4

Sympathetically maintained pain: myth or reality?

MICK THACKER AND LOUIS GIFFORD

Introduction

Sympathetically maintained pain (SMP) is often assumed to be the major feature of complex regional pain syndrome; it may not be. Also, and perhaps to the detriment of the patient who has the condition, a focus on the sympathetic system seems to underpin the diagnostic and therapeutic decision-making.

SMP is a controversial topic with some authorities now seriously questioning its existence. As already described in Chapters 2 and 3, involvement of the sympathetic nervous system (SNS) in the generation of pain and other symptoms can be suspected from patient's presentation. There is a commonly held belief that changes in blood flow, altered skin colouration and disturbance of sweating are a result of SNS involvement. Hopefully the reviews in the last two chapters indicate that this stance, though reasonable, may need tempering. Thompson (2001) recently wrote 'the direct involvement of the SNS has perhaps been overestimated at the detriment of other indirect mechanisms,' suggesting that we may have focused on what appear obvious explanations at the expense of more involved mechanisms.

Simple explanations have many advantages but we must guard against complacency. Pat Wall (1999) once said: 'It is almost impossible to replace widely accepted medical dogmas, especially where the paradigm being challenged has to be replaced with a more complicated one!'

Paramedical professionals have been accused of over diagnosing CRPS Type I (Janig 1996). This over diagnosis appears to be based on their assumption that they are observing signs of sympathetic dysfunction, which is now thought to be erroneous in the light of current research. Janig (1996) states that 'it is impossible to implicate the sympathetic

nervous system in the production of signs and symptoms from physical examination alone.' It is important that we realise the full implication of research for clinical diagnosis and the potentially dangerous repercussions for our patients, such as requests for invasive blocking procedures and continued investigation (see next chapter) when they may be highly inappropriate.

History

Roberts (1986) is widely acknowledged as the originator of the term Sympathetically Maintained Pain. It appears that he was heavily influenced by the seminal work of Livingstone, in particular his viscous circle hypothesis (Livingstone 1943). Briefly, this stated that pain led to alterations in sympathetic discharge leading to a decrease in circulation and to muscle spasm that resulted in further pain.

Together with several co-workers, Roberts performed numerous experiments to investigate the role of the sympathetic nervous system (SNS) in the generation of pain. His findings led him to describe a mechanism by which painful input to the nervous system is maintained (and generated) by activities of the SNS.

Over a decade before Robert's work, Wall and Gutnik (1974, 1974a) demonstrated that damaged sensory nerve fibres showed an increased sensitivity to adrenaline and noradrenaline. Around the same time John Hannington-Kiff (1974) had described the successful use of guanethidine, a drug known to inhibit noradrenaline release from sympathetic neurones, to relieve the pain of patients suffering from reflex sympathetic dystrophy. It is interesting to note that none of these authorities deemed it fit to suggest that their findings revealed a novel pain mechanism.

Since Robert's (1986) work there has been an enormous amount of 'space' devoted to the controversy of whether there is such a phenomenon as SMP. More recently there have been increasing attempts to clarify the clinical situation. Such attempts have faced many confounding findings, including the observation that sympathectomy can actually lead to *increased* pain and associated epiphenomena that are usually ascribed to sympathetic over-activity (Perl 1994, Kramis et al 1996).

At present there is a widely held belief that SMP represents a condition of altered sensitivity to noradrenaline (Campbell et al 1992, 1994) with central repercussions. The underlying peripheral mechanism is thought to be due to upregulation of adrenoreceptors in peripheral nervous tissue (Campbell et al 1992, 1994; see also previous chapter). The result of this is a peripheral increase in sensitivity to noradrenaline whose presence then drives an increased afferent barrage into the CNS. Changes in central sensitivity follow the afferent barrage. The vicious circle hypothesis then predicts that the central sensitisation leads to an increased sympathetic output, thus promoting the release of noradrenaline, and thereby completing the out–to in–to out positive feedback 'circle.'

This chapter attempts to offer a balanced account of the topic and to highlight the clinical points for the practising therapist. The majority of the chapter focuses on human studies as these are thought most relevant for the clinician, but some animal work is included in order to give a full picture of current thinking.

Sympathetic blocks

For most clinicians SMP may only be suspected from the clinical history since it cannot be identified via features of pain, history, or standard physical testing. Currently, the only known way of identifying it is to perform a 'sympathetic block' and see if the patient's pain, or a component of the patient's pain, is quickly relieved (Campbell et al 1992, 1994). Recall from Chapter 2 that pain can be viewed as being 'sympathetically independent' (SIP) and that a given patient may have varying proportions of SIP and SMP.

The introduction of the sympathetic blocking agent guanethidine into the clinical management of CRPS Type I (RSD) by Hannington-Kiff (1974) was mentioned above. Guanethidine has its actions by causing the postganglionic sympathetic neurons to discharge their stores of noradrenaline and ultimately to reduce its concentrations within the nerve so that it becomes impotent to later stimulation. *(**Clinical Note**: In those with adrenosensitivity if the guanethidine block is performed without local anaesthetic, the initial 'discharge' of noradrenaline can lead to marked increases in pain until the noradrenaline is washed away by the circulation.)* Not only does guanethidine 'empty' the stores of noradrenaline, it also delays any re-uptake of the released chemical by the sympathetic nerve fibres.

Recently the efficacy of guanethidine and related compounds as therapeutic agents (reviewed in Glynn et al 1993, McQuay & Moore 1998, and Kingery 1997), and as diagnostic tools has been challenged. For example, in his extensive review of treatment trials for CRPS, Kingery (1997) states that '…intravenous regional blocks with guanethidine are ineffective analgesics compared to placebo or no treatment.' One of the trials cited in the review is described here:

Ramamurthy and Hoffman (1995) randomised 60 CRPS patients to receive either up to four regional guanethidine blocks with lignocaine (local anaesthetic), or to a patient control group that received an injection of lignocaine and saline only. The results revealed that there was no difference in outcome between the guanethidine and the control groups. Also, patients in all groups showed a decrease in oedema, as well as sweating, trophic and vasomotor changes. All those in the guanethidine group had at least one block and those receiving up to four blocks had no greater degree of pain relief.

These findings strikingly show that the effectiveness of guanethidine blocks for presumed SMP, as well as non-pain related clinical features that may be associated with sympathetic impairment, can be manipulated just as effectively with a local anaesthetic whose normally short lived effects most

of us have witnessed after dental care! It also adds credibility to the idea that the patient's own system may have the ways and means of achieving positive change given the right inputs or triggers. These may be injections but could also be any variety of non-invasive treatments too.

Supporters of sympathetic blocking procedures may counter findings like these by stating that multiple blocks are sometimes needed to produce a good outcome and that the trials only offer one, or a few at best. It is staggering to find that there are various reports suggesting that anywhere from 1 to over 300 blocks may be required for successful therapeutic effect (Wynn-Parry 1996). The main issue is surely that proponents of multiple blocks need to come up with better evidence harvested from much higher quality trials than are currently available.

The results of reviews of trials like those cited above challenge clinicians to think very carefully before referring patients for guanethidine blocks or any blocking procedures. Physiotherapists are often asked by patients for their opinion regarding such procedures. The advice here is that we should provide honest answers that are based on the results and findings of well structured double blind trials like those above.

However, although challenged (see Kingery 1997), many other sympathetic blocking agents that are reported do have some validity in the management of presumed SMP. For example Baron et al (1999a) reported that 85% of patients showed positive early responses to blocking procedures, but that this figure reduced to 42% at follow up 1–6 months later.

Whether the success of blocking procedures is sufficient to establish the existence of SMP has to be seen in the light of interesting alternative explanations for their effect:

- Phentolamine is an alpha adrenoreceptor antagonist. Its supporters suggest that its use is superior to that of other blocking agents and recommend its use for the determination of the presence of SMP (Campbell et al 1992, 1994). However, the emerging picture regarding phentolamine's specific blocking action at the adrenoreceptor is slightly less clear than originally conceived. There is now evidence that it may be responsible for relief of pain via its sodium ion channel blocking action. Sodium ion channels have a well established role in the propagation of impulses and in the production of pain (Dotson 1993, Bennett 1999, Black et al 2001). This means that phentolamine should be effective for a great many more classes and mechanisms of pain.
- Other components that could account for the effectiveness of blocking agents include its method of delivery. For example, there are data to suggest that both saline and the application of a tourniquet can have similar short term outcomes to the infiltration of an active compound (Janig 1992, Kingery 1997, Price at al 1996, Bennett 1999). Either or both of these technical aspects could account for early, post block, pain relief and hence result in a false positive result for SMP. For those who may be puzzled by this, it is important to consider on the one hand the placebo effect (see below and Volume 4 in this series), and on the other that

compression or squeezing, as in the tourniquet test, is a common way of relieving pain in all of us. It probably has its effect via classic, simple peripherally induced (increased Aβ fibre activity) gate control.

- Price and co-workers (Price et al 1996, 1998) have focused on the difficulties of separating 'true' responses from those of placebo in the identification of SMP. They published an excellent paper comparing the effects of local anaesthetic blocks with saline in CRPS Type I patients (Price et al 1998). They were able to show that both interventions relieved pain, but the duration of pain relief was longer with the local anaesthetic.

In their 1998 paper, Price and colleagues raise several important points that illustrate how difficult it is to pinpoint a pain mechanism based on a comparison of results of any intervention. First, they noted that both saline and the sympathetic blocking anaesthetic relieved pain. Since saline does not block the sympathetic system this demonstrates that saline relieves the pain via a different process. It also suggests that the pain may not be sympathetically maintained at all. However the sympathetic blocks do change sweating and skin temperature, which are measures of sympathetic activity, whereas the saline showed no effect on this.

An important message from this is that alterations to signs and symptoms following diagnostic procedures, or any treatments that are assumed to be targeting the SNS, *do not necessarily* indicate that they really are! Unfortunately we simply cannot make totally confident judgements about a given source or mechanism of pain or any other symptom, based on the outcome of interventions and treatments. This applies to biomedical interventions just as much as to physiotherapy techniques and treatments applied to any condition. The idea that a 'localised' technique has only a local effect needs revision. Modulation of pain via modulation of nervous system activity is a complex process that is unlikely to be resolved to a single process even though it may appear so. It seems that altering the input to the system, from virtually anywhere, by virtually anything, may be capable of modulating the output! It is important to reason that all interventions have a multidimensional impact. For example, in the physiotherapy process the integration of things like exercises, examinations, advice, manipulations, skill acquisitions and even demonstrations may all consciously or subconsciously change an individual's perception or relevance of a particular feature of a condition and this may be enough to alter the expression of the system. It is possible that many of the benefits of a multidimensional reasoning model and approach in physiotherapy, for SMP or virtually any other pain condition, has its role by affecting all components of the patient's pain. This may be why attempts to isolate treatment effects in well controlled research trials fail to demonstrate clear benefits. The very structure and nature of a clinical trial seems to result in the intervention being unnaturally severed from the sum total of the therapeutic interaction (see the Noon 2002 chapter in Volume 4 of this series) and the benefits of the 'psychosocial placebo' described in by Richard Shortall in the same volume (Shortall 2002).

This section has discussed some of the challenges that surround the assumptions about diagnostic and therapeutic blocking. Clearly, the foundations of the procedures are not proving to be as substantial as they once were thought to be. Sympathetic involvement in pain generation is still taken seriously however and the challenge for medical research may be to find more water-tight diagnostic testing procedures and, by understanding pain mechanism and pain processing better, to devise more potent treatment protocols. The news is not all bad for drug management. For example, the successful trials of the use of systemic drugs such as clonidine and prazocin (alpha adrenoreceptor antagonists) in the management of CRPS Type I patients still supports the concept of sympathetic involvement and this pharmacological route for pain management (Schwartzman & McClellan 1987). A simple plea would be for those who advocate a pharmacological management paradigm to start to appreciate that other dimensions of pain and physical function relevant to the patient's life need attention at the same time.

A note on sympathectomies

As far back as 1916 Leriche (cited in Scadding 1999) described the relief of pain, sweating changes and skin discoloration following sympathectomy of patients with causalgia. Apparently, the causalgia in the first patient he described was caused by a brachial plexus injury and thrombosis of the brachial artery. The sympathectomy performed involved resecting the adventitia of a length of the brachial artery. Later, this 'peri-arterial sympathectomy' was replaced by preganglionic sympathectomy for the treatment of painful nerve injuries sustained by soldiers during the two World Wars. The relief of causalgic pain by sympathectomy lead to the assumption that the sympathetic system was involved in its pathogenesis. But, there was no critical evaluation of its effectiveness. Since this time, sympathectomy has been a common treatment for causalgia and RSD. A commonly repeated statement regarding efficacy of sympathectomy runs '…it is recognised by those regularly treating these patients that while temporary pain relief may occur, long-term results are poor…leading most to abandon the procedures' (see Scadding 1999). That pain frequently returned after sympathectomy led to the assumption that the original sympathectomy had been incomplete or that a new sympathetic innervation had occurred. Animal experiments suggest another cause: that sympathectomy itself may induce SMP (Bennett & Roberts 1996)! These animal studies show that injury to sympathetic postganglionic fibres may induce a situation where intact C fibre nociceptors become adrenosensitive and that sympathectomy may induce the same phenomenon. Bennett and Roberts (1996) suggest that returned pain or increased pain and often new proximal pain that follows after sympathectomy be described as a new syndrome: 'postsympathectomy neuralgia'!

While sympathectomy is not a good treatment option, the results of sympathectomy do suggest that the SNS is involved in production and maintenance of pain.

Rekindling of pain via sympathetic agents or sympathetic stimulation

Further support for the existence of SMP comes from the well cited observation that following successful sympathetic blocking (pain relief), the designated SMP can be rekindled by the introduction of an 'alpha adrenoreceptor agonist' (e.g. noradrenaline) into the area of pain relief. The noradrenaline 'agonist' is introduced either by injecting under the skin or iontophoretically (Torebjork et al 1995, Ali 2000).

The reasoning here is that if pain is maintained sympathetically, it should be relieved by blocking the sympathetic system, but also should be re-established with the return of the stimulating agent produced by the sympathetic system. It is interesting to note that only 28% (seven of 25) of the SMP diagnosed patients in the Torebjork et al (1995) study (diagnosed by a positive response to sympathetic block) responded with an *increase* in pain following injection of noradrenaline into an area of sensitive skin. This is quite a discrepancy. However, in their study they noted that noradrenaline applied to the skin in all 10 patients with sympathetically *independent* pain (SIP), had no effect on the pain. Clearly, the relative proportion of patients responding to a noradrenaline challenge was higher in the SMP group than the SIP group. A greater number of patient trials may help clarify the situation.

Why is it though, that in some patients with SMP the pain can be made worse or brought back by the introduction of noradrenaline (the seven), while in others (the remaining 18) it cannot? As ever, thoughtful and considered (potential) explanations for this finding were offered by Wall (1995). He suggested that these patients might have already had all their available adrenoreceptors 'occupied' preventing further pain exacerbation when noradrenaline was introduced. Simply, the noradrenaline had no available receptor targets to act on. Alternatively the actual adrenosensitive structures could be sited deeper than the skin and therefore would be unlikely to respond to the subdermal injection or the iontophoresis. Another possibility suggested was that these individuals may have had a different focus of their adrenosensitivity; perhaps the portion of their nervous system sensitive to adrenaline was more centrally placed - on the dorsal root ganglion cell bodies of the affected fibres (see Chapter 3). Wall (1995) pointed out that there may be a subset of patients who, as a result of having this more proximally situated site of adrenosensitivity, might be incorrectly diagnosed as having SIP following a negative response to guanethidine blocking. Recall that guanethidine block only immobilises the SNS in the limb where it is introduced. Thus, patients with only a proximal 'dorsal root ganglion' site

of noradrenaline sensitivity, may be wrongly diagnosed as 'SIP' following a negative response to guanethidine block. However, a sympathetic block applied to the ganglion on the sympathetic chain *would* immobilise the SNS supply to the dorsal root ganglion which would then produce the relief and hence the SMP diagnosis. Thus, negative responses to a *peripheral* blocks are not 100% reliable in indicating that SMP is *not* present.

In their patient study, Torebjork et al (1995) found that all but one of the 12 patients they followed up, converted from having SMP in the early stages, to having SIP at reassessment many years later. Also, most of those who were made worse by noradrenaline in the early stages, when they were 'SMP,' were shown to be unaffected by it at the later time, when they were 'SIP.'

Again Wall (1995) offers a commentary suggesting that damaged sensory nerves may well undergo 'phenotypic' switches. In other words, they change their structural make-up over time and as a result change their sensitivity states. For example, initially their cell walls may be well endowed with a high population of active adrenoreceptors, but later on the numbers drop away significantly. As Wall (1995) puts it, there is a '…plasticity in which they [the damaged nerves] evolve from one pathological state to another.' Things change and move as time goes on. Wall (1995) reports that in animal studies of experimentally produced peripheral nerve injury he and Devor '…observe a striking period of adrenaline sensitivity which lasts only from the period 1 week after the lesion to 3 weeks after the lesion.' He introduces the idea of 'temporary adrenaline sensitivity'. He also pleads for longer term studies to be done and notes that in those animal studies of nerve injury that have looked longer, they all resolve spontaneously unlike the majority of human cases which do not.

Does this mean that given the right conditions early on, human nerve injury could resolve too? What might these conditions be? Could the biological impact of psychosocial factors that so powerfully predict poor outcome play a part in setting up or facilitating unnecessary long term changes? For example, fear of pain, focus on pain, and the consequent immobility that sometimes occurs may promote plastic changes that favour the pain mechanisms rather than pain inhibition and dampening. Or is there such a difference in make up between rats and humans that we may have to learn to live with the sometimes devastating consequences of long term nerve injury?

For clinicians who administer blocking agents, the finding that pain mechanisms can change and shift with time indicates that they are in a limited position to be able to indicate confidently not only who will benefit, but also, when the benefit will occur.

If one can trust the validity of findings from dated literature it is interesting to note that Walker and Nulson (1948) showed that electrical stimulation of the sympathetic chain led to an increase in pain in those suffering SMP, with no effect on those demonstrating SIP. These findings were reproduced some years later by White and Sweet (1969).

An elegant study performed jointly in Germany and America by Baron and co-workers (Baron et al 1999) assessed the effect of sympathetic stimulation on pain induced by sensitisation of primary afferent C fibres in

humans. They produced experimental pain by the infiltration of capsaicin (the chemical responsible for producing the heat sensation from chili peppers) into the skin. This is known to produce a typical pain presentation including spontaneous pain, hyperalgesia, and an axon reflex induced vasodilation. They recorded the individuals' pain reports (intensity), axon reflex (via laser doppler flowometry), size of flare, and area of hyperalgesia. The skin temperature at the recording site was kept constant but they used a thermal 'body-suit' to allow them to produce whole body cooling or warming in order to alter sympathetic discharge.

Their results demonstrated no differences in any of the scores between high and low sympathetic discharge states. This suggests that the sympathetic system is not capable of altering the pain response in this experimental paradigm. The authors are correctly reluctant to over state the importance of their findings in the debate over the existence of SMP. They point out that their study was performed on normal subjects and freely recognise that the changes seen in clinical conditions are different.

Their results would appear to be in contrast to those published earlier by Drummond (1995). He demonstrated that sympathetic discharge increased the reporting of hyperalgesia (following the application of capsaicin) and concluded that sympathetic activity increases pain from the skin. The contrast in results may be due to the differences in the experimental paradigms used. It is interesting to note that Baron et al (1999) did not cite the Drummond (1995) paper.

This example is included for several reasons. First, in depth reviews of this topic consistently produce differing results. Secondly, the results of studies are often affected by even small differences in experimental design; and lastly, literature reviews often fail to identify previous work even when of high relevance. The reader is therefore urged to attempt to maintain a healthy circumspection and scepticism when reading any account even when it has undergone peer review and is written by experts—and that includes these authors!

To end this subsection, it is worth noting that in their editorial, Max and Gilron (1999) suggest that much of the work discussed above should, at least, modify the concept of SMP and the basis of current management. For example, they recommend that the results of Baron et al (1999) call into question the practice of permanent ablation of the sympathetic nervous system until a better methodology is in place to determine who exactly, if anyone, is likely to benefit from such procedures.

Animal studies

Conclusions from animal studies are complicated and unfortunately do not provide a definitive answer or easily stated case either way to the question raised in this chapter. However, the weight of the research findings and the inferences of internationally recognised experts in the field seems to favour the existence of SMP in animal models.

Nerve lesion models

Most of the animal studies into SMP involve surgically produced nerve lesions followed by interventions that impact the sympathetic supply. Interventions that target the SNS include surgical or chemical sympathectomy or the application of adrenoreceptor blocking agents or adrenoreceptor agonists. Changes in pain behaviour and changes in sensitivity to mechanical forces or temperature are then tested/observed. A common protocol is to perform some kind of sympathetic blocking procedure, and then, if the pain behaviour and hyperalgesia is diminished or relieved, to see if it can be rekindled by later introducing noradrenaline, or by chemically, physically, or electrically stimulating the sympathetic system.

Since the models used involve nerve lesions their findings are relevant to CRPS Type II only. Work on animal models relating to CRPS Type I is discussed later.

There are several types of experimental lesion models (see Baron et al 1999, Cepeda 1995, Bennett and Roberts 1996, Bennett 1999).

1. *Ligation and transection.* Here, a peripheral nerve, usually either the sciatic or the saphenous nerves, is exposed in the leg, ligatured, and then cut through just distal to the ligature. This effectively destroys many axons and leaves the proximal surviving component of the nerve cells. The surviving neurones are said to be 'axotomised.'
2. *Partial lesion of the sciatic nerve.* In this model, a ligature is passed through between one-third and one-half of the nerve in the upper third of the thigh. The ligature is pulled tight, which in effect transects the proportion of the nerve ligated. This model thus produces a 'partial' nerve injury (axotomy). Both this and the last model result in 'neuroma' formation at the site of transection.
3. *Spinal nerve transection model.* The nerve lesion in this model is produced nearer the spine. The procedure is essentially the same as the ligation and transection one described above. The lesion is produced in the ventral ramus of the spinal nerve before it unites with other rami to form the brachial, lumbar, or sacral plexuses. Experimental designs using rat L5 spinal nerve usually describe the nerve being 'transected and cut about 1–1.5 cm distal from the DRG' (e.g. Habler et al 2000). It is therefore not a nerve root lesion.
4. *Chronic constriction injury of the sciatic nerve.* Here, the sciatic nerve at mid thigh level is ligatured loosely to produce only a constriction effect. This light ligature causes the development of intraneural oedema whose swelling is prevented by the ligature and results in a 'self-strangulation' effect. This type of insult produces a degeneration, or interruption, in nearly all large myelinated and a great many of the smaller thinly myelinated Aδ fibres. A large percentage of unmyelinated (C fibres) afferents survive.

All four of these models of nerve injury lead to the animal exhibiting behavioural signs of pain—hence, they demonstrate autotomy or self-

mutilation behaviour (Wall et al 1979), as well as signs of increased mechanical and thermal sensitivity in the territory of the injured nerve. The animals also show signs of ongoing pain, such as limping and guarding of the affected paw/limb, and develop some of the non-pain symptoms traditionally associated with RSD and causalgia. Hence, hypertrophic nail growth and abnormal skin temperature regulation, but swelling, even in the early stages is not seen and is therefore different to the situation seen in CRPS patients (Bennett & Roberts 1996).

But do the nerve injury models and the subsequent manipulation of the sympathetic nervous system prove that SMP exists? Bennett and Roberts (1996) are categorical: 'There is no question whatsoever that SMP exists in animals. In the partial and spinal nerve transection models sympathectomy or pharmacological sympathetic block appears to completely eliminate the abnormal pain sensations.' Also, '…the animal work has taught us that SMP is a real organic phenomenon' (pp. 115–116).

However, writing some five years later and reviewing the topic, Janig and Baron (2001) are more cautious about the interpretations of many of the experiments used to support the concept. They offer several warnings. For example:

- Not all laboratories agree with each others' findings—they cite many instances where conclusions do not concur and also offer alternative models and mechanisms for the effects noted.
- Small changes in experimental procedures can create major behavioural changes.
- In those experiments that manipulate the SNS using systemic pharmacological interventions, there may be widespread effects on a variety of other targets.
- Just as in humans, there may be significantly different mechanisms for quite similar symptoms between different individuals that have received the same injury. Just as some humans may be prone to developing post nerve injury CRPS with SMP or without it, so may different rats.
- The doses of pharmacological agents used to block or to stimulate the SNS in the experiments are frequently massive and unlikely to be 'physiological' (i.e. to occur naturally.)
- Surgical preparation of the animals can result in rapid changes in the expression of receptors and ionic channels so that longer-term abnormalities need to be interpreted with caution.
- Many observations made of *in-vitro* animal models do not match those of patients with SMP.

These observations and the authors' cautionary comments are certainly not to be taken as proof that SMP does not exist. What is clear is that sympathetic-afferent coupling can occur in pathophysiological conditions and that this does involve increased expression of adrenaline receptors on the lesioned afferent nerves as well as other 'plastic changes' in both the sympathetic and the afferent systems. Their warning is that the experimental

interventions used seem out of proportion to biological events and hence should be interpreted with 'utmost caution'.

In their summary they conclude that:

1. Human models clearly show that the SNS is involved in pain and most likely produces associated tissue changes in patients with CRPS Type I and CRPS Type II.
2. Nerve lesions in animal models do alter the ongoing and reflex activity of the SNS and that a coupling between the SNS and the sensory system exists. This coupling has been found to occur, or may occur:
   - At the site of the nerve lesion.
   - Anywhere along the length of an unmyelinated nerve fibre that has regenerated to its target tissue following nerve injury.
   - In nociceptor fibre endings of intact cutaneous nerves whose nerve trunk has suffered a partial nerve injury.
   - Anywhere along the length of afferent nerve fibre axons proximal to the nerve injury.
   - In the dorsal root ganglion of injured nerves (see also, Michaelis 2000).
3. Many of the morphological changes observed in the nerve lesion models can be correlated with changes in function that may be relevant to SMP in CRPS Type -II, but not CRPS Type I.

As more and more experimental models wrestle with the problem there is an increasing recognition that the mechanisms are complex, multiple and changing even when the symptom picture remains relatively stable. For example, Habler et al (2000), investigating SMP using an animal model, assessed the effect of electrical stimulation of the lumbar sympathetic trunk and the application of noradrenaline on recorded activity of damaged (axotomised) afferents following L5 spinal nerve transection as described above. Surprisingly, they were unable to demonstrate excitatory behaviour in the majority of the nerves they stimulated at physiological levels, or applied noradrenaline to. In other words, there was no evidence of SMP. However, if the researchers first produced a vasoconstriction effect of the circulation to the L5 dorsal root ganglion, sympathetic stimulation did then produce a significant activation of the axotomised afferents. These researchers concluded that for a sympathetic-afferent coupling to occur following a spinal nerve transection injury, a significant vasoconstriction is required. A transient ischaemia may therefore be an important precondition for SMP in this region of the nerve.

As a clinical aside, or leap, it seems easy to envisage a situation of relative ischaemia in patients whose pain has led them to a situation of gross underactivity and very little cardiovascular load. Promoting immobility in the management of any condition walks hand in hand with the potential aggravating effects of ischaemia (see Chapter 2.) Immobility and the concomitant ischaemia that may occur could conceivably be a factor that predisposes to the development of sympathetic-afferent coupling and hence, SMP. Promoting or maintaining good circulation via regular action, exercise and normal movements in a way that, at least initially, avoids aggravating

pain, may be an important preventative measure in the early management of nerve or tissue injury pain.

Models without nerve lesions

Bennett and Roberts (1996) rightly identified the need to explore the production of SMP in models without nerve damage in order to advance our understanding of CRPS Type I.

As noted in the previous chapter, early work has shown that the hyperalgesia which occurs in inflamed skin is made worse by noradrenaline and better by adrenoreceptor blockers and can be partially prevented by prior sympathectomy (see Levine et al 1986, Sato et al 1993). This C fibre noradrenaline sensitivity may be a normal physiological occurrence that disappears as inflammation subsides. Bennett and Roberts (1996) suggest that SMP would appear if either the inflammation persisted or the C-nociceptor noradrenaline responsiveness did not disappear with healing.

A further key finding of this work, also discussed in Chapter 3, is that skin nociceptor sensitisation that occurs as a result of experimental chemical irritation, requires the presence, but not the activity, of sympathetic terminals. The weight of the findings suggest that terminals act as a kind of docking station for the production of inflammatory agents like prostaglandins (see Levine et al 1986, Drummond 1995, Andreev et al 1995). This appears to offer further evidence that there is no requirement for sympathetic over-activity in the genesis of SMP in CRPS Type I. The physical presence of the sympathetic system seems to be an important factor.

Conclusions

Hopefully, many interesting points have emerged from this account and the evidence and discussions of the last two chapters. Here are a few that come to mind:

1. In CRPS there may or may not be SMP and it is impossible to tell whether it is present from the history or via physical testing.
2. In cases of CRPS with SMP there is little evidence for SNS over-activity in relation to pain; the current focus of attention is on abnormal adrenaline/noradrenaline sensitivity of the sensory/nociceptive system.
3. In CRPS, though still very unclear and poorly researched, there is a general assumption that changes in sympathetic activity may play a part in the development of non-pain symptoms like swelling, circulatory changes, oedema, temperature changes, sweating abnormalities and trophic dysfunction (see Chapter 2.) These changes may secondarily influence nociceptive sensitivity and activity (Janig 1996).
4. Sensory afferent nerve fibres can become maladaptively sensitive to the secretions of the SNS, i.e. to noradrenaline and adrenaline. This provides an efferent–afferent connection between the SNS and the nociceptive system that is not available in normal homeostatic conditions. It can thus

be seen as pathological/maladaptive. If there is some adaptive function provided by this injury-induced connection, no one has yet identified it or addressed its purpose.
5. There is a difference between animal models and patients in the behaviour and reproducibility of SMP.
6. Injury to different sites of the nervous system result in different mechanisms of pain and symptom production. For example, it seems that distally placed experimental nerve lesions, rather than proximal ones, are more likely to result in SMP.
7. Pain mechanisms change with time, often quite rapidly, even though the symptom picture may appear stable.
8. Simple answers based on simple constructs can be misleading and may lead to poorly reasoned and potentially harmful interventions.
9. The belief here is that CRPS and the SMP/SIP that are characteristic of it, are maladaptive symptoms in a maladaptive condition and as such *should* be preventable. Some individuals may be at risk to develop the condition.
10. Thinking and reasoning that is confined to peripheral tissues and nerves is untenable. Complex pain states involve all levels of the nervous system—input systems, scrutinising systems, and output systems. All models of understanding must include psychological and environmental factors.
11. Greater knowledge of mechanisms of pain, like those described here and in previous chapters and volumes should add to our profession's knowledge base and provide us all with an increased confidence. Patients should be the beneficiaries.
12. Physiotherapists have an important role to play in the continued development of the understanding of pain. Unbiased clinical observations may be particularly important. Most descriptions of diseases, syndromes, and disorders are derived from long out-of-date texts or standard textbooks that rely on observations of patients recorded a great many years ago and which have not been subjected to serious scrutiny. What patients feel and what clinicians think the patient feels may be quite different.

This chapter has outlined the evidence and controversies surrounding the concept of sympathetically maintained pain. The evidence suggests that there is value to this concept; but what constitutes it remains in need of further clarification.

REFERENCES

Ali Z, Raja SN, Wesselmann U, Fuchs PN, Meyer RA, Campbell JN 2000 Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. Pain 88:161–168

Andreev NY, Dimitrevia N, Koltzenberg M, McMahon SB 1995 Peripheral administration of nerve growth factor in the adult rat produces a thermal hyperalgesia that requires the presence of sympathetic postganglionic neurones. Pain 63:109–115

Baron R, Wasner G, Borgstedt R, Hastedt E, Schulte H, Binder A, Kopper F, Rowbotham M, Levine JD, Fields HL 1999 Effect of sympathetic activity on capsaicin evoked pain, hyperalgesia, and vasodilation. Neurology 52:923–932

Baron R, Levine JD, Fields HL 1999a Causalgia and reflex sympathetic dystrophy. Does the sympathetic nervous system contribute to the generation of pain. Muscle and Nerve 22:678–695

Bennett GJ 1999 Scientific basis for the evaluation and treatment of RSD/CRPS syndromes: laboratory studies in animals and man. In: Max M (ed) Pain 1999—an updated review. IASP Press, Seattle

Bennett GJ, Roberts WJ 1996 Animal models and their contribution to our understanding of complex regional pain syndrome I and II. In: Janig W, Stanton-Hicks M (eds) Reflex Sympathetic Dystrophy: A Reappraisal. IASP Press, Seattle

Black JA, Dib-Hajj S, Cummins TR et al 2001 Sodium channels as therapeutic targets in neuropathic pain. In: Hansson PT, Fields H, Hill RG et al (eds) Neuropathic Pain: Pathophysiology and Treatment, Progress in Pain Research and Management, Vol 21. IASP Press, Seattle 19–36

Campbell JN, Meyer RA, Raja SN 1992 Is nociceptor activation by alpha-1 adrenoreceptors the culprit in sympathetically maintained pain? American Pain Society Journal 1:3–11

Campbell JN, Raja SN, Selig DK, Belzberg AJ, Meyer RA 1994 Diagnosis and management of sympathetically maintained pain. In: Fields HF, Liebeskind JC (eds) Pharmacological Approaches to the Treatment of Chronic Pain: New concepts and clinical issues. IASP Press, Seattle

Cepeda MS 1995 Autonomic nervous system and pain. Current Opinion in Anaesthesiology 8:450–454

Dotson R 1993 Causalgia—Reflex sympathetic dystrophy—sympathetically maintained pain: myth and reality. Muscle and Nerve 16:1049–1055

Drummond PD 1995 Noradrenaline increases hyperalgesia to heat in skin sensitised by capsaicin. Pain 60:311–315

Glynn CJ, Stannard C, Collins PA, Casale R 1993 The role of peripheral sudomotor blockade in the treatment of patients with sympathetically maintained pain. Pain 53: 39–42

Habler HJ, Eschenfelder S, Liu X-G, Janig W 2000 Sympathetic-sensory coupling after l5 spinal nerve lesion in the rat and its changes in dorsal root ganglion blood flow. Pain 87:335–345

Hannington-Kiff J 1974 Intravenous regional sympathetic blockade. Lancet 1: 1919–1920

Janig W 1992 Can reflex sympathetic dystrophy be reduced to an alpha-adrenoreceptor disease? American Pain Society Journal 1 (1): 16–22

Janig W 1996 The puzzle of 'reflex sympathetic dystrophy': mechanisms, hypothesis, open questions In: Janig W, Stanton-Hicks M (eds) Reflex Sympathetic Dystrophy: A reappraisal. IASP Press, Seattle

Janig W, Baron R 2001 The role of the sympathetic nervous system in neuropathic pain: Clinical observations and animal models. In: Hansson PT, Fields HL, Hill RG et al (eds) Neuropathic Pain: Pathophysiology and treatment. Progress in pain research and management Vol 21. IASP Press, Seattle 125–149

Kingery WS 1997 A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain 73: 123–139

Kramis RC, Roberts WJ, Gillette RG 1996 Post sympathectomy neuralgia: hypothesis on peripheral and central mechanisms. Pain 64: 1–9

Levine JD, Taiwo YO, Collins SD, Tam JK 1986 Noradrenaline hyperalgesia is mediated through interaction with sympathetic postganglionic neurone terminals rather than activation of primary afferent nociceptors. Nature 323:158–160

Livingstone WK 1943 Pain Mechanism. Macmillan New York

Max MB, Gilron I 1999 Sympathetically maintained pain: Has the emperor no clothes? Neurology 52:905–907

McQuay H, Moore A 1998 An Evidence-based Resource For Pain Relief. Oxford University Press, Oxford
Michaelis M 2000 Coupling of sympathetic and somatosensory neurons following nerve injury: Mechanisms and potential significance for the generation of pain. In: Devor M, Rowbotham MC, Wiesenfeld-Hallin Z (eds) Proceedings of the 9th World Congress on Pain, Progress in Pain Research and Management, Vol 16. IASP Press, Seattle 645–656
Noon M 2002 Placebo and the therapeutic alliance. In: Gifford LS (ed) Topical Issues in Pain 4. Placebo and nocebo. Muscles and Pain. Pain Management. CNS Press, Falmouth
Perl ER 1994 A reevaluation of mechanisms leading to sympathetically related pain. In: Fields HF, Liebeskind JC (eds) Pharmacological approaches to the treatment of chronic pain: New concepts and clinical issues. IASP Press, Seattle
Price DD, Gracely RH, Bennett GJ 1996 The challenge and the problem of placebo in assessment of sympathetically maintained pain. In: Janig W, Stanton-Hicks (eds) Reflex Sympathetic Dystrophy: A reappraisal. IASP Press, Seattle
Price DD, Long S, Wilsey B, Rafii A 1998 Analysis of peak duration of analgesia produced by local anaesthetic injected into sympathetic ganglia of complex regional pain syndrome patients. The Clinical Journal of Pain 14:216–226
Ramamurthy S Hoffman J 1995 Intavenous regional guanethidine in the treatment of reflex sympathetic dystrophy/causalgia: a randomised, double-blind study. Anaesthesia and Analgesia 81: 718–723
Roberts WJ 1986 A hypothesis on the physiological basis for causalgia and related pains. Pain 24:297–311
Sato J, Suzuki S, Iseki T, Kumazawa T 1993 Adrenergic excitation of cutaneous nociceptors in chronically inflamed rats . Neuroscience Letters 164:225–228
Scadding JW 1999 Complex regional pain syndrome. In: Wall PD, Melzack R (eds) The Textbook of Pain 4th edn Chruchill Livingstone, Edinburgh 835–849
Schwartzman RJ, McClellan TL 1987 Reflex sympathetic dystrophy: A review. Archives of Neurology 44:555
Shortall R 2002 The powerful placebo—hit or myth? In: Gifford LS (ed) Topical Issues in Pain 4. Placebo and nocebo. Muscles and Pain. Pain Management. CNS Press, Falmouth
Thompson SWN 2001 Is the sympathetic nervous system a pain? Neuroscience News 4 (3): 35–41
Torebjork E, Wahren L, Wallin G, Halling R, Koltzenburg M 1995 Noradrenaline-evoked pain in neuralgia. Pain 63:11–20
Walker AE, Nulson F 1948 Electrical stimulation of the upper thoracic portion of the sympathetic chain in man. Archives of Neurology and Psychiatry 59:559–560
Wall PD 1995 Noradrenaline-evoked pain in neuralgia. Pain 63: 1–2
Wall PD 1999 Personal communication
Wall PD, Gutnik M 1974 Ongoing activity in peripheral nerves: The physiology and pharmacology of impulses originating from a neuroma. Experimantal Neurology 43:580–593
Wall PD, Gutnik M 1974a properties of afferent nerve impulse from a neuroma. Nature 248:740–743
Wall PD, Devor M, Inbal R 1979 Autotomy following peripheral nerve lesions: experimental anaesthesia dolorosa. Pain 7:103–113
White JC, Sweet WH 1969 Pain and the Neurosurgeon: A forty year experience. C C Thomas, Springfield
Wynn-Parry CB 1996 Rehabilitation of reflex sympathetic dystrophy. Clinical Orthopaedics 1, (2): 327–338