Introduction

Complex regional pain syndrome (CRPS) is the same now given to a group of conditions previously described as reflex sympathetic dystrophy (RSD), causalgia, algodystrophy, Sudeck's atrophy, and a variety of other diagnoses (Box 18.1; see Rizzi et al 1984). These conditions share a number of clinical features including pain with associated allodynia and hyperalgesia, autonomic changes, trophic changes, oedema, and loss of function. The term causalgia was retrospectively applied by Mitchell to describe a syndrome of burning pain, hyperesthesia, glossy skin, and colour changes in the limbs of soldiers sustaining major nerve injuries from gunshot wounds, seen during the American Civil War (Mitchell et al 1864, Richards 1967a, b). It was later recognized that a very similar clinical picture could be produced by a variety of other illnesses and injuries that did not include major limb nerve injury, and the term RSD has, for many years, been used to embrace these conditions (Evans 1946, Bonica 1979).

Involvement of the sympathetic nervous system in causalgia and reflex sympathetic dystrophy: historical aspects

It is worthwhile re-examining the early observations that led to a widespread acceptance that the sympathetic nervous system is crucially involved in the pathogenesis and maintenance of these syndromes. This has influenced subsequent thinking to the extent that some have even proposed response of the conditions to sympathetic blockade or
sympathectomy as diagnostic criteria. However, this illogical and scientifically unjustified approach to conditions of uncertain, and quite possibly heterogeneous, pathogenesis has now been abandoned.

Leriche (1916) described the relief of causalgia in a patient with a brachial plexus injury and thrombosis of the brachial artery by surgical sympathectomy, resecting the adventitia of a length of the brachial artery. In this and subsequent patients, pain relief combined with an improvement in discoloration and sweating changes led Leriche to conclude that the sympathetic nervous system was involved in the pathogenesis of causalgia (Leriche 1939). As described by Schott (1995), periarterial sympathectomy was replaced by preganglionic sympathectomy and became standard treatment for painful nerve injuries sustained during the two World Wars, although without further critical evaluation of effectiveness.

For the conditions without major nerve or blood vessel injury, later described by the term RSD, in which very similar clinical features to causalgia are present, attempts to relieve pain and restore function by sympathectomy or repeated sympathetic blockade have, for many years, been standard treatment. Evidence of efficacy is examined later but it is recognized by those regularly treating these patients that while temporary pain relief may occur, long-term results are poor. It is probable that sympathetic block has only survived as standard treatment because of the lack of more effective therapy.

### Causes of complex regional pain syndrome

According to the previous IASP definitions of causalgia and RSD, causalgia referred to the syndrome associated with nerve injury, while RSD included patients whose pain and associated features followed a variety of insults, most commonly relatively minor, and normally fully recoverable injuries. These are listed in Box 18.2 (Richards 1967a, Schwartzman and McLellan 1987).

### Definition and taxonomy of complex regional pain syndrome

The need for a new classification and terminology stems from a poor understanding of the clinical limits of the conditions concerned, the underlying pathophysiology and how variable this may be, and the unsatisfactory existing terminology and particularly RSD with its clear pathogenic implication. The term ‘sympathetically maintained pain’ (SMP) is discussed later in this chapter.

The new definition results from an IASP conference (Stanton-Hicks et al 1995) summarized in Box 18.3, reproduced from Boas (1996). The first criterion for CRPS is that the initiating noxious event. However, there are patients otherwise fulfilling the diagnosis for CRPS in whom there is no history of initiating event (Veldman et al 1993).

### Clinical features of complex regional pain syndrome

It can be seen from Box 18.3 that CRPS I in respects similar to CRPS I, except that the definition is the additional condition follows a nerve injury and thus corresponds to condition previously known as causalgia.

The symptoms and signs of CRPS are regional distribution, often widely in a limb, both types of CRPS the symptoms and signs spread well beyond the limits of the injured territory.

**Pain**

Spontaneous and evoked pain (allodynia and hyperalgesia) coexist in the great majority of cases and CRPS. Pain is disproportionate to the cause in distribution, severity may have various qualitative aspects including burning, aching, or sharp pain. In the case of CRPS II, symptoms are common. Allodynia and hyperalgesia are often so severe that the affected part an extreme of the limb is turned may lead to severe pain, stiffness, and discomfort with concomitant factors in C
Complex regional pain syndrome

Autonomic signs

The definition of CRPS is careful to state that autonomic signs are, or have at some time, been present, but are not necessarily constant features in a particular patient. Abnormalities of temperature, colour, and sweating are common. Oedema is often present as an early sign (Blumberg and Janig 1994), which later resolves in about half of patients. These autonomic changes could, in part, be secondary to immobilization.

Motor signs

Objective motor signs are variable, but loss of function of the affected part is almost universal. Wasting and weakness are common; tremor and dystonia are observed in a small proportion of patients.

Dystrophic changes

Some dystrophic changes may simply result from prolonged disuse. Skin changes include thinning, with a shiny appearance, or flaky, thickened skin. Hair may be lost or abnormally coarse and the nails may be thickened. Osteoporosis, explicable on the basis of disuse, is a frequent finding in many patients, but a more profound loss of bone mineral content also occurs (Sudeck’s atrophy).

Predisposition to CRPS

It has been postulated that certain individuals might be predisposed to the development of CRPS but there is no conclusive evidence in favour of this (Covington 1996).

Psychological factors

The absence of a clear pathogenesis and pathophysiological basis for CRPS and the disproportionate pain and loss of function have led to examination of potential psychological aetiology. Patients with conversion disorder and factitious illnesses may present with symptoms that can closely resemble CRPS and indeed, because diagnosis of CRPS is based on assessment of symptoms and signs, it is not surprising that some patients with primary psychiatric morbidity are erroneously diagnosed as having CRPS. A diagnosis of CRPS as distinct from conversion disorder may only emerge after a series of diagnostic assessments.

The severe pain of CRPS with loss of function and lack of a clear diagnosis produces anxiety, fear,
and depression in many patients. Whether such secondary psychological features developing early following an injury might then predispose to the development of CRPS remains controversial (Covington 1996).

Some of the patients reported by Ochoa and Verdugo (1995) with so-called pseudoneuropathy mimicking CRPS type I undoubtedly had primarily psychiatric illnesses, emphasizing the need for careful and often repeated clinical assessment over a period of time.

Relative frequency of clinical features in CRPS

Case ascertainment is clearly a difficulty in CRPS and all the large series reported in the literature suffer from referral bias. Prospective studies examining patients after a particular known cause, for example Colles fracture (Bickerstaff and Kanis 1994), avoid such bias but only provide a single cause perspective of the condition. A report from a centre known to have an interest in CRPS, and thus attracting referrals from many other hospitals in The Netherlands, inevitably suffered from referral bias to some extent, but analysis of 829 patients with CRPS from all causes provides a fairly reliable insight into the relative frequency of the various symptoms and signs composing CRPS (Veldman et al 1993). These were categorized by Veldman et al (1993) as inflammatory, neurological, dystrophic and sympathetic and were evaluated with respect to duration of CRPS. Table 18.1 presents data from Veldman et al (1993).

Staging of clinical features in CRPS

Earlier studies of RSD suggested that three stages could be recognized: an acute warm phase in which pain and oedema predominated, a dystrophic phase categorized by muscle wasting and vasoconstriction with pale cyanotic skin, and a later atrophic stage categorized particularly by bone and skin changes (Blumberg and Janig 1994). The value of staging has been questioned as patients do not follow the same course, the duration of recognizable phases is variable, and not all patients progress to the third stage (Walker and Cousins 1997). Veldman et al (1993) found that in 95% of their patients the acute phase was categorized as

<table>
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<th>Table 18.1 Symptoms and signs of complex regional pain syndrome</th>
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<td><strong>Symptom/sign</strong></td>
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<tr>
<td>Inflammatory</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Colour difference</td>
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<td>Temperature difference</td>
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<td>Exacerbation with exercise</td>
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<td>Oedema</td>
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<td>Muscle spasm</td>
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<td>Paresis</td>
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<td>Changed hair growth</td>
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<td>Changed nail growth</td>
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*Data adapted from Veldman et al (1993).*
The analysis of 829 patients provides a fairly reliable frequency of the various CRPS (Veldman et al 1993). In 1994, Veldman et al categorized by Veldman et al: neurovascular, dystrophic, and arterial. Dystrophic, evaluated with respect to children and adults. ACR two-phase isotope bone scans are frequently abnormal (Goldsmith et al 1989), but a normal bone scan does not always exclude the diagnosis. Although the existence of a sympathetic influence on pain in CRPS and other pain states has been questioned (Ochoa et al 1994, Schott 1995), there is substantial experimental and clinical evidence of such an influence (see later discussion; Loh and Nathan 1978, Loh et al 1980, Torebjork et al 1993). Symptomatically maintained pain (SMP) is the component of pain maintained by efferent noradrenergic sympathetic activity and circulating catecholamines; symptomatically independent pain (SIP) is the component that is not (Roberts 1986). Neurogenic pains, central as well as peripheral, may be partly responsive to sympathetic blockade (Loh et al 1980, Bonica 1980, Arner 1981, Raja et al 1991, Wahren et al 1991). A conceptual framework for the relationship between SMP and some painful conditions is shown in Fig. 18.1 (Boas 1996). SMP as assessed clinically by the effect of sympathetic blockade is a variable component of pain in CRPS I and II. SMP is correctly not included although comparisons are not easy due to the higher rate of spontaneous resolution or cure in children than in adults.

### Diagnostic tests: sympathetically maintained pain and sympathetically independent pain

There are no diagnostic tests for CRPS. Three-phase isotope bone scans are frequently abnormal (Goldsmith et al 1989), but a normal bone scan does not exclude the diagnosis. Although the existence of a sympathetic influence on pain in CRPS and other pain states has been questioned (Ochoa et al 1994, Schott 1995), there is substantial experimental and clinical evidence of such an influence (see later discussion; Loh and Nathan 1978, Loh et al 1980, Torebjork et al 1993). Symptomatically maintained pain (SMP) is the component of pain maintained by efferent noradrenergic sympathetic activity and circulating catecholamines; symptomatically independent pain (SIP) is the component that is not (Roberts 1986). Neurogenic pains, central as well as peripheral, may be partly responsive to sympathetic blockade (Loh et al 1980, Bonica 1980, Arner 1981, Raja et al 1991, Wahren et al 1991). A conceptual framework for the relationship between SMP and some painful conditions is shown in Fig. 18.1 (Boas 1996). SMP as assessed clinically by the effect of sympathetic blockade is a variable component of pain in CRPS I and II. SMP is correctly not included although comparisons are not easy due to the higher rate of spontaneous resolution or cure in children than in adults.

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### Fig. 18.1 Diagrammatic representation of the relationship of sympathetically maintained pain (SMP) and some painful conditions, demonstrating the existence of SMP in these conditions. (Reproduced from Boas 1996 with permission.)

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**Complex regional pain syndrome**

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**Less common clinical features of CRPS**

Very infrequently, CRPS may be migratory or relapsing or occur in two or more extremities (Johnson 1943, Bentley and Hameroff 1980, Veldman et al 1993). In 53% of the patients with relapsing or multiple RSD described by Veldman et al (1993), no initiating injury or illness could be identified, raising the possibility that very rarely a predisposition to develop CRPS may exist in certain subjects. Other less common features of CRPS include intractable or relapsing skin infections (associated with chronic oedema), spontaneous haematomas, increased skin pigmentation, nodular fasciitis of palmar or plantar skin, and clubbing of the nails (Veldman et al 1993).

**CRPS in children**

It is only relatively recently that the occurrence of CRPS in children has been recognized (Wilder 1996). The lower limb is much more frequently affected than the upper limb (ratio about 5:1), whereas the opposite is true in adults. Most studies of CRPS in adults show a female preponderance, but this is more marked in children (ratio about 4:1). Sufferers are typically pubertal adolescent girls. Approximately half the children affected will get better with complete resolution of symptoms and signs, and only a small proportion continue to experience severe pain. Recovery may be helped by physiotherapy, transcutaneous electrical stimulation, and cognitive and behavioural pain management techniques. Many children with CRPS participate in competitive sports, putting them at greater risk of musculoskeletal injury.

Interest has focused on the role of psychological factors with the suggestion that injury and persistent pain provide a means of escape from stressful competition and the parental expectations associated with this (Sherry and Weisman 1988). Sympatholytic treatment is as unpredictable in its efficacy as it is in adults and long-term results are disappointing.
in the diagnostic criteria for either type of CRPS. A useful algorithm for the diagnosis of CRPS is shown in Box 18.4.

Indicence and natural history of complex regional pain syndrome

One of the problems with the current defining diagnostic criteria for CRPS of both types is establishing the limits of the diagnosis. When is pain judged to be disproportionate in severity, distribution, and duration to the initiating event? Furthermore, some degree of oedema or vasomotor or sudomotor change following many injuries is extremely common. At what stage can these changes be said to be excessive and indicative of the development of CRPS? These uncertainties, together with the fact that there are very few prospective studies, limit conclusions about incidence and natural history.

In a prospective study of 274 patients with Colles fractures of varying severity, Bickerstaff and Kanis (1994) measured tenderness of the fingers, hand swelling, and grip strength, together with symptomatic assessment of pain, vasomotor symptoms, and finger stiffness at intervals up to 1 year following the fracture. At 2 weeks following removal of the plaster cast, 54% had one of the measured features, swelling being the most common (45%). However, only 28% had all four features (bone tenderness, vasomotor symptoms, swelling, and stiffness). These patients were more likely to complain of pain in the hand or shoulder and had a more markedly impaired grip strength. At 1 year, 18, 14, and 12% still had finger tenderness, pain, and swelling respectively, and these features were usually found in the same patients. Some 60% of patients still had finger stiffness. These authors’ conclusion that each of these symptoms indicated the presence of algodystrophy is at variance with the new diagnostic criteria for CRPS (Stanton-Hicks et al 1995), and it would not be accepted that about 20% of their patients had developed CRPS at 1 year. However, the study of Bickerstaff and Kanis (1994) does indicate that careful prospective study, following a common fracture usually considered to be associated with excellent recovery, presents a truer picture and draws attention to the underestimation of continuing painful symptoms. Prospective study has yielded similar results in other conditions potentially giving rise to chronic painful symptoms, for example amputation (Carlen et al 1978).

Other estimates for the incidence of CRPS, not from prospective studies, include 1–2% after fractures

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<th>BOX 18.4</th>
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<td><strong>Algorithm for the diagnosis of complex regional pain syndrome</strong> (Reproduced from Wilson et al 1996)</td>
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</table>

**Pain**

The diagnosis of CRPS cannot be made in the absence of pain; it is a pain syndrome. However, the characteristics of the pain may vary with the initiating event and other factors. The pain is often described as burning, and might be spontaneous or evoked in the context of hyperalgesia or allodynia. Both spontaneous and evoked pain may occur together.

**History**

- Develops after an initiating noxious event or immobilization
- Unilateral extremity onset (rarely may spread to another extremity)
- Symptom onset usually within a month

**Exclusion criteria:**

- Identifiable major nerve lesion (CRPS II)
- Existence of anatomical, physiological, or psychological conditions that would otherwise account for the degree of pain and dysfunction

**Symptoms (patient report)**

A. Pain (spontaneous or evoked)
   - Burning
   - Aching, throbbing
B. Hyperalgesia or allodynia (at some time in the disease course) to mechanical stimuli (light touch or deep pressure), to thermal stimulation, or to joint motion
C. Associated symptoms (minor)
   - Swelling
   - Temperature or colour: asymmetry and instability
   - Sweating: asymmetry and instability
   - Trophic changes: hair, nails, skin

**Signs (observed)**

- Hyperalgesia or allodynia (light touch, deep pressure, joint movement, cold)
- Oedema (if unilateral and other causes excluded)
- Vasomotor changes: colour, temperature
- Instability, asymmetry
- Sudomotor changes
- Trophic changes in skin, joint, nail, hair
- Impaired motor function (may include components of dystonia and tremor)

**Criteria required for diagnosis of CRPS I**

**History of pain:**

- Plus allodynia, hyperalgesia, or hyperaesthesia
- Plus two other signs from the above list

**Characteristics of spontaneous pain:**

- Sympathetically maintained pain (SMP)
- Sympathetically independent pain (SIP)
- Combined SMP + SIP
Complex regional pain syndrome

Pathophysiology of complex regional pain syndrome

Animal and human investigations into the underlying mechanisms of CRPS have focused on three areas: firstly, evidence of abnormal coupling between the efferent sympathetic nervous system and sensory afferents; secondly, the nature and importance of inflammatory processes in peripheral tissues, both with and without nerve injury; and, thirdly, the development of secondary central changes, explaining the wide radiation of the clinical features of CRPS and the maintenance(612,798),(982,973)

The sympathetic nervous system and pain: nerve damage

Three sites of sympathetic sensory interaction after nerve injury have been identified: the region of the nerve damage itself, undamaged fibres distal to the nerve lesion, and the dorsal root ganglion.

Following severe injury, for example nerve section with neuroma formation, somatodendritic fibres develop an abnormal sensitivity to catecholamines, an effect mediated by α receptors. Both circulating catecholamines and endogenously released transmitter following sympathetic trunk stimulation can be shown to stimulate damaged sprouting sensory fibres. This also occurs when continuity of the nerve is restored by resuture following nerve section and other, milder forms of nerve injury (Shyu et al 1990, Sato andPerl 1991). The noradrenergic sensitivity can be reduced by sympathectomy, phenolamine, or guanethidine (Kim et al 1993). All classes of afferent fibre, from both skin and deep tissue, including C fibres, are affected (Janig 1996, Devor and Seltzer 1999).

The normal spontaneous discharge of dorsal root ganglion neurons is enhanced by peripheral nerve injury (Kirk 1974, Wall and Devor 1983), and this may be further increased by sympathetic stimulation (Devor et al 1994). However, subsequent studies have indicated that this sympathetic sensory coupling occurs mainly in non-nociceptive afferents and is present only transiently following nerve injury. Furthermore, at later intervals, sympathetic stimulation may exert an inhibitory effect on dorsal root ganglion neuron activity (Michaelis et al 1996).

There are limited but important human investigations that indicate a sympathetic influence on pain following peripheral nerve injury. Walker and Nilsen (1948) showed that intraoperative sympathetic chain stimulation exacerbated pain in patients with causalgia. In patients with successful treatment, Wallin et al (1976) found that the patient's original pain could be rekindled by cutaneous application of noradrenaline (norepinephrine). Injection of noradrenaline (norepinephrine) around amputation stump neuromas may cause severe pain (Chabal et al 1992).

In the investigation of Torebjörk et al (1995) some of the patients examined in the earlier study of Wallin et al (1976), and who at that time had SMP, were found at the later examination to have pain that did not respond to sympathetic blockade. In addition, only 28% of patients with nerve injury and pain previously responsive to sympathetic blockade (SMP) experienced an increase in their pain when noradrenaline (norepinephrine) was injected into their sensitive skin. This indicates changing pathophysiology in CRPS over long periods of time, presenting further difficulties in targeting treatments.

In a clinical condition that may be likened to experimental situations in which partly damaged regenerated or undamaged afferents in partial nerve injury become sensitive to catecholamines, Choi and Rowbotham (1997) showed that intracutaneous injections of noradrenaline (norepinephrine) or adrenaline (epinephrine) in an area affected by postherpetic neuralgia increased both spontaneous pain and allodynia.

The sympathetic nervous system and pain: without nerve damage

Investigation of possible sympathetic influences on painful sensation without nerve injury, in other words, in conditions more representative of the clinical situations in which CRPS type I may develop, has been more recent than the studies of nerve injury. The complex mechanisms underlying the development of spontaneous pain, hyperalgesia, and allodynia to various types of stimulation following experimental heat and chemically induced cutaneous inflammation using irritants such as mustard oil and capsaicin are summarized by...
Koltzenburg (1996). Both peripheral and central factors are involved. Some components of experimental cutaneous inflammation have been shown to be influenced by noradrenergic receptor agonists or antagonists. Drummond (1995) reported an increase in heat-induced hyperalgesia in skin inflamed by topical capsaicin after iontophoresis of noradrenaline (norepinephrine). In inflammation produced by intradermal capsaicin, Kinman et al. (1997) showed that spontaneous pain could be evoked by locally injected phenolamine, although evoked pain in capsaicin-induced inflammation was not reduced by intravenous phenolamine in the experiments of Liu et al. (1996).

It might be argued that the demonstrated sympathetic influence occurred as a secondary effect of altered local blood supply in the area of inflammation. However, in a microneurographic study, Elam et al. (1996) found that the discharge from axons sensitized by cutaneous application of mustard oil was not influenced by physiological reflex alterations of sympathetic vasomotor neurons. In addition, Baron et al. (1998) have reported that cutaneous sympathetic vasomotor activity does not alter the intensity of ongoing pain induced by capsaicin inflammation.

The sensitization of somatosensory afferents may be caused by direct stimulation by noradrenaline (norepinephrine) or indirectly through release of inflammatory substances, particularly prostaglandins. Levine and others have shown that in certain experimental situations, noradrenaline (norepinephrine) released from sympathetic postganglionic neurons causes release of prostaglandins (Levine et al. 1986, Gold et al. 1994). In an experimental sciatic neuropathy in rats, Tracey et al. (1995) found hyperalgesia was enhanced by local injection of noradrenaline (norepinephrine) and decreased by injection of indomethacin, strongly suggesting mediation of the hyperalgesia by prostaglandins and possibly other inflammatory substances.

Pain in CRPS related to inflammation and independent of the sympathetic nervous system

The experimental animal and human evidence outlined above would appear to indicate an important adrenergic sympathetic postganglionic influence in the processes that may lead to pain, both with and without nerve injury. The singular lack of long-term effectiveness of sympathetic blockade and sympathectomy in clinical practice in CRPS, both type I and type II in the majority of patients, has led some to question the existence of any significant sympathetic involvement in the condition, or indeed any type of pain syndrome. Arguments are based on the poor quality of clinical investigations, including lack of proper control or questionnaires, together with questionable relevance of animal models to human situation, together with possible estimation of psychological factors (Ochoa-Verdugo 1995; Schott 1995, 1997). Schott (1997) proposes a mechanism for the analgesia of sympathetic blockade that does not depend on reduction of peripheral noradrenergic activity and suggests that pain relief after sympathectomy may be explained by a reduction of activity of nociceptive fibres that travel in sympathetic nerves (Cervero 1994, Schott 1994), rather than by a peripheral effect on effenter noradrenergic fibres.

Schott (1995) proposes inflammatory mechanisms that may be independent of noradrenergic function as the cause of pain in CRPS (Dray 1995). In a subsequent paper Schott (1997) draws attention to the evidence indicating an inflammatory role for the bone atrophy that occurs in CRPS, leading to its extreme form of Sudeck's atrophy. This role is reviewed by Kozin (1992) and Oyen et al. (1992) and the role of bone loss in CRPS. Treatments, including calcitonin to reverse the bone atrophy that occurs in CRPS, have been advocated in the past but without controlled trials. Interest recently has focused on the bisphosphonates, which prevent bone loss by inhibiting osteoclast activity and dissolving calcium phosphate crystals. However, this proposed role for bisphosphonates is unlikely to explain the rapid relief of bone pain that has been observed in CRPS bone pain due to cancer, and it is possible that additional effects of bisphosphonates on bone metabolism may be responsible for analgesia (Strang 1993). Further investigation may clarify the mechanism of bone pain in CRPS and possibly atrophy in other tissues, which are frequent features of CRPS.

Histopathological studies in limbs amputated from patients with CRPS have shown microstructural atrophy changes, leading to the suggestion that there is a component of damage may be an important component of the pathogenesis of the condition (van der Leek et al. 1998). Relevant to the issue of visceral and somatic pain, pain in sympathetic nerves, Kramis et al. (1995) review a curious but well-recognized consequence of sympathetic chain interruption, the development of a new pain that occurs days to weeks after sympathectomy, and propose mechanisms for this so-called sympathalgia.
pain. This so-called sympathalgia, or postsympathectomy pain, tends to be distributed in the proximal parts of the sympathectomized limb and extends onto the trunk. Distally in the limb there is usually evidence of sympathetic denervation, but proximally there may be excessive sweating and other features include deep muscular tenderness and proximal cutaneous allodynia and hyperalgesia (Raskin et al 1974). The incidence of postsympathectomy pain following sympathetic trunk lesioning, but not after local anaesthetic block or more distal sympathetic nerve blockade with either local anaesthetic or guanethidine, is estimated to occur in 30-50% of patients, although it is not usually severe. Kramis et al (1996) propose that postsympathectomy pain develops as a result of transection of paraspinal somatic and visceral afferents travelling within the sympathetic trunk, and that this in turn leads to cell death of many of the axotomized neurons, causing central deafferentation. Pain related to the deafferentation may be worse as a result of prior sensitization of dorsal horn cells produced by the painful state for which the sympathectomy was performed.

Central nervous system changes

Central nervous system physiological changes secondary to nerve injury are reviewed in Chap. 17. There is evidence indicating that prolonged nociceptive inputs, not resulting from nerve injury, are capable of inducing similar secondary central changes (Doubell et al 1999).

Such changes may clearly be important in relation to the pain of CRPS.

Summary of mechanisms in CRPS

The pathophysiology of pain and other clinical features in CRPS remains poorly understood, and although experimental studies outlined here represent a considerable advance in knowledge, we are still some way from a clear understanding of these conditions. The diagrammatic representation in Fig. 18.2 sets out some components of CRPS currently thought to be of importance in pathogenesis. The basic concept of a vicious circle, first proposed by Livingston (1943), remains evident. The importance of the sympathetic nervous system

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**Fig. 18.2** Relationship of various peripheral and central factors important in the mechanisms of pain and other clinical features of CRPS types I and II. See text for further explanation. (Reproduced from Janig 1996 with permission.)
Clinical pain states

may be overrated, and that of chronic inflammatory changes in deeper tissues underestimated, in the scheme presented. The potential for some central changes to become permanent, and thus possibly limit the effectiveness of any treatment directed towards the initiating peripheral event, is not shown in Fig. 18.2. These factors, together with further knowledge of the somatic and visceral sensory sympathetic coupling in peripheral tissues, require elucidation through further research.

Treatment of complex regional pain syndrome

Few conditions can match CRPS types I and II for the variety of treatment modalities and drugs suggested—a sure indication that no single treatment is superior to others and that nothing is consistently successful. Controlled trials have been few and comparisons of treatments in different reports are made difficult by patient populations heterogeneous in causation, clinical features, and severity. This is not surprising in a condition that has proved so difficult to define and whose limits, even with the now generally accepted definition provided by the IASP consensus conference, are uncertain. The older term, RSD, has focused undue attention upon sympatholytic procedures to the exclusion of consideration of other treatments, although this is now changing. The research on mechanisms of CRPS types I and II is recent, particularly for type I, and many treatments suggested have previously been based on ideas and speculation rather than fact. This state of affairs is now set to change. Controlled trials of treatment in CRPS are reviewed by Kingery (1997) and Perez et al (2001).

Does early treatment improve outcome

It has long been accepted that early recognition and institution of active treatment improves the outcome in CRPS. While this seems intuitively correct, it has never been subjected to systematic study. Clearly, the management of injuries and diseases known to have the potential of leading to the development of CRPS should be optimally managed in the acute stages, but again there is no evidence that it is only badly managed patients who are prone to develop CRPS. However, immobilization and disuse are undoubtedly factors that contribute to the development of CRPS, and it makes sense to minimize these factors by instituting physiotherapy at an early stage after injury.

This raises an important point about the treatment in established cases of CRPS. It is gratifying, both to patient and clinician, to find analgesia by whatever means, but pain relief is insufficient. A hallmark of CRPS is loss of function of the affected part, and every period of even brief analgesia should be utilized to begin mobilization and rehabilitation. This emphasizes the importance of a multidisciplinary approach to treatment.

Sympatholytic procedures

Intravenous regional guanethidine

Guanethidine reduces noradrenaline (norepinephrine) concentrations in adrenergic neurons and reuptake. The technique of intravenous regional guanethidine block (IVRGB) described by Hannington-Kiff (1974) quickly became established as a simple and reliable method of sympathetic blockade and is now widely used. Treatment has, however, only been investigated in controlled studies in recent years. In practice, it has been common experience that some patients respond, usually transiently, for hours or days, but many do not and some patients have a transient increase in pain following IVRGB blocks over a period of time have been advocated. While the technique has often been suggested as a treatment for CRPS (Tasker 1990) but without clear rationale. Komin (1992) analysed reports of sympathetic blocks in nociceptive conditions and concluded that 46% of these involved CRPS. Again, with some success. Wang et al (1995) treated 27 patients with CRPS type II with IVRGB and 43 patients treated with sympathetic blocks and reported that 12 patients treated with sympathetic blocks had improved, compared to 27 patients treated with IVRGB.

The ganglion block

The sympathetic stellate ganglion or T-1 ganglion block has been much used in the treatment of inadequately controlled sympathetic symptoms and would be difficult to disentangle from other treatment (Tasker 1990). However, it is better evaluated in CRPS. While a sympathetic block by T-1 ganglion block may be used in CRPS, and many patients with CRPS have been treated with T-1 ganglion blocks, it is generally accepted that this is due to its role in the treatment of CRPS.

Surgical sympathectomy

Surgical sympathectomy is only rarely used in CRPS treatment. However, it is possible that surgical sympathectomy may be more effective in terms of pain relief and function than other forms of treatment. The use of surgical sympathectomy in CRPS is controversial, and the decision to proceed with surgery should be made with caution.

Radiofrequency denervation

Radiofrequency denervation is a controversial treatment for CRPS. While it may provide temporary pain relief, it is not effective in the long term and is associated with a high complication rate.

Educational Note

It is important to note that the use of pain medications and injections, as well as other treatments, should be individualized based on the specific needs and circumstances of each patient. The treatment of CRPS is complex and requires a multidisciplinary approach involving physiotherapy, medication, and sometimes surgery. The decision to proceed with any treatment should be made with caution and in consultation with a medical professional.
lidocaine (lignocaine), control injections being lidocaine (lignocaine) and saline. Although there was no difference between guanethidine- and control-treated patients, patients in all treatment groups showed a decrease in oedema and pseudomotor, trophic, and vasomotor changes. All patients had at least one IVRGB and those receiving up to four blocks gained no greater degree of pain relief. Campbell et al. (1988) investigated the effects of a tourniquet inflated to suprasystolic pressure as used in IVRGB. Hyperalgesia was relieved but temperature sensation was not affected. It was suggested that hyperalgesia was mediated via Aβ-mechanoreceptor fibres, those being most susceptible to pressure block.

**Sympathetic ganglion block**

Local anaesthetic stellate ganglion or lumbar chain blocks have been much used in the treatment of CRPS but no adequately controlled study has been done, and indeed would be difficult to do. Aggressive early treatment has often been suggested (Wang et al. 1985, Bonica 1990) but without clear supporting evidence. Kozin (1992) analysed reports in seven studies of sympathetic blocks in more than 500 patients and concluded that 46% of patients had significant prolonged analgesia. Again, these were uncontrolled observations. Wang et al. (1985) compared 71 patients with CRPS treated over a 3-year period. Twenty-seven patients did not receive sympathetic blocks and 45 patients did. At 3 years 41 and 65%, respectively, had improved, suggesting some effect from the treatment.

In patients with early CRPS associated with severe limb swelling, sympathetic blocks may dramatically reduce swelling and produce pain relief. It is suggested that this is due to interruption of vasoconstrictor activity with opening of venules (Blumberg and Janig 1994).

The intravenous phentolamine test has been advocated as a test to assess the likely efficacy of subsequent sympathetic blocks (Arner 1991). Patients who may obtain pain relief with IVRGB or sympathetic ganglion block may not respond to phentolamine due to the less complete α-adrenergic receptor blockade achievable with systemic rather than local administration. The phentolamine test is widely used in many centres to identify those likely to respond to more prolonged local sympathetic blockade.

**Sympathectomy**

Surgical, chemical, or radiofrequency sympathectomy may produce good short-term results but long-term pain relief is poor (Tasker 1990, Rocco 1995), leading most to abandon these procedures. The problems of sympathalgia following sympathectomy have already been discussed.

**Other drugs used in regional blocks**

Kelanserin, a selective serotonin type II receptor blocker, and bretylium, which reduces release of noradrenaline (norepinephrine), have both been given by the Biers block technique and in controlled trials have been found to be analgesic in CRPS (Ford et al. 1988, Hanna and Peat 1989). Clonidine was not effective by the same root (Glynn and Jones 1990). The non-steroidal anti-inflammatory drug ketorolac, which reduces prostaglandin release, has been reported to be effective in a small group of patients with CRPS, of interest in relation to pathophysiology (Vanos et al. 1992).

**Calcitonin and corticosteroids**

Evidence for an analgesic effect of calcitonin and corticosteroids in CRPS is conflicting, but in controlled trials, a therapeutic effect for calcitonin (Gobelet et al. 1992) and for corticosteroid (Christensen et al. 1982) has been reported.

**Epidural and intrathecal drugs**

The role of long-term administration of drugs by the epidural or intrathecal root is uncertain. When CRPS involves the lower limb opiates, with or without local anaesthetic, will produce partial analgesia, although often at the cost of impaired bladder and bowel sphincter function and some degree of weakness. In patients with severe allodynia and hyperalgesia, short-term percutaneous infusions for 1–2 weeks may help by allowing weight bearing on a previously useless leg and the start of rehabilitation. Long-term intrathecal morphine has been reported to produce useful analgesia in CRPS (Becker et al. 1995).

Clonidine, an alpha-2 receptor agonist given epidurally, has been reported to relieve pain in CRPS affecting both upper and lower limbs over long periods (Rauk et al. 1993, Walker and Cousins 1997). Given orally, clonidine is limited by adverse effects and does not produce analgesia in CRPS (Walker and Cousins 1997).

**Oral drugs**

Numerous drugs have been tried in CRPS by the oral route. Many patients report analgesic effects from simple analgesics, codeine, and non-steroidal
anti-inflammatory drugs, and continue to take these drugs in the absence of more effective treatment. No controlled trials substantiate the effectiveness of these drugs in CRPS. Of the anticonvulsant drugs, recent interest has focused on gabapentin, which is reported to help in CRPS, but again controlled trials are awaited (Mellick and Mellick 1997). Other reports of benefit in uncontrolled studies include phenoxycbenzamine (Ghothie et al 1984, Muizelaar et al 1997), tricyclic antidepressants (Wildier et al 1992), phenytoin (Chaturvedi 1989), and nifedipine (Prough et al 1985, Muizelaar et al 1997). Bisphosphonates via the intravenous route have been reported to relieve pain in CRPS in open label studies (Adami et al 1997, Cortet et al 1997). Trials with oral bisphosphonates are awaited.

Transcutaneous and dorsal column stimulation

Transcutaneous electrical nerve stimulation has been reported to be beneficial in children with CRPS (Wildier et al 1992) but not in adults. Dorsal column stimulation may be helpful (Law 1993).

Psychological measures and rehabilitation

As in all chronic pain syndromes, psychological interventions may have a vital part to play in treatment. Fear, anxiety, depression, loss of function, job, and income, and domestic and marital stresses may all take their toll in CRPS. Many patients find psychological management extremely helpful, particularly when, as is often the case, physical treatments fail. Efforts to rehabilitate the patient as far as is possible should be initiated at an early stage and pursued with vigour. The role of straightforward support for these unfortunate patients cannot be overemphasized. Patients with established CRPS should always be referred to a centre where a multidisciplinary programme of pain management is available.

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Nerve root

The chapter reviews pain felt in the neck and lower cranial nerve. If these conditions are responsive to medications or not caused by serious or curable by surgery, such as chronic post-herpetic pain with epidermol fibroplasia, among the most refractory pain. Few generalities emerge. Lesions of single nerve root in young individuals are apt to be self-limited, often due to benign mechanical or stretch of the root. Pain c is often a diffuse degenerative inflammatory cause, from root pain due to mechanical root is more amenable to root damage.

It is not the only issue for disorders. Root pain involves weakness, over restriction of movement and bladder control. Some of these deficiencies vary in severity of physical examinative.