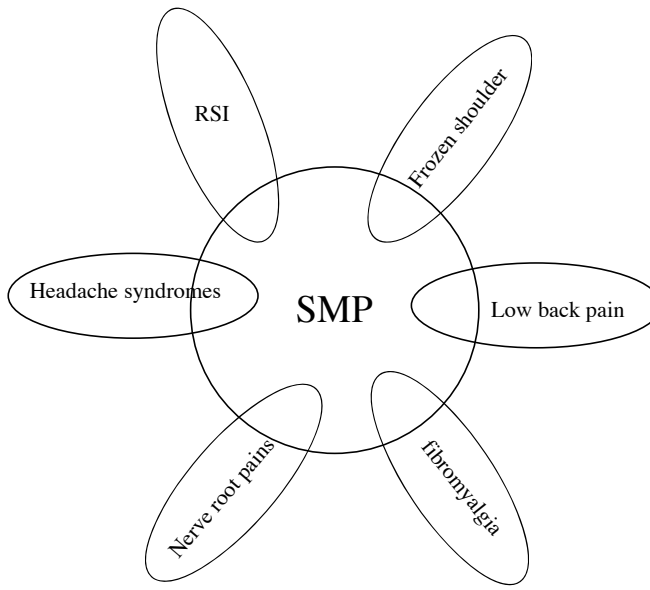

Fig. 2.2 As Figure 2.1 but including many common conditions seen by physiotherapists. Note that a 'sympathetic pain' component to these disorders is unproven at this stage.

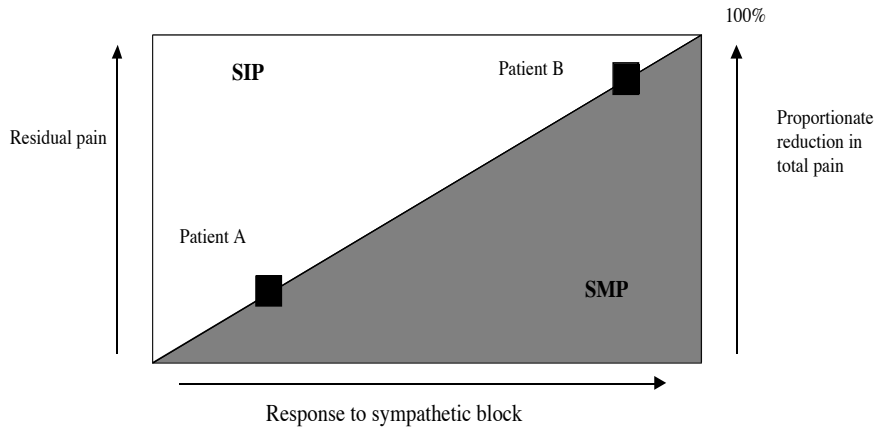

Fig. 2.3 The relative contribution that SMP may have to the overall pain. A: a person whose pain is predominantly unresponsive to sympathetic block. B: a patient with pain that is almost totally sympathetically maintained. Points A and B may represent different patients or the same patient at different times. In other words mechanisms of pain generation may well alter and change with time.

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Boas (1996) notes that a CRPS category III was also considered for 'those difficult cases that contained pain and sensory changes, with either motor or tissue changes, but did not comply fully with the more classic forms.'

Presentation and symptoms of CRPS Types I and II

Main sources: (Baron et al 1996, Low et al 1996, Birklein & Handwerker 2001)

Onset

CRPS Type I is almost always preceded by a noxious event usually to the affected extremity. Such trauma may be quite minor, such as a simple knock or bruising. But bone fracture, operations like carpal tunnel release or fascial releases for Dupytren's contracture, shoulder trauma, myocardial infarction or even CVA have been noted. A key feature is that the symptoms are often way out of proportion to the inciting event and have a tendency to generalise to the distal parts of the limb.

CRPS Type II is always preceded by a partial injury of a peripheral nerve or its major branches.

Sensory symptoms include pain and loss of sensation

- Intense ongoing pain.
- Pain frequently starts up and continues for no apparent reason. The literature describes this type of pain as 'spontaneous pain.'
- Ongoing hypersensitivity of the skin to touch and hypersensitivity to movement—i.e. touch and movement-related hyperalgesia/allodynia.
- Skin hypersensitivity, described as 'brush evoked pain' in reality is severe allodynia said to affect one-third of patients and an even higher incidence in chronic stages (a hallmark of central sensitisation.)
- Hypersensitivity of the skin to cold (cold allodynia). Found to be more frequent in CRPS Type II (60%, compared to 30% in CRPS Type I.)
- Pain quality is variable, often aching, burning, pricking or shooting in character and usually deep in the tissues.
- Sensory deficits tend to occur in a glove or stocking type distribution on the affected limb and often spread beyond the limb into the trunk.
- There is a sensory paradox. Areas where there is pain and hypersensitivity may also demonstrate decreased sensitivity/loss of sensation. For example patients are unable to feel the sharpness of a pin-prick in an area of skin that is painful when palpated. The suggestion is that a part of the problem has to be one of processing (a nervous system functional problem) rather than a structural one.
- The deep diffuse pain is often worse with the limb dependent by the side and better if it is raised up—the so called 'orthostatic' sign.
- Many patients find relief is also obtained by pressure around the affected area or proximal to the area. The use of the so-called 'ischaemia test' to diagnose RSD/CRPS is of interest here, because ischaemia, caused by the application of a suprasystolic cuff around the affected hand or foot produces significant relief of patients' deep diffuse pain (see Baron et al 1996). According to these workers, a positive ischaemia test has a 'high prognostic value' for pain relief generated by sympatholytic interventions. The mechanism by which this relieves pain is uncertain; Baron et al (1996) feel that it is likely that the ischaemia, as a result of decreased vascular filling, causes a decrease in activity of small diameter deep somatic afferents. The impact of ischaemia on symptom *development* in CRPS is discussed later.

Motor symptoms

- Weakness, tremor, exaggerated tendon reflexes, 'dystonic' posturing and myoclonic jerks. Dystonic means abnormal tone, and myoclonic jerks are shock-like contractions of groups of muscles, of variable regularity synchrony and symmetry. In classic medical literature these jerks are usually attributed to CNS lesions.
- In the acute phase there may be muscle weakness—possibly explained by pain inhibition or fear of harm/pain as it is a giving way type of weakness.

- In chronic stages it is hypothesised that weakness may be due to impaired muscle nutrition or/as well as abnormalities of central processing. Fear of pain and loss of confidence should also be a consideration.
- Tremor, myoclonic jerks and dystonia are reported to be more common in CRPS Type II.
- Reduced range of motion—by joint effusion and pain in acute stages and by contraction and fibrosis in chronic stages. Again, fear of pain and/or damage may be an important consideration.
- About 45% have exaggerated tendon reflexes on the affected side. Yet no pyramidal tract signs—but good correlation to level of pain. Therefore there may be a pain facilitation of tendon reflexes.

Autonomic symptoms

- Distal limb oedema.
- Skin colour changes—red in the early stages, turning bluish later.
- Skin temperature differences from affected side to good side—usually about 1°C. The affected side is warmer in the acute stages and cooler in the more chronic.
- In 50% of patients with CRPS increased skin sweating changes can be observed in the affected limb.
- Some researchers report that sweating may be increased or decreased and that it occurs most commonly on the palmar surface of the hand or plantar surface of the foot (Blumberg et al 1994). It is also noted that patients report a strange reaction of the skin temperature to changes of environmental temperature. For example, the affected hand in comparison with the healthy hand cools too slowly or too quickly when exposed to cold. Abnormal responses of skin blood flow to warming or cooling compared to the non affected side have been demonstrated in patients with RSD (Blumberg et al 1994).

Trophic changes

- Trophic changes occur in more than 50% of cases. Within a few weeks of the initiating traumatic incident there may be increased hair and nail growth. Thus there is an upregulation of growth in the early stages—so called 'plus signs.'
- Later, a decrease in tissue growth is observed—'minus signs'—here there is decreased hair and nail growth and atrophy of the skin. Skin may become thin and glossy and in severe cases there may even be skin ulcers.
- Other trophic changes noted are: changes in the *texture* of the skin, nails and hair; the skin may become fibrotic; there may be alterations in subcutaneous tissues as well as in bone density (osteoporosis). Plain radiographs show a diffuse and spotty distal distribution of demineralisation of small bones with a periarticular dominance at the longer bones (Baron et al 1996). These changes may not occur for many months. However, changes in bone metabolism picked up by 'three phase bone scans' apparently appear quite early on in CRPS Type I. Intraossary

plasma extravasation has also been demonstrated, which lends support to those who view the condition as an inflammatory disorder.
- It is not clear whether trophic changes are responsible for joint stiffness and tendon shortening. Disuse and functional motor changes may also have a role to play.

Note that it can be difficult to diagnose CRPS from some of the above reactions in the acute stage as many are the symptoms of normal trauma. For example, oedema, skin temperature differences and pain are commonly observed. Birklein & Handwerker (2001) state that the best symptoms to use for early recognition are motor signs, trophic changes and increased sweating.

Diagnostic tools

- In research laboratories and specialist clinics some workers use skin temperature differences—by measuring the affected and non-affected limbs repeatedly over time and in a variety of room temperature settings.
- Increased sweating in both the acute and chronic stages of the disorder are measured using a sudorometer.
- X-rays can reveal 'spotty osteoporotic changes' within 4–8 weeks, but only in 40% of cases. There is some evidence for increased bone metabolism.
- MRI scans show that muscle and periarticular tissues may become oedematous and there is an increased permeability of blood vessels, but it is a good deal less dramatic than that seen in arthritis.
- Diagnostic blocks alone are not helpful to diagnose CRPS but they are the only method to date that can indicate the possibility of a sympathetic component to the pain (see Chapter 4).
- Ischaemia test noted above.

Stages of the disorder

For some time CRPS (RSD/causalgia) has been considered to pass through three distinct stages (Bonica 1990) as an accepted fact in the literature. The stages or phases that were described by Bonica are:

1. The acute stage, characterised by pain and vasomotor changes such as generalised oedema, warm skin and sweating changes in areas not affected by the preceding lesion. These symptoms may occur within hours or days of the preceding incident.
2. The 'dystrophic' stage at 3–6 months after onset, characterised by more marked pain and sensory dysfunction, continued evidence of vasomotor abnormalities and markedly increased trophic and motor changes. The skin tended to shift from warm to cold.
3. The 'atrophic' last stage, with a decrease in pain/sensory disturbance, but continued vasomotor disturbance and markedly increased motor and trophic changes. For example, atrophy of muscle and bone and contractures of joints. This stage is seen as permanent.

This concept has now been challenged seriously. Recently Bruehl et al (2002), using a cluster analysis technique to look for stages in the disorder as well as different subgroups, were unable to support the existence of sequential stages. Their conclusions pointed to the existence of three different sub-types of the disorder:

1. A relatively limited syndrome in which vasomotor signs predominate.
2. A relatively limited syndrome in which neuropathic pain/sensory abnormalities predominate.
3. A florid CRPS syndrome similar to descriptions of classic RSD.

Interestingly, in their discussion Bruehl et al (2002) noted that in this third subgroup, work on animals as well as humans was suggesting a significant contribution of disuse to the development of the CRPS changes. They listed allodynia, hyperalgesia, motor dysfunction and temperature/colour changes. The negative effects of immobility are discussed further in the next section.

The results of this analysis reveal how highly respected and prominent individuals in a specialist area may be publishing unsubstantiated or even inaccurate material. We may need to be more wary of trusted experts and always in mind to check the sources on which their information is provided. Sadly, a good deal of the clinical 'facts' physiotherapists rely on may come into the same category and are really due for serious scrutiny.

Some mechanistic perspectives on CRPS

Immobilisation and disuse

Physiotherapists who have worked in a fracture clinic will be familiar with the appearance of a patient's limb when it is freshly taken out of plaster. On removal of the cast the limb is invariably atrophied, often with abnormal hair growth; it may be significantly warm with the skin being blotchy in appearance; it is markedly stiff; and occasionally it is very painful to touch and move. It actually looks very much like classic 'RSD.' Fortunately, only relatively few cases are known to go on to have a *documented* case of RSD or CRPS. However, the clinical reality, which urgently needs quantifying, is that many of the stubborn conditions physiotherapists treat have often had significant periods of quite unjustified immobility or disuse imposed on them.

That the features of CRPS may relate to disuse has been noted and the effects of immobilisation on humans and rats has been investigated (see Butler et al 2000). For example, Ushida and Willis (1996) immobilised rat wrists in full flexion for 3–4 weeks, some with radius fractures and some without. The results showed an increase in mechanosensitivity (touch and movement allodynia) in both groups and central plastic changes in spinal cord dorsal horn cells that process sensory information from the immobilised areas. Even immobilisation of rat hindpaws for one week will increase levels of sensitivity to heat, cold and mechanical stimulation (Maves & Smith 1996).

Four week immobilisation of the wrist in 21 human volunteers (Butler et al 2000) showed:

- All subjects had a temperature difference compared to the non-immobilised side ranging from 0.5–2.7°C (10 were warmer and 11 cooler). In three of the subjects the difference persisted longer than two weeks.
- 16 subjects had decreased range of movement of the thumb, 12 had altered sensation to sensory testing, of whom 4 had summation to pinprick (an amplifying sensation, often termed 'hyperpathia,' with every pinprick), and another four had hyperalgesia to pin prick.
- Pain was present in seven of the subjects—burning in two and aching in five.
- 18 reported stiffness and 14 had symptoms and signs of a 'neglect-like state.'
- Six subjects had abnormal sweating, seven had skin, hair or nail changes, and one had abnormal swelling.
- There was great variability in sensitivity to different and changing temperatures—some subjects becoming more sensitive while others became less. For example, in some there was a decreased tolerance to cold, often producing cold pain on the immobilised side. In contrast, some (two-thirds) had pain at a higher temperature on the immobilised side, indicating a decreased sensitivity; seven of the subjects were found to be able to detect the sensation of warmth earlier on their immobilised side; while in five others their warmth detection threshold was raised significantly.
- Some of the above changes lasted many weeks, but most were back to normal by 4–5 weeks.

There are some important clinical messages:

- Immobilisation is not healthy, it is detrimental. Immobilisation of normal wrists, let alone an injured one, causes quite dramatic changes in sensory processing, physical function, and physiological processing that can take quite a long time to recover in some individuals. Recovery appears to need activity and movement for return to normal. It seems that normal sensitivity and tissue health is maintained by normal use, a vital consideration for all those who would promote immobility or rest as a significant element of their intervention. What seems clear is that immobilisation is not a good thing and quickly leads to marked and quite remarkable changes that are not compatible with normal function, or normal sensory or physiological processing.
- We need to understand that there is great variability between individuals—there does not seem to be any typical response pattern. In an evolutionary setting 'in the wild' (see Gifford's Chapter in Volume 4 of this series, Gifford 2002a), immobility is only a very short term option no matter what is wrong. It is unlikely that an adaptive, biologically useful response has evolved to combat longer term immobility. Immobility is simply not compatible with survival. As a result, immobility can perhaps be classified from the very beginning as maladaptive.
- The constellation of findings associated with immobilisation are very similar to many of those found in CRPS Type I. It is not difficult to envisage

that a combination of injury and immobilisation in certain vulnerable individuals could lead to a long term disruption of sensory, motor and local physiological homeostatic mechanisms typical of those found in the CRPS conditions.

- The findings of the studies discussed provides some useful and reassuring information that can be passed on to patients who have been immobilised and are concerned about what they feel and see as well as the slow rate of progress. For example, even normal non-injured individuals immobilised for four weeks can have changes in temperature and touch sensitivity (up or down), swelling, pain, changes in skin and nail health, and sweating changes that can take many weeks to return to normal after cast removal. For the patient it is very reassuring to know that this is normal.

Neurogenic inflammation

Since the time of Sudeck at the turn of the last century the symptoms associated with the conditions now classified as CRPS (formerly Sudeck's atrophy, RSD, causalgia etc.) have been similar to inflammation, i.e. swelling, redness, pain and impaired function.

An important perspective is to look upon early inflammation following tissue injury as an *adaptive* process. Inflammation, albeit a much maligned process, should really be seen as the response that not only provides a hostile environment for potential invaders and attackers but also sets the scene for subsequent healing processes to develop. Part of the healing process of course, is for inflammation to subside and to be followed by processes of regeneration, repair, and remodelling. If inflammation continues on too long, in effect outstaying its welcome, it can then be seen as maladaptive. The ongoing, unsupressed nature of CRPS signs and symptoms, including those that appear inflammatory in nature, are surely maladaptive and hence have a negative impact.

Although classic humoral inflammation has never been proved, there is now good evidence to suggest that various measurable inflammatory and immune reactions are occurring in CRPS (see Veldman 1999). There are also some workers in the field who have pointed out how much of what is observed in CRPS resembles neurogenic inflammation (Birklein & Handwerker 2001, Weber et al 2001).

Recall that neurogenic inflammation is the effect caused by the stimulation of unmyelinated primary afferents—the C fibre nociceptors. Classically the 'axon reflex' is described as leading to the triple response: redness, flare and wheal in the skin following scratching. This circulatory response is known to be due to the release of neuropeptides from C fibres in the tissues of the skin.

The important message is that C fibres have a secretory or 'efferent' function (see Raja et al 1999) as well as a sensory or 'afferent' function. The end terminals of C fibres contain vesicles of neuropeptides that can be released into the tissues. Neuropeptides are thought to have an important trophic function in the skin (Tanaka et al 1988, Raja et al 1999) in that they

support the tissues and help maintain their health. Think of C fibres as chemically sampling the tissues they supply, scrutinising what they find, and then helpfully responding if something is amiss by secreting various neuropeptides. In this way the C fibres effectively 'look after' the tissues they innervate and thus support their needs in times of difficulty. Thus, injured tissues need neuropeptides to activate a healing response.

It is known that activated C fibres release the neuropeptides CGRP (calcitonin gene related peptide) and SP (substance P) from vesicles in their nerve endings. CGRP release stimulates local blood flow by causing vasodilation of arterioles, and SP induces oedema by stimulating plasma extravasation from venules. Even though it has long been thought that plasma proteins are released during plasma extravasation in healthy skin, recent experimental studies, using high intensity TENS or capsaicin (chilli peppers), to stimulate the axon reflex, now show this may not to be the case (see Weber et al 2001). However, similar stimulation of the axon reflex and neurogenic inflammation in some CRPS patients, shows a clear early and short lived increase in plasma protein levels (Weber et al 2001). These findings led the authors to speculate that the presence of plasma proteins following the axon reflex should be viewed as a pathological finding.

What is apparent is that the observed swelling and increased skin vasodilation found in the early stages of CRPS strongly resembles neurogenic inflammation. The suggestion here is that for some unknown reason, either larger amounts of neuropeptides than normal are released from C fibres and/or their subsequent inactivation is physiologically impaired in someway. One group of researchers (Tanaka et al 1988) have suggested that an abnormal release of neuropeptides may be responsible for inducing the trophic changes observed in CRPS. Hence, increased hair growth rate in skin overlying the sites of fractures. Backing the role of neuropeptides as trophic stimulants is the finding that they play an important role in bone remodeling after fractures, that skin thickens near scars and that healing of wounds is accelerated by the presence of neuropeptides from sensory nerve endings. Denervation on the other hand reduces thickness of the epidermis and skin becomes hypotrophic (see Weber et al 2001). In CRPS patients, Weber and colleagues (2001) observe that in the acute phase there is an increase in hair growth in the affected area but that in the later stages skin becomes atrophic.

Another spin on peripheral vascular effects and neurogenic inflammation which fits the generally observed increased skin circulation, temperature, and redness of early CRPS noted above, may relate to 'antidromically' triggered vasodilation (Serra et al 2001). The mechanism here involves impulses passing down small afferent sensory fibres from the CNS to the periphery, i.e. the 'wrong way' or antidromically, with the subsequent release of CGRP. In the experimental situation, if freshly cut sensory fibres of nerve roots are stimulated electrically to produce antidromic impulses the skin supplied by that nerve root, i.e. its dermatome, reddens. Also, microstimulation of nerve fascicles that project to the skin of the hand, at intensities that produce a noxious effect, will cause a warming of the skin.

These effects have been shown to be independent of the sympathetic nervous system, as it occurs even after sympathetic postganglionic blockade.

It seems that neurogenic inflammation may have two sources: one where the impulses originate in the periphery—hence the well known 'axon reflex'; and the other where impulses actually originate from the CNS. In CRPS Type I, where symptoms and signs are critically distal or out of the territory of the inciting tissue injury, it seems that central origins of these impulses are likely. Certainly Sluka (1995) has addressed the physiology of a central origin to neurogenic inflammation via a 'dorsal root reflex'. It seems feasible that increases in central sensitivity and spread of sensitivity to segments beyond those immediately connected to the original injured tissues could have repercussions for the generation of increased antidromic activity to fundamentally normal tissues.

Oxygen-derived free radicals, oxidative stress, and ischaemia

In animal models intra-arterial infusion of compounds that produce oxygen-derived free radicals (oxygen radical donors) have been shown to cause reactions very similar to those of CRPS—oedema, increased skin temperature, impaired function, and pain behaviour (van-der-Laan et al 1998). Free radicals are therefore pro-inflammatory and their excessive production may result in destruction of healthy tissues. The significance of this is that trauma, inflammation, ischaemia, and circulatory reperfusion after ischaemia all trigger the release of these free radicals and support the potential for further negative effects.

In an article discussing the inflammatory aspects of RSD Veldman (1999) notes that even though there may be an increased blood supply through the affected tissues, there may still be poor oxygen saturation in the tissues themselves due to an oxygen delivery impairment. There may be plenty of blood, highly saturated in oxygen, but the tissues just seem not to receive it, hence they become hypoxic and suffer the effects of 'oxidative stress.' This may include a rise in oxygen-derived free radicals with the consequences already noted.

The reason for poor oxygen delivery is either that the blood coming into the area is shunted directly from arteries to veins, bypassing the microcapillary bed, or that it is a result of impaired diffusion from capillaries to cells. According to Veldman (1999) the second explanation is the most likely since 'an inflammatory reaction causes swelling of the intimal layers of the small blood vessels and their basal membranes, and hence a physical barrier to diffusion' (note the discrepancy here with the discussion in Chapter 3). Examination of the muscle biopsies from chronic RSD sufferers have shown evidence of oxidative stress—a decrease of Type I fibres, atrophic fibres, thickening of the basal membrane layers of capillaries, swelling and vesiculation of mitochondria, blebbing of the sarcolemnal membrane and

disintegration of myofibrils. Thus, inflammation causes changes that lead to poor oxygen delivery which in turn causes hypoxia with yet further inflammatory effects. Part of the effect may well be driven by toxic build up of oxygen-derived free radicals.

Veldman (1999) feels quite strongly that oxidative stress may be the cause of post exercise pain flare-ups so often reported by these patients. He noted that patients often state that at the start of physical therapy exercises complaints of pain are mild, but by the end of the session and in the following few hours pain levels rise in parallel with the signs of inflammation. He states, 'RSD patients are not unwilling to perform exercises but are unable to recover from exercise' (Veldman 1999). While this has to be seen as a reasonable tissue-based explanation, other explanations relying on the effects of central nervous system hypersensitivity and phenomena such as wind-up and altered or impaired gating effects must be considered too (see Chapters 3 & 4.)

Interestingly, Veldman's thinking is supported by promising results of some preliminary trials using anti-inflammatory treatments specifically targeting free radicals with drugs that 'scavenge' for them. Two drugs that are used are mannitol and dimethylsulfoxide (DMSO), but Vitamin C is also a well known free radical scavenger.

According to Veldman (1999) a recent placebo-controlled trial by Zollinger et al (1998) using Vitamin C early on for patients with Colles fracture showed a marked prophylactic effect for prevention of RSD! Apparently, the results demonstrated a reduced incidence of post-Colles fracture RSD from a rate of 22% to only 8%. Veldman (1999) enthusiastically noted that this was the first report 'proving that RSD can be prevented.' It would be interesting to know the patient numbers, but unfortunately, the Zollinger et al (1998) article is in Dutch! In the bigger picture, as part of a multidimensional package of management, it is quite easy to encourage any patient with any form of injury or inflammatory problem to increase their intake of Vitamin C and to tell them that it helps in preventing long term problems with recovery.

A point made by Veldman (1999) is of interest and provides a useful thought to connect with the section that follows. He notes that there are only two animal models which induce RSD-like symptoms, the most well known being chronic constriction of the sciatic nerve model, and the other is via arterial infusion of an oxygen radical donor as noted above. The interesting question Veldman (1999) raises is whether it is the nerve injury that produces the oxygen derived free radicals or the oxygen radicals that produce the nerve injury!

Lastly, a few findings suggest that some of the increases in mechano-sensitivity in CRPS/tissue inflammation may in part relate to circulatory stress. For example, iontophoresis of the vasoconstrictor agents angiotensin II and vasopressin (Drummond 1998) slightly enhances hyperalgesia in skin that has been irritated and inflamed by capsaicin. Occlusion of blood flow has a similar effect (Drummond et al 1996).

Temperature changes, impaired sympathetic function, and supersensitivity development

The reader may recall from the previous chapter that noxious stimulation of viscera and the consequent sensory afferent barrage caused a *change* in sympathetic activity resulting in increased skin sweating and increased skin circulation with a consequent temperature increase. This activity may be relevant to the mechanisms proposed for abnormal skin temperature observed in CRPS. It may also provide one possible pathway for the development of the condition following deeper tissue injury. It would be interesting to know whether noxious stimulation of deep muscles or joints produces a similar change in sympathetic activity.

According to Veldman et al (1993) within the first weeks of CRPS, skin temperature and sweating on the affected limb are increased in nearly all patients, with the exception of a very few 'primary cold' cases. For those patients with increased temperature, this suggests, that sympathetic activity is in fact *reduced*. *Increased* sympathetic activity to skin causes vasoconstiction and hence *less* circulation to the skin (but see last paragraph below). Increased sweating on the other hand, is due to an *increase* in sudomotor sympathetic activity to sweat glands. Since most patients present with increased temperature and increased sweating it is suggested that the impairment of sympathetic output function (down for one, up for the other) is most likely to be of central origins (Wasner et al 2001)—but may have been instigated by afferent sensory barrages from injury or disease to other, possibly deeper, tissues.

If the clinical picture was one of increased temperature with a *decrease* in sweating the most obvious explanation, biased to the sympathetic system, would be loss of SNS activity. This might be due to pre- or postganglionic fibre injury / neuropathy / dysfunction, or to more complex central inhibitory effects.

Later on in the condition, when the disorder becomes chronic, skin temperature of the affected limb is almost always reduced compared to the good side. Patients complain that their limbs feel constantly cold. Indeed, clinical experience suggests that this is commonly the case in many chronic pain patients who may not necessarily be diagnosed as having CRPS. Is it due to altered or impaired sympathetic activity, or should we view it as merely the most likely consequence of disuse related to pain and hypersensitivity? Biomedical research tends not to think like this and mostly argues the case for altered physiological mechanisms. What mechanisms could explain this change in presentation?

Oedema

Most early CRPS presentations combine a heat increase with oedema of the distal limb. Could it be that the oedema is partly responsible for the second phase cooling? Oedema may produce an increase in tissue pressure sufficient to overcome normal venous filling pressure, causing collapse of the vessel

and hence a point whereby circulatory perfusion is prevented. Once superficial blood flow velocity decreases or stops surface skin temperature will adapt to the ambient temperature which is normally colder than the core temperature. Loss of superficial circulation like this could also explain the tendency for skin health to suffer and lesions to develop. Clinically, and normally when we have cold hands or feet, it takes only a few minutes of active limb work to increase the circulation to the point where our extremities are very warm.

Oedema is discussed further below.

Supersensitivity development

In the nervous system it is known that following a peripheral nerve injury where nerve cells are actually killed and degenerate, i.e. where there is a frank neuropathy, the central sensory cells that normally connect to these primary sensory fibres that are 'lost', can develop a 'supersensitivity' state. It seems that central nerve cells involved in sensory pathways need their normal peripheral inputs and if they lose them they increase their sensitivity in an attempt to try and restore them. It is as if they are desperately looking for the slightest sign that their former fellows may still be found and the relationship rekindled.

This process of 'supersensitivity' development may occur outside the nervous system too. For example, with relevance here, it is postulated that a 'supersensitising' process may occur in the blood vessels of the skin when they are subjected to a decrease, or 'loss' of normal sympathetic activity (Birklein & Handwerker 2001). This may be due to ongoing reduced activity in sympathetic vascular output (discussed above), or, due to actual die-off of sympathetic postganglionic fibres if there has been a frank nerve injury (Wakisaka et al 1991).

Decreased sympathetic activity to the skin vascular bed effectively means reduced levels of the catecholamine transmitter noradrenaline in them. It is postulated that if this goes on for long enough the smooth muscle in the vasculature starts to increase its sensitivity to noradrenaline, for example by up-regulating the number of adrenoreceptors (Drummond et al 1996), with the result that they go on to develop 'catecholamine supersensitivity'. The vessels now become hyper-reactive to adrenaline whether derived from the sympathetic nerve terminals or from the adrenal glands via the circulation itself, and hence shift their activity state from being predominantly one of vasodilation to vasoconstriction. Support for this reasonable model is still thin (Birklein & Handwerker 2001) and alternative models have been proposed. One is the development of supersensitivity of central neurones associated with the production of vasoconstriction—hence a shift towards hyperactivity of skin vasoconstrictor neurones. This obviously requires an intact peripheral sympathetic supply. Another relates to the finding that re-innervated vessels demonstrate increased responses to sympathetic discharge and also to circulating levels of noradrenaline and adrenaline (Janig 1993). A possibility here is that, in the early stages, increased temperature relates

to loss of sympathetic neurones while, later, decreased temperature relates to the supersensitivity that accompanies reinnervation.

Before leaving this section, with its interesting and competing hypotheses that attempt to explain temperature, sweating and circulatory changes, it is worth noting that there is some research available demonstrating a vasodilatory effect of the SNS to the skin on the dorsum of the hand and foot (Bell 1983, Lundberg et al 1989, Janig 1991). This is in direct contrast to the conventional belief, outlined at the beginning of this section and in the last chapter, that the activity of the SNS on the skin vasculature always causes vasoconstriction. For CRPS, the circulatory innervation and control to the dorsum of the hand and foot are of obvious interest. One wonders whether the innervation of CRPS sufferers is anatomically and functionally different from normals.

What some of the mechanisms highlighted in this section illustrate, whatever the underlying causative pathobiology, is that a decrease or loss of sympathetic activity needs to be entertained in the understanding and development of CRPS. What is also illustrated is the shifting nature of the mechanisms, the possible plethora of mechanisms and the potential for a wide symptomatic presentation, all of which serve to make any targeted biomedical approach to the problem very difficult. Unfortunately, the stability myth of nearly all pain states is often held down by diagnostic labels like 'reflex sympathetic dystrophy' and 'sympathetically maintained pain' (see Chapter 4).

Circulatory effects: sympathetically generated oedema

Blumberg et al (1994) describe four fascinating case histories of patients who developed 'RSD' with significant oedema that was dramatically relieved by sympathetic blocking procedures. The article is well worth reviewing and contains some very convincing pictures of the patients' condition before and after management.

To whet your appetite, what is so fascinating is the history of each and the dramatic onset of symptoms. For example,in the first case, a 37 year old healthy male merely banged his left elbow doing housework, carried on, had a nap for two hours and then woke to find severe swelling of the left hand and loss of sensation. The swelling was reduced dramatically by guanethidine blocks. The second patient, a 50 year old male who had kidney dysfunction for which he was on regular dialysis, underwent surgery to remove a subperitoneal haematoma. After coming round from the operation he complained of pain in his left leg that over the next few days focused on his foot and was accompanied by a massive swelling of the whole leg, in particular his thigh. The lower leg and foot were not only swollen but developed blisters. Here again, guanethidine blocks significantly and progressively alleviated the swelling and helped the problem to resolve.

These authors, in attempting to explain the oedema in these patients, after ruling out clear cut circulatory impairment, myocardial dysfunction or renal impairment, go on to dismiss an inflammatory or a neurogenic mechanism and propose a model that embraces an abnormal sympathetic discharge affecting in particular the vasoconstriction of veins.

The proposed hypothesis can be summarised:

- A lesion generates a nociceptive barrage into the CNS that sensitises 'spinal circuits' (see Chapter 3).
- The result of this spinal circuit excitation is an abnormal discharge pattern of sympathetic vasoconstrictor fibres.
- The oedema is generated because of the biased effect of the vasoconstrictor activity to the venous/postcapillary side rather than the arterial/precapillary side. Blood can flow in but cannot get out, hence an increased 'filtration pressure' which forces fluid out of the circulation and into the tissues.
- Increased pressure within the oedematous tissues then excites and activates their nociceptive population producing an afferent barrage that further maintains the sympathetic vasoconstrictor tone.

Whether vasoconstriction biased to the post-capillary side of the vascular bed is possible is discussed. Two things are proposed to support their hypothesis. First, that each section of the vascular bed is innervated separately by postganglionic neurones and therefore provides the potential for independent regulation of the calibre of pre- and postcapillary vessels. Second, pre- and postcapillary vessels react differently to the same activity in postganglionic vasoconstrictor neurones, the predominant action being biased towards the venous side.

A key element of the management paradigm is that it requires the existence of a vicious circle which can be interrupted in some way. Blocking the sympathetic side of the circle produced dramatic results. Vicious circles, if they are well founded, also leave open other therapeutic options; for example, could similar results be obtained by blocking the afferent traffic in nerves from the area affected? Since a peripheral nerve block prevents both afferent and efferent (hence sympathetic) activity it is feasible that this might be another approach.

Further, anything that could reduce the impact of afferent traffic or the potential for ongoing central sensitisation may be appropriate. Thus any form of therapy that reduces nociception or reduces the psychological impact of pain may be of some help. In a sense this is a simple plea for the possibility of multiple management strategies used 'in parallel' (Gifford 2002). This includes at one end of a spectrum cognitive-behavioural strategies and normal movement approaches and at the other the careful use of any active or passive input to help reduce the impact of nociceptive activity. Clearly, physiotherapists have a wide variety of skills and techniques to offer.

Unhealthy target tissues: a source of nociceptive input

This chapter needs now to hand on to the next two that take a closer look at the role of the sympathetic nervous system in pain. A final point before doing so is that associations between output systems and the input systems linked to pain may be quite indirect. Sympathetic or autonomic activity has the capacity to change the tissues that it innervates—for example a significant part of the discussion above relates to competing hypotheses focused on changes in circulatory perfusion. Thus, it seems quite feasible that altered sympathetic activity, especially if it is functionally disturbed in some way and is persistent (i.e. maladaptive), can lead to detrimental effects and impairments in the tissues it regulates and fosters. Long-term altered circulation, hence altered interstitial pressures and altered nutrition, oxygenation and clearance, is an example that cannot be compatible with positive tissue health. Nociceptive detection or 'sampling' systems may pass this information into the central nervous system with the potential to set up central sensitivity changes and hence pain states that may contain complex and multifaceted vicious circles.

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