

Complex? Regional? Pain? Syndrome?

G D Schott

The story of complex regional pain syndrome (CRPS) begins in 1864. During the American Civil War, the father of American neurology, Silas Weir Mitchell (fig 1), together with Morehouse and Keen, observed that soldiers sustaining major nerve injuries affecting their limbs sometimes experienced long-lasting pain that was burning in quality, and "so frequent and terrible as to demand from us the fullest description".¹ Soon afterwards he termed the condition *causalgia* (Greek: *kausos* (heat) + *algos* (pain)). Mitchell's account, in which he graphically describes many of the associated features shown in table 1, is one of the classics of neurology.

At the beginning of the 20th century, Paul Sudeck made two important contributions.² First, only five years after x rays had been discovered, he identified the localised bone atrophy ("Knochenatrophie") that can develop in the presence of acute, focal limb disorders—and so, strictly speaking, the term *Sudeck's atrophy* should be reserved for the radiological appearance of osteoporosis. Second, he postulated an inflammatory



Figure 1
Silas Weir Mitchell (1829–1914).

("entzündliche") cause—a concept now thought increasingly plausible.

The next landmark contribution was the paper from the famous French vascular surgeon, René Leriche. Thinking the limb of

G D Schott
Consultant Neurologist, The
National Hospital for Neurology
and Neurosurgery, Queen Square,
London WC1N 3BG, UK;
geoffrey.schott@uclh.nhs.uk

TABLE 1 The various accompanying features seen in complex regional pain syndrome

Erythematous, cyanosed, pale or blotchy skin
 Excessive, reduced or absent sweating
 Inappropriate warmth or coldness
 Swelling or atrophy of skin
 Loss of skin wrinkles, or glossiness
 Excess or loss of hair
 Nails ridged, curved, thin, brittle or clubbed
 Subcutaneous atrophy or thickening
 Stiffness and restriction of passive limb movements
 Dupuytren's and other contractures
 Osteoporosis—spotty, localised or widespread
 Muscle wasting, weakness, loss of dexterity, difficulty in initiating movements, "motor neglect"
 Involuntary movements—tremor, unsteadiness, spasms, dystonia, myoclonic jerks
 Visuospatial and other perceptual disturbances
 Detrusor and urinary sphincter dysfunction

Modified from Schott GD. Pain and the sympathetic nervous system. In: Mathias CJ, Bannister R, eds. *Autonomic failure*, 4th edition. Oxford: Oxford University Press, 1999:520–26. (Reproduced with permission from Oxford University Press.)

patients with causalgia resembled an ischaemic limb, and recalling that sympathectomy was used to treat ischaemic limbs, in 1916 he described how he had performed extensive stripping of the peri-arterial nerve plexus from the affected limb of a patient with causalgia, and pain relief ensued.³ Stemming from this pivotal report of a single case (fig 2), the conceptual leap, whereby the sympathetic nervous system became implicated in the phenomenon of causalgia, resulted in the 100-year search for sympathetically mediated mechanisms, and vast numbers of diverse procedures being performed with the aim of

Figure 2

Leriche's 1916 paper which first postulated the involvement of the sympathetic nervous system in mechanisms subserving causalgia.

**DE LA CAUSALGIE
 ENVISAGÉE COMME UNE NÉVRITE DU SYMPATHIQUE
 ET DE SON TRAITEMENT
 PAR LA DÉNUDATION ET L'EXCISION DES PLEXUS
 NERVEUX PÉRI-ARTÉRIELS
 Par R. LERICHE
 Agrégé à la Faculté de Lyon.**

interrupting the sympathetic outflow in an attempt to alleviate the pain.

Some decades after causalgia had been described, others noted that sometimes a milder syndrome could occur, but in the absence of major nerve injury. Various terms were introduced for this syndrome, including minor causalgia, algodystrophy, and reflex sympathetic dystrophy. Still much used today, this last term was introduced in 1946 by Evans, because he postulated that trauma that generated activity in afferents set up a reflex in the spinal cord which stimulated activity in sympathetic efferents, which in turn resulted in dystrophic changes in the periphery of the limb.⁴ Evans developed the prevailing theory of that time that central changes in the spinal cord could spread and even affect the brain—a remarkably prescient view in the light of current research findings. However, the role of the sympathetic nervous system and the therapeutic benefit of interrupting it remain controversial;^{5–7} increasingly, attention is now being paid to the contribution of neurogenic pseudo-inflammation—returning full circle back to Sudeck.

WRESTLING WITH DEFINITIONS AND CLASSIFICATION

Uncertainties about delineating the major from the minor forms of these disorders, and about the involvement of the sympathetic system, set the scene for nosological chaos. In 1986, the International Association for the Study of Pain (IASP) simultaneously provided two slightly different definitions of causalgia, and sympathetic hyperactivity was included in its definition of reflex sympathetic dystrophy. By 1994, the IASP had abandoned the sympathetic component and had introduced the new term complex regional pain syndrome, yet continued to divide the syndrome into its two familiar subtypes, reflex sympathetic dystrophy and causalgia, but now designated Types I and II respectively (table 2).⁸

The term CRPS, however, generates more questions than answers. Why "complex", when there is nothing more complex about these pains than, for example, phantom pain or anaesthesia dolorosa? And why "regional", when, for example, pain in the hand after a

fracture can spread to affect the whole arm, or more widely? And what about the "pain", which can vary from the trivial to the overwhelming and, occasionally, can even be absent?^{4, 9} And does "syndrome" refer to the variable pain state, or the accompanying features, and if so, to all of them or only some? Just a few years after the term CRPS was invented, it seems doubtful that the diagnostic criteria will stand the test of time. New criteria are under discussion in which Types I and II are no longer distinguished (table 3),¹⁰ and perhaps another new term will be spawned. In the meanwhile, however, use of the traditional terminology is dwindling, and as CRPS is a term now used routinely by pain specialists and increasingly so by neurologists and in the neurological literature, it will be retained here.

WHAT ARE THESE DISORDERS?

These extremely heterogeneous disorders are characterised by pain, along with various accompanying features (table 1).^{9, 11} The pain itself is:

- spontaneous and characteristically burning in quality but can be of almost any type
- of proportion to the inciting cause
- often accompanied by various sensory features (table 4), including allodynia—the term describing the phenomenon in which innocuous sensory stimuli are felt as pain.

Other accompanying neuropathic features include the motor disorders, such as the variable weakness and wasting, as well as the wide range of involuntary movements—although the contribution of psychological factors remains controversial (see below).

Among the remarkably large number of diverse and similarly variable associated phenomena shown in table 1 are those with pseudo-inflammatory, vascular, trophic or musculoskeletal features. Even in the absence of major nerve injury, many of these associated features may yet be caused in part by neurally-mediated mechanisms, blurring the distinction between typical neuropathic and non-neuropathic processes.

CRPS often shows considerable temporal variation. This variation includes short-term, hour-by-hour or diurnal changes, and far

TABLE 2 IASP classification of the complex regional pain syndrome (from Merskey and Bogduk, 1994⁸)

Type I (reflex sympathetic dystrophy)	Type II (causalgia)
<p><i>Definition:</i> A syndrome that develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of oedema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia</p> <p><i>Diagnostic criteria</i> (2–4 must be satisfied):</p> <ol style="list-style-type: none"> 1. The presence of an initiating noxious event, or a cause of immobilisation 2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event 3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain 4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction 	<p><i>Definition:</i> Burning pain, allodynia, and hyperpathia usually in the hand or foot after partial injury of a nerve or one of its major branches</p> <p><i>Diagnostic criteria</i> (all three must be satisfied):</p> <ol style="list-style-type: none"> 1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve 2. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain 3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

TABLE 3 Proposed modified research diagnostic criteria for complex regional pain syndrome (from Harden *et al*, 1999¹⁰)

- (1) Continuing pain disproportionate to any inciting event
- (2) At least one *symptom* in each of the four categories, and
- (3) One *sign* in two or more of the four categories. The four categories are:
 - sensory
 - vasomotor
 - sudomotor/oedema
 - motor/trophic
 and each category has several subcomponents*

*For details of subcomponents, see appendix C in Harden *et al*, 1999.¹¹

TABLE 4 The characteristics of the pain in complex regional pain syndrome

- spontaneous
- typically burning
- unexpectedly severe considering any inciting cause
- mainly distal in the limb but spreads
- does not conform with peripheral nerve or root territory
- worse when limb dependent
- accompanied by various sensory disturbances, eg numbness, hypo- and hyperalgesia, hypo- and hyperpathia, allodynia
- worse with various stimuli
 - touch
 - movement
 - temperature changes

longer changes extending over weeks, months and years. Typically, during the first few weeks the affected limb is warm compared with the opposite limb; during the next few months it can be warmer or cooler; and then after many months or years it tends to be cooler. The temporal changes are highly variable in their degree and timing, and more recent studies have questioned such temporally-determined staging.^{9, 12}

In the light of these very heterogeneous features, it becomes obvious that it is extremely difficult to say what condition(s) are being talked about, and the most honest, albeit facetious, description is of "a 'funny' pain in a 'funny-looking' limb".⁵ Furthermore, no single unifying explanation can account for all the diverse features, and perhaps the least uncertainty is that CRPS comprises a spectrum of disorders, with the most severe

CRPS Type II (causalgia) at one end and the more minor Type I (reflex sympathetic dystrophy) at the other.

CRPS Type II (causalgia)

It is unusual for a neurologist to see a patient with this extremely severe condition, but once seen, the patient is often unforgettable (fig 3). Usually a devastating injury has occurred, which by definition has caused a major nerve injury (although "major" has never been clarified). Often there is also significant vascular damage. While the musket ball injury may not feature much in district general hospital practice, and bullet and knife wounds are rarely seen, the commonest traumatic cause is brachial plexus avulsion, often following a motorcycle accident. The burning pain is often of extreme severity and dominates the patient's life, and Weir Mitchell's remarkable description of the pain and accompanying features has never been bettered.¹

CRPS Type I (reflex sympathetic dystrophy)

Although CRPS Type I is far commoner than Type II, it is nevertheless only infrequently encountered in neurological practice. Some of the accompanying features shown in table 1 are illustrated in figures 4–7. The most common causes are shown in table 5, but in about one quarter of cases no precipitating cause can be found.⁹ Easily the commonest *peripheral* cause, perhaps accounting for about 50% of patients, is some form of limb trauma. Such trauma is usually distal

**Figure 3**

The terrible suffering caused by causalgia. The obviously distressed soldier immobilises the painful right arm struck by a bullet. From Mayfield FH, Devine JW. Causalgia. *Surg Gynecol Obstet* (now *J Am Coll Surg*) 1945;**80**:631–5. (Reproduced with permission of the American College of Surgeons.)

and can be mild or indeed trivial; it can be accidental—causing, for example, an ankle sprain, a crush injury to the hand, or scaphoid fracture; or it can follow surgery—for instance, for Dupuytren's contracture, carpal tunnel decompression or correction of hallux valgus.

Limb trauma is often followed by self-imposed *immobility*, and after surgery the relevant part is usually immobilised in a



Figure 4

The red and sweaty right hand in a patient with CRPS Type I that followed surgery, the scar from which is easily visible above the wrist.

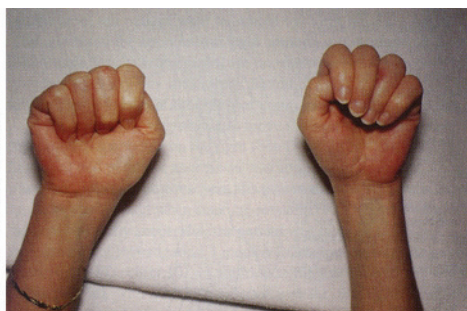


Figure 5

The puffy left hand with an inability to close the fist in a patient with CRPS Type I. From Blumberg H, Hoffmann U, Mohadjer M, *et al.* Clinical phenomenology and mechanisms of reflex sympathetic dystrophy: emphasis on edema. In: Gebhart GF, Hammond DL, Jensen TS, eds. *Progress in pain research and management, volume 2*. Seattle, Washington: IASP Press, 1994:455–81. (Reproduced with permission of the International Association for the Study of Pain.)

bandage or cast for days if not weeks. It is now clear that such immobilisation, although necessary, can also have drastic and even unfortunate consequences. This view is strikingly supported in studies of healthy volunteers undergoing immobilisation alone, in whom prolonged casting causes features very similar to CRPS: muscle atrophy, stiffness, changes in skin colour, and trophic changes affecting the skin, subcutaneous tissues, and nails.¹³ Variable changes in skin temperature, altered sensory thresholds and, after the cast is removed, clumsiness similar to that found in CRPS, have all been found, and pain, while not a typical feature seen after immobility, can occur.¹⁴ Thus immobility itself can induce many features typically associated with CRPS, and sometimes, as with a fracture needing surgery and immobilisation, it is impossible to know which is the specific trigger for the ensuing CRPS—the initial injury, the operation or the immobilisation.

Disorders of the *central* nervous system, and systemic illness and other factors can cause CRPS too. The commonest central cause is stroke, but evaluation can be complicated by variable degrees of weakness and immobility, sensory loss and inattention, other accompanying medical conditions such as diabetes, and musculoskeletal factors such as shoulder subluxation. Doubtless this

heterogeneity, and variation in definition, account for the quoted post-stroke frequency ranging from 1.5 to 61%.¹⁵

All of these ill-defined features of CRPS result in several uncertainties:

- The occurrence of the syndrome is unpredictable, and it is unrelated to the severity of the causative insult. It is also unrelated to age, because individuals of



Figure 6

The shiny skin with loss of wrinkles, curved and elongated nails, and tapered fingers, in a patient with CRPS Type I affecting the left hand.



Figure 7

The swollen, dusky-red foot in a patient with CRPS Type I affecting the right foot.

TABLE 5 Causes of complex regional pain syndrome Type I (reflex sympathetic dystrophy)**Peripheral**

- limb trauma
- electric shock

Mixed peripheral and central

- herpes zoster
- brachial plexus avulsion and other injuries

Central

- stroke
- multiple sclerosis
- spinal cord injury
- cerebral tumour
- brain injury

Drugs

- phenobarbital
- isoniazid

Cardiopulmonary disorders

- post-myocardial infarction
- post-cardiac surgery
- lung disease

Idiopathic and other causes

- occurrence in children (often affecting lower limbs)
- immobility
- transient forms, eg pregnancy
- flitting and recurrent forms

any age, including children and adolescents, can be affected. Presumably, therefore, it is some idiosyncratic response to, or the consequences of, the initiating event (rather than the event itself) that generates the condition.

- It is unclear when pain becomes abnormal. A knee replacement may result in some long-term discomfort on walking and this would be accepted as normal; a knee that after many months remains extremely painful, particularly when there are accompanying features such as swelling, warmth, and extreme sensitivity of the overlying tissues, is obviously abnormal. But the boundary between normal and abnormal is uncertain.
- The incidence of CRPS is very difficult to gauge. Uncertainty about the frequency following stroke has been discussed above. The most recent study suggested an overall incidence of CRPS of over 26 per 100,000 person years, and found the highest incidence occurred after an upper limb fracture in women in later life.¹⁶ However, the frequency of CRPS after

distal radial fractures has ranged from 1–2% when reported retrospectively, to up to 38% when reported prospectively.¹⁷ In the lower limb, knee replacement has been used as a clinical model, and whereas 20 years ago there were no reports of CRPS, it is now a very well recognised problem. In a recent prospective series of 52 patients, at 6 months after surgery 19% of patients met the criteria for CRPS.¹⁷

PREDISPOSING FACTORS?

Two factors may be relevant as to whether an individual develops CRPS: their underlying psychological predisposition, and their genetic make-up.

What is the role of psychological factors?

Evaluating both the background and the prevailing psychological and psychiatric aspects relating to pain in these patients is a subject fraught with difficulties. Further problems arise because of various reported perceptual disturbances, including neglect phenomena and visuospatial distortions, which are receiving increasing attention but remain ill understood. Perhaps not surprisingly, therefore, the role of psychological factors has been the subject of vigorous controversy.

One view is exemplified by Ochoa and Verdugo, who consider most cases of CRPS as "A common clinical avenue for somatoform expression",¹⁸ including the subset of patients exhibiting abnormal movements and postures.¹⁹ A particularly difficult issue concerns those patients who have post-traumatic fixed dystonia and who fulfil the diagnostic criteria for CRPS; in many patients a diagnosis of psychogenic dystonia, a somatisation disorder, or both, can be made, and there appears to be overlap between fixed dystonia and CRPS.²⁰

Whether *antecedent* psychological factors predispose patients to developing CRPS remains unclear. Two prospective but limited studies have addressed this issue. One carried out many years ago, which would be considered inadequate by today's standards, indicated that prediction of outcome was possible by a preoperative psychological assessment;²¹ the other study did not find

prediction possible,²² and at present satisfactory data are not available to foretell which individuals are likely to develop CRPS.²³ My personal impression is that while sufferers may become seriously affected psychologically, and sometimes show features of major depression (as expected in anyone who is in constant pain, and who may have lost their job and had their family and social life shattered), they often seem to have led a psychologically unremarkable life before the condition developed.

Two additional factors are pertinent. First, as trauma is so often the cause, litigation not infrequently lurks in the background. Second, very rare instances of malingering, as revealed by covert video recordings, have also been reported.¹⁹

Genetic factors?

Patients with CRPS have been found more likely than controls to have the HLA tissue types HLA-DQ1, HLA-DR13 and HLA-DR2, and other susceptibility loci for CRPS have also been reported.²⁴ The significance of these observations, and the putative link between any of these loci and the receptor for GABA, remain unclear.

INVESTIGATIONS

These are rarely helpful in diagnosis, but are usually necessary to exclude other disorders ranging from tumours to arthritis, as well as any underlying or associated neurological causes. CRPS is not accompanied by abnormalities on conventional haematological or biochemical tests, and finding a raised ESR or abnormal immunological or bone profile studies means an alternative cause needs to be sought. Occasionally neurophysiological tests are helpful in CRPS Type I in excluding a radiculopathy or peripheral nerve lesion.

Plain radiographs may or may not show osteoporosis (fig 8), which can be focal or quite widespread, but any changes are non-specific. Increased uptake of isotope can occur on bone scanning, but also after sympathectomy, and changes on isotope, CT and MR scans are not diagnostic of CRPS, though such scans may reveal another cause for the symptoms.

Many other techniques have been used for investigating these patients: quantitative

sensory testing and sweat measurement, thermography, sympathetic skin responses, indium-111-immunoglobulin scintigraphy to assess extravasation, skin, nerve, muscle and synovial biopsies, functional MRI, SPECT and MEG studies. Such investigations are of research interest rather than useful in clinical practice.

Thus CRPS remains a clinical diagnosis. It is my experience that many patients who carry this diagnosis, however defined, do not fulfil the necessary prevailing criteria. Some of these patients will prove to have a different, often musculoskeletal cause, but in others the diagnosis remains unclear. CRPS, reflex sympathetic dystrophy and the like are all too often labels of convenience which some patients find reassuring and others find confusing or worrying, and these labels sometimes appear to be a "dustbin" diagnosis hiding uncertainty.

SOME COMMENTS ON POSSIBLE MECHANISMS

At the *periphery*, if there is major nerve damage as in CRPS Type II, the cascade of mechanisms associated with neuropathic pain comes into play. But what happens in CRPS Type I when there is no major nerve injury?

At least in those patients with CRPS following peripheral disease or damage, these insults seemingly result in activation and

Complex regional pain syndrome remains a clinical diagnosis

Figure 8

Radiograph showing extensive osteoporosis with deformity of the right hand in a patient with CRPS Type I. Whenever possible, it is useful to x ray both limbs on the same plate for comparison



TABLE 6 Clinical features for and against involvement of the sympathetic nervous system in complex regional pain syndrome

For	Against
<ul style="list-style-type: none"> • Some of the clinical features (eg, temperature changes, sweating) are or appear to be phenomena subserved by sympathetic nerves • Interrupting the sympathetic supply may alleviate pain in an <i>individual</i> patient • Pain and sensory features relieved by sympathetic block can be rekindled by local noradrenaline • Pain is increased by stress and cold, which increase sympathetic activity • Pain that is apparently sympathetically maintained can be increased when the patient, excluding the thermally isolated limb, is cooled. This central phenomenon is associated with increased activity in cutaneous vasoconstrictor nerves 	<ul style="list-style-type: none"> • Some of the clinical features (eg, warmth, swelling, redness) are mediated by vasoactive substances (substance P, calcium gene related peptide (CGRP), ATP, histamine, 5-HT, neurokinins, etc) released from small-diameter sensory afferents, damaged blood vessels, etc • <i>Group</i> studies have established that interrupting the sympathetic supply is no more effective than placebo • There is no relation between any pain relief achieved and the typical effects following sympathetic blockade, in respect of time of onset, duration or degree • On microneurography, the peripheral sympathetic outflow is physiologically normal. There is reduced local venous noradrenaline and 3,4-dihydroxyphenylethyleneglycol (DHPG), leading to possible denervation hypersensitivity • The syndrome is not a feature of excessive (eg, thyrotoxicosis) or reduced (eg, autonomic failure) sympathetic activity. CRPS has been described in a sympathetically denervated limb

sensitisation of primary nociceptor afferents; furthermore, a variety of neuropeptides and neuromodulators, pro-inflammatory cytokines, and other substances appear to be released peripherally (and centrally) from these afferents,^{9, 11} and perhaps from sympathetic nerve endings, as well as from damaged blood vessels. The resulting neurogenic pseudo-inflammation probably leads to the afferent neuron developing abnormal sensitivity to mechanical and thermal stimuli together with adrenergic supersensitivity, resulting in pain and other sensory features. A number of factors arguing for and against involvement of the sympathetic nervous system are included in table 6, and further details and references have been summarised elsewhere.²⁵ Of particular note is that, contrary to previous thinking, the sympathetic outflow in these disorders is *not* hyperactive.

Bearing some resemblance to the pseudo-inflammatory changes seen in diabetic and

non-diabetic Charcot joints,²⁶ pseudo-inflammation in CRPS may underlie the increased blood flow and vascular permeability, skin warming, hypervascularity of synovia and muscle, immune infiltration of the skin, and osteoporosis¹¹—and hence the trophic features of the syndrome. There may also be an autoimmune component in some instances.²⁷

Concerning vascular factors, a disorder similar to CRPS has been produced experimentally in rats, when reperfusion follows a period of limb ischaemia caused by prolonged tourniquet application.²⁸ The clinical relevance of this finding is that it recalls those patients in whom CRPS is associated with limb immobilisation in a cast, especially if applied too tightly, when the consequences of ischaemia may compound those due to trauma and immobility and which were discussed above.

These heterogeneous peripheral neural, pseudo-inflammatory and vascular components may explain the equally heterogeneous clinical features seen among different patients.

With regard to *central* mechanisms, not only can CRPS result from central nervous system lesions (table 5), but peripherally-triggered CRPS often has features suggesting the central nervous system has become secondarily implicated (see below). Conversely, a central nervous system lesion such as stroke or tumour can produce the peripheral features of CRPS, and so it is not particularly helpful to distinguish rigidly between peripheral and central causes when considering the underlying mechanisms—one can consider there to be functional neural continuity. Yet there are several clinical and experimental aspects which mean that the central nervous system perhaps always becomes involved:

- The distribution of the pain and other features which conforms to neither a peripheral nerve nor root territory, and can show bilateral, mirror, quadrant or hemibody involvement.²⁹
- Detailed neurovascular studies have shown evidence of an abnormal unilateral reflex pattern of sympathetic vasoconstrictor neuronal activity in the affected limb of patients in the early stages of CRPS Type I;³⁰ this pattern, and in other

patients the presence of hyperhydrosis, is in keeping with central mechanisms.

- The PET scan changes which are seen with immobility alone, and which are reminiscent of those seen in acute and central pain. In these conditions, the PET scan changes, among others, include increased blood flow in the cingulate and somatosensory cortices.¹⁴
- The temporally-evolving metabolic changes in the thalamus. A SPECT study has demonstrated a changing pattern, with initial hyperperfusion in the thalamus contralateral to the limb affected by CRPS, and then a gradual change to hypoperfusion over some months, possibly due to adaptive mechanisms (fig 9).³¹
- Changes in the somatotopic map of patients with CRPS. Magneto-encephalographic studies in patients with CRPS affecting the hand have shown that the distance between the projections of the first and fifth fingers in the somatosensory cortex shrinks compared with the normal side, and the cortical projection of the hand also moves towards the lip area. With recovery, the pattern returns to normal (fig 10).³² These phenomena suggest cortical reorganisation but are not specific to CRPS, and similar findings have been found in other pain states.

MANAGEMENT

A note first on prevention. Recalling that immobility is often a major factor in these disorders, it is highly desirable that casting, bandaging, etc are continued for as short a time as possible, and for gradual mobility to be encouraged early (if need be, with the help of physiotherapists and occupational therapists).

The evidence base for the various therapeutic options is nearly always inadequate, and treatment of CRPS is often unsuccessful and invariably unpredictable—not least because of uncertainties concerning the underlying condition and its natural history. Although there continue to be novel approaches, including “off-licence” trials of different drugs, all too often an enthusiastic initial report is followed by silence.

Therapeutic options include:

- drugs
- interruption of the sympathetic supply

- other interventional procedures
- physical forms of treatment
- psychological approaches.

Drugs

Standard drugs used for neuropathic pain are used in CRPS on a trial-and-error basis.³³ Unfortunately, even drugs such as opioids, gabapentin and tricyclic antidepressants have not yet been shown in randomised controlled trials to be effective in CRPS. As a result, drug treatment is based, not unreasonably, on experience gained in the treatment of neuropathic pain in general.

From the practical point of view it seems sensible to use drugs in the customary fashion:

- probably starting with gabapentin (licensed for peripheral neuropathic pain) or pregabalin (the latter is now licensed for central as well as peripheral neuropathic pain, and has an easier dosage regime).
- tricyclic antidepressants including nortriptyline and amitriptyline have been used for far longer, but are associated with more adverse effects, particularly in elderly patients; they are thought to be more beneficial than selective serotonin re-uptake blockers, but are unlicensed for the treatment of pain.

Standard drugs used for neuropathic pain are used in complex regional pain syndrome on a trial-and-error basis

Figure 9

Correlation between contralateral thalamic uptake index (the ratio of contralateral to ipsilateral thalamic perfusion, determined by iodine-123-labelled iodoamphetamine SPECT) and time since onset of CRPS. From Fukumoto *et al*, 1999,³¹ (reproduced with permission from Elsevier).

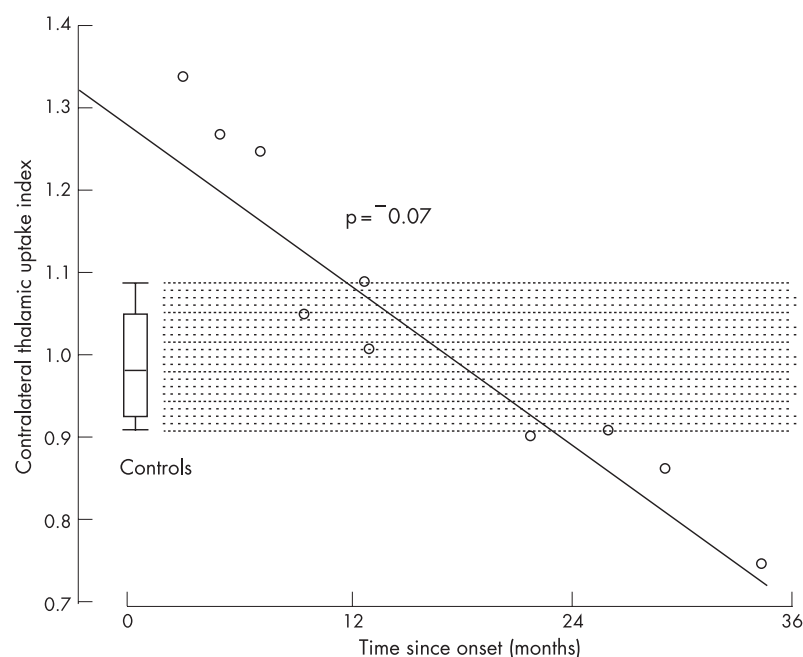
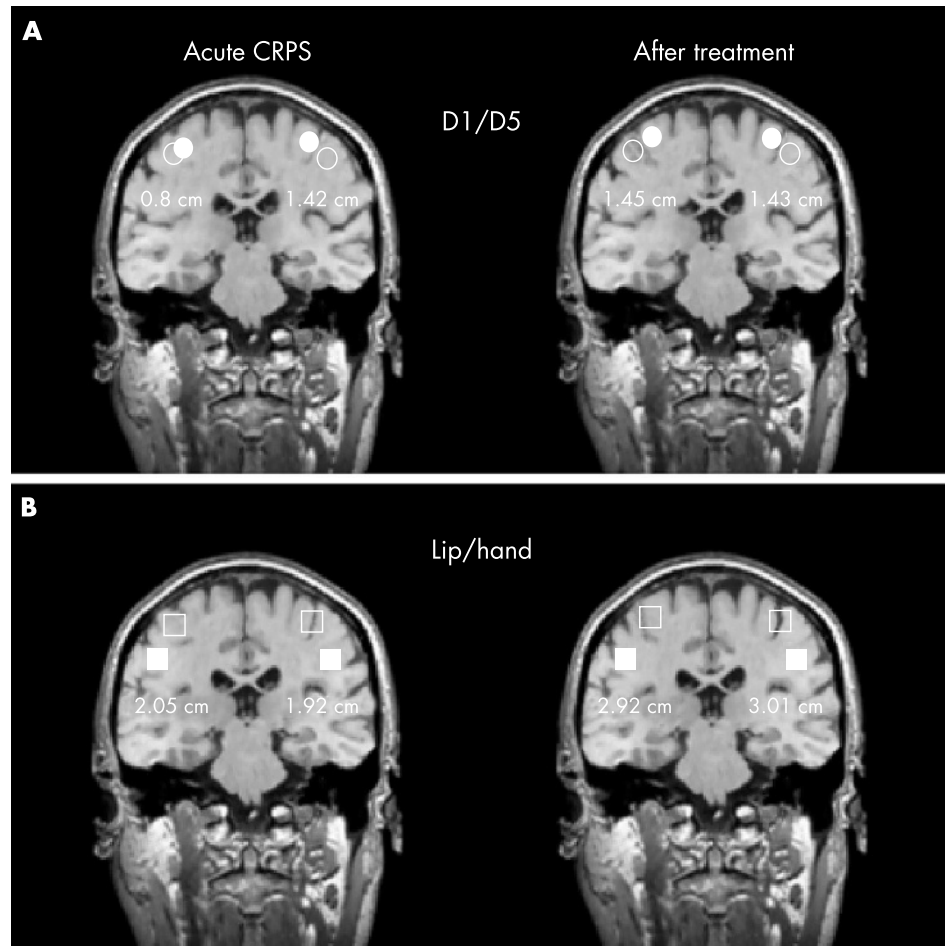


Figure 10

(A) Projection of sensory representations of the first (filled circle) and fifth (open circle) fingers in a patient with CRPS before and after treatment, obtained by magnetic encephalographic imaging. The technique involves recording somatosensory evoked magnetic fields obtained by tactile stimulation of the fingers or lip, mathematically determining the likely intracranial site of the magnetic source induced, and then displaying that site anatomically using MR brain scans. The affected side shows a reduced distance between the first and fifth finger projections, with normalisation back to the inter-finger distance of the control side after treatment. (B) A similar phenomenon relating to the distance between the centre of the hand (open squares) and the lower lip (filled squares) before and after treatment. From Maihöfner *et al*, 2004,³² (reproduced with permission from Lippincott, Williams & Wilkins).



- duloxetine, a serotonin and noradrenaline re-uptake blocker, is also worth a try (and is licensed for diabetic neuropathic pain).
 - the use of opiates for chronic, non-malignant pain is a contentious issue, but the pendulum is swinging to their more ready acceptance; however, it would be best to enlist the help of a pain specialist and the patient's general practitioner before considering long-term opiate prescription.
- A variety of other non-licensed and often experimental drug treatments have been reported, and include:
- Previously calcitonin was advocated, but recently there have been reports of (at least short-term) benefit from a number of bisphosphonates, including pamidronate, clodronate and alendronate.³⁴ To what extent any pain relief is due to effects on bone metabolism, raised pH and decreased sensitivity of peripheral nerves, or modulation of spinal cord transmission is unclear.
 - Corticosteroids were reported to be beneficial in various anecdotal studies several decades ago, and more recent reports have suggested some efficacy compared with control drugs or placebo. For example, patients with CRPS after stroke who received oral prednisolone 40 mg/day for 14 days, followed by 10 mg/week taper, did better than a control group receiving the anti-inflammatory drug piroxicam.¹⁵
 - An anecdotal case report indicated benefit from intravenous immunoglobulin and, as with steroids, this novel but highly experimental approach seems reasonable in view of possible underlying immune mechanisms.²⁷
 - A double-blind, placebo-controlled trial of high dose vitamin C reported efficacy, postulated to be due to the vitamin's antioxidant properties which in turn were thought to be important when impaired

blood flow and venous stasis are present.³⁵

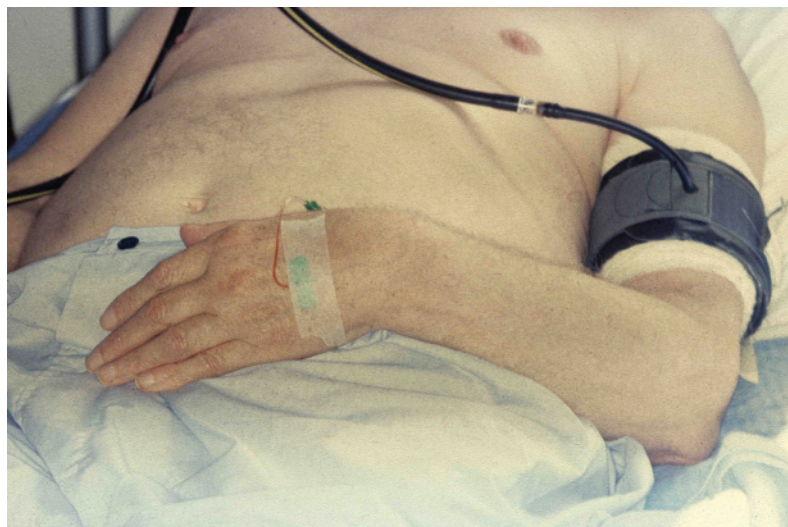
- Some improvement in pain was reported in three of eight patients with dystonia and CRPS treated with intrathecal baclofen.³⁶

Interrupting the sympathetic supply

In the light of the issues discussed above, this therapeutic avenue deserves consideration in its own right. Techniques of interrupting the proximal cervical or lumbar sympathetic outflow have included surgical sympathectomies of various types, sympathetic blocks with local anaesthetics or destructive neurolytic agents, and thermocoagulation. At the periphery, interruption has been achieved using regional intravenous blockade with guanethidine or other agents (fig 11).³⁷ However, there is now ample evidence that interrupting the sympathetic supply is generally futile,⁵⁻⁷ and the procedures carry risks, some potentially life threatening. In mitigation, a case has been well argued for still considering sympatholytic procedures pending further rigorous studies.³⁸ Furthermore, in any *individual* patient the response to such procedures is unpredictable. With so little to offer therapeutically, it seems not unreasonable to consider one or two sympatholytic procedures on an empirical basis. If benefit ensues, a trial including placebo treatment might then be appropriate.

Interventional procedures

"Invasive therapies have long held a place in the treatment of CRPS ... Holding out hope for patients with increasingly invasive and destructive procedures becomes increasingly questionable for choosing among the options."³⁹ This sanguine conclusion emphasises clearly that considerable circumspection is needed when advocating invasive procedures, which—apart from procedures on the sympathetic system—include spinal cord and peripheral nerve stimulation, implanted spinal medication pumps, and deep brain stimulation. For example, a recent report of spinal cord stimulation showed in a randomised controlled, but not blinded, study that 15 of 24 patients in whom stimulation was continued for two years reported "much improvement". However, there was only a



modest fall in the visual analogue pain rating scale, and complications occurred in nine patients.⁴⁰

These procedures are not part of the therapeutic armamentarium of the clinical neurologist, and patients for whom they are being contemplated need to be referred to a pain anaesthetist or neurosurgeon. The neurologist's role, however, may sometimes be to restrain an over-enthusiastic colleague contemplating invasive treatment of doubtful efficacy.

Physical forms of treatment

The roles of the physiotherapist and occupational therapist need no emphasis, and there is evidence that physiotherapy is, indeed, beneficial (although the benefit of occupational therapy is perhaps less compelling).⁴¹ Intuitively, even if not proven, the earlier treatment is begun the better. However, sometimes therapy is difficult, or impossible, if the limb is too painful for contact and movement to be possible. Rarely, extremely cautious mobilisation under anaesthetic—regional or general—is undertaken; such an approach seems reasonable but is unproven.

Psychological approaches

Pain psychologists frequently have a crucial part to play in the management of CRPS, and it is very helpful to involve them early on during what is nearly always multidisciplinary pain management. A recent technique employing psychologically-mediated effects on sensory processes is the use of a mirror

Figure 11

Intravenous regional intravenous blockade. A butterfly needle is inserted into a peripheral vein. The limb is then isolated from the circulation for 20 min using a sphygmomanometer cuff inflated to supra-systolic level. Guanethidine or another sympatholytic drug is then injected through the needle. The procedure is often painful, and the drug is therefore usually combined with local anaesthetic.

PRACTICE POINTS

- Complex regional pain syndrome (CRPS) is an umbrella term introduced by the International Association for the Study of Pain for conditions known previously by different names—in particular causalgia (in which there is major nerve injury), and reflex sympathetic dystrophy (without major nerve injury). Type I is synonymous with reflex sympathetic dystrophy, Type II with causalgia.
- These conditions have in common burning pain. CRPS typically affects a limb, mainly distally, and is variably accompanied by a host of other features which include sensory, thermal, sweating, motor and trophic phenomena.
- CRPS Type I occurs much more frequently than Type II and has many causes, peripheral trauma being by far the commonest. Limb immobility is increasingly recognised to be an important factor.
- Involvement of the sympathetic nervous system is no longer considered an essential component. Pseudo-inflammation in the periphery, and involvement of the central nervous system, are receiving increasing attention.
- The diagnosis remains clinical, and is sometimes inappropriately applied to any odd pain in a limb. Investigations are not useful in clinical practice, although are essential for excluding other causes.
- Treatment remains highly unsatisfactory, and no specific measure has been established as reliably beneficial, although restoration of mobility seems crucial. Various unlicensed drug treatments, interventional procedures, physical forms of treatment and psychological management are the usual approaches, but benefit is always unpredictable. The natural history of CRPS remains poorly understood.
- CRPS may well consist of a variety of different conditions subserved by different mechanisms.

box.⁴² More intriguing than useful, this technique was originally developed for the treatment of phantom pain and employs visual feedback. Rather equivocal results have been obtained in treating pain in CRPS, and the mirror box has yet to show promise in the long term.

PROGNOSIS

The outcome for patients with CRPS is very difficult to predict. Weir Mitchell reported that "Many cases of burning pain last but a few weeks",¹ but he and others were all too aware of patients whose pain continued indefinitely. Some patients with CRPS continue to suffer for years, with weakness, sleep disturbance and disability being prominent, in addition to pain,⁴³ but there are no adequate long-term studies.

CONCLUSIONS

"Complex regional pain syndrome ... remains endlessly fascinating to all persons interested

in pain management. No other chronic pain syndrome is as shrouded in confusion and controversy."³³ The unfortunate sufferer will doubtless agree with the latter statement, but not necessarily the former. There is a long way to go in effectively treating what will surely turn out to be several different conditions.

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