23

PRINCIPLES OF COMPLEX REGIONAL PAIN SYNDROME

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INTRODUCTION

During the American Civil War, Silas Weir Mitchell described a syndrome that occurred in patients who had suffered gunshot injuries to major nerves.[120] Noting that a leading feature was burning pain, he called the condition *causalgia.* At the beginning of the twentieth century, Paul Südeck, a clinician in Hamburg, Germany, used the newly invented technique of roentgenology to investigate patients with severe pain after injury.[145,146] He described a post-traumatic pain syndrome with edema, trophic changes, and osteoporosis. In 1979, the AO group advocated open reduction and rigid internal fixation to prevent fracture disease, which was defined as a combination of circulatory disturbance, inflammation, and pain as a result of dysfunction of joints and muscles.[121] In an intriguing vignette, Channon and Lloyd[32] noted that finger stiffness after Colles fracture could be either simple or associated with swelling and changes in hand temperature. In the latter case, it did not respond well to physiotherapy. The modern term for the syndrome described in different circumstances by these researchers is *complex regional pain syndrome*, usually abbreviated as CRPS.

CRPS consists of abnormal pain, swelling, vasomotor and sudomotor dysfunction, contracture, and osteoporosis. It used to be considered a rare, devastating complication of injury, caused by abnormalities in the sympathetic nervous system (SNS) and seen mainly in psychologically abnormal patients. Modern research is altering this view radically. This review will specifically examine CRPS within the context of orthopaedic trauma surgery. For this reason, the emphasis, descriptions, and concepts differ slightly from those routinely found in publications from the International Association for the Study of Pain (IASP). It is important to appreciate that these apparent differences are merely counterpoints. The theme is identical.

SOME IMPORTANT DEFINITIONS

A cardinal feature of CRPS is abnormalities of pain perception, which are mainly foreign to orthopaedic surgeons. They have been codified by Merskey and Bogduk[119] and because they will be used throughout this text, they are described here.

- *Allodynia* (literally "other pain") is a painful perception of a stimulus that should not usually be painful. Thus, for example, a patient will find gentle stroking of the affected part

painful. Allodynia differs from referred pain, but allodynic pain can occur in areas other than the one stimulated. There are several forms of allodynia:

- *Mechanical* (or *tactile*) *allodynia* implies pain in response to touch. It may be further subdivided into *static mechanical allodynia*, implying pain in response to light touch or pressure, and *dynamic mechanical allodynia*, where the pain occurs as a result of brushing.[107]
- In *thermal (hot or cold) allodynia*, the pain is caused by mild changes in skin temperature in the affected area.

- *Hyperalgesia* is an increased sensitivity to pain, which may be caused by damage to nociceptors or peripheral nerves. Thus, the patient finds gentle touching with a pin unbearably painful. Hyperalgesia is usually experienced in focal, discrete areas, typically associated with injury. Focal hyperalgesia may be divided into two subtypes:
  - *Primary hyperalgesia* describes pain sensitivity that occurs directly in the damaged tissues.
  - *Secondary hyperalgesia* describes pain sensitivity that occurs in surrounding undamaged tissues.

Rarely, hyperalgesia is seen in a more diffuse, bodywide form.

- *Hyperpathia* is a temporal and spatial summation of an allodynic or hyperalgesic response. Thus, the patient finds gentle touching painful, but repetitive touching either on the same spot or on another part of the affected limb becomes increasingly unbearable and the pain continues for a period (up to 30 minutes) after the stimulus has been withdrawn. In severe cases, the pain may be accentuated by unusual and extraneous things such as the sudden noise of a door shutting or a draft of cold air.

It is important for the orthopaedic surgeon to realize that these patients are not malingering or mad. These are absolutely real perceptions of pain.

A HISTORIC VIEW OF TAXONOMY

A historic review of nomenclature will help to elucidate much confusion that surrounds this condition. In the past, CRPS was diagnosed using a variety of nonstandardized and idiosyncratic diagnostic systems derived solely from the authors' clinical experiences, none of which achieved wide acceptance. The condition was given a number of synonyms (Table 23-1) reflecting site affected, cause and clinical features. During the American Civil War, Mitchell et al.[120] noted the burning nature of pain following nerve trauma and described this as *causalgia* (from the Greek "burning pain"). In contrast, in the 1900s, Südeck[145,146] investigated conditions characterized by severe osteoporosis, including some cases of CRPS. The condition was named *Südeck's atrophy* by Nonne in 1901.[123] Leriche[99,100] demonstrated that sympathectomy could alter the clinical features associated with *post-traumatic osteoporosis,* and De Takats[38] first suggested *reflex dystrophy* in 1937. Evans[46] introduced the term *reflex sympathetic dystrophy*, based on the theory (following Leriche's observations) that sympathetic hyperactivity was involved in the pathophysiology, and this term was popularized by Bonica.[18] In 1940, Homans[85] proposed *minor causalgia* to imply a relationship between Mitchell et al.'s causalgia, renamed *major causalgia,* and similar conditions arising without direct nerve injury. AQ2

TABLE 23-1 Synonyms for Complex Regional Pain Syndrome

- Complex regional pain syndrome
- Reflex sympathetic dystrophy
- Südeck's atrophy
- Causalgia
- Minor causalgia
- Mimo-causalgia
- Algodystrophy
- Algoneurodystrophy
- Post-traumatic pain syndrome
- Painful post-traumatic dystrophy
- Painful post-traumatic osteoporosis
- Transient migratory osteoporosis

Causalgic state[37] and *mimo causalgia*[126] followed to add to the confusion. Today the term *causalgia* is reserved for Mitchell et al.'s original use, in which a major nerve injury produces burning pain.[141]

Steinbrocker[143] introduced the term *shoulder hand syndrome* for a condition that may be separate from true CRPS, and *algoneurodystrophy* was suggested by Glik and Helal.[69,70] *Algodystrophy*, from the Greek meaning "painful disuse," was introduced by French rheumatologists in the late 1970s.[44] AQ3

Sympathetically maintained pain consists of pain, hyperpathia, and allodynia, which are relieved by selective sympathetic blockade. The relationship between CRPS and sympathetically maintained pain is disputed.[141] In CRPS a proportion of the pain is usually sympathetically maintained and is therefore relieved by sympathetic blockade. However, in CRPS a process is also taking place that leads to initial tissue edema followed by severe contracture. This is not an inevitable part of sympathetically maintained pain.[91] Sympathetically maintained pain is not a particularly helpful concept for the orthopaedic surgeon; however, it will be explored further when the etiology of CRPS is considered.

MODERN TAXONOMY AND DIAGNOSIS

Fortunately, all the above confusion is now of historic interest. The International Association for the Study of Pain (IASP) has undertaken a major work in analyzing the features of CRPS and reclassifying the condition.[119] A brief history of this work will help to understand the current position. The name of the condition was changed to complex regional pain syndrome (CRPS) at a consensus workshop in Orlando, Florida, in 1994, [16,141] and a new set of standardized diagnostic criteria was laid down[119] (Table 23-2). To complement the diagnostic criteria, a broad description of CRPS was offered later[22,80]:

> CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional

TABLE 23-2 The Original International Association for the Study of Pain Diagnostic Criteria for Complex Regional Pain Syndrome (CRPS)

1. The presence of an initiating noxious event, or a cause of immobilization (not required for diagnosis; 5–10% of patients will not have this)
2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom)
4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction.

If the condition occurs in the absence of "major nerve damage," the diagnosis is CRPS type 1.

If "major nerve damage" is present, the diagnosis is CRPS type 2.

Adapted from Merskey and Bogduk.[119]

(not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings, including osteoporosis. The syndrome shows variable progression over time.

CRPS was arbitrarily divided into CRPS2 type 2, where the cause was believed to be damage to a major nerve, and CRPS type 1, where it was not.

Clinical Features

Because the etiology of CRPS is obscure, the diagnosis must be clinical and therefore precise descriptions of symptoms and signs acquire great importance. Classic descriptions of the condition describe three stages occurring sequentially.[17,38,44,68,137,138] Modern evidence, however, suggests that CRPS does not invariably pass through these stages[13,157,173,174] and supports the clinical impression that this evolution is seen in more severe cases (as might be expected from historic series). Nevertheless, the classic descriptions provide the greatest information concerning the clinical features, and the description that follows draws on these and will therefore refer to the staging system where it is helpful to the description.

Regardless of whether a particular patient will pass through the three classic stages, it is essential to grasp the concept that CRPS is a biphasic condition with early swelling and vasomotor instability giving way over a variable timescale to late contracture and joint stiffness.[44] The hand and foot are most frequently involved, although involvement of the knee is increasingly recognized.[35,36,93] The elbow is rarely affected, whereas shoulder disease is common and some cases of frozen shoulder are probably CRPS.[143] The hip is affected in transient osteoporosis of pregnancy.

CRPS usually begins up to a month after the precipitating trauma, although the delay may be greater. Antecedent trauma is not essential but within an orthopaedic context it is almost invariable.[44] As the direct effects of injury subside, a new diffuse, unpleasant, neuropathic pain arises.[168] Neuropathic pain is pain that occurs without any precipitating noxious stimulus, and spontaneous or burning pain, hyperalgesia, allodynia, and hyperpathia are common but not universal features.[119] Pain is unremitting (although sleep is often unaffected), worsening and radiating with time. The pain may be increased by dependency of the limb, physical contact, emotional upset, or even by extraneous factors such as a sudden loud noise or a blast of cold air.

Early Phase of Complex Regional Pain Syndrome

Vasomotor instability (VMI) and edema dominate the early phase (Fig. 23-1), although this is less marked with more proximal CRPS. The classic description of the temporal evolution of the condition divides the early phase of CRPS into two stages depending on the type of the vasomotor instability.[44] In this description, initially the limb is dry, hot, and pink (vasodilated, Stage 1) but after a variable period of days to weeks, it becomes blue, cold, and sweaty (vasoconstricted, Stage 2). As noted, this classic evolution is rarely seen. Most commonly, especially in more mild cases, the vasomotor instability is an increase in temperature sensitivity, with variable abnormality of sweating. Alternatively, some patients remain substantially vasodilated,

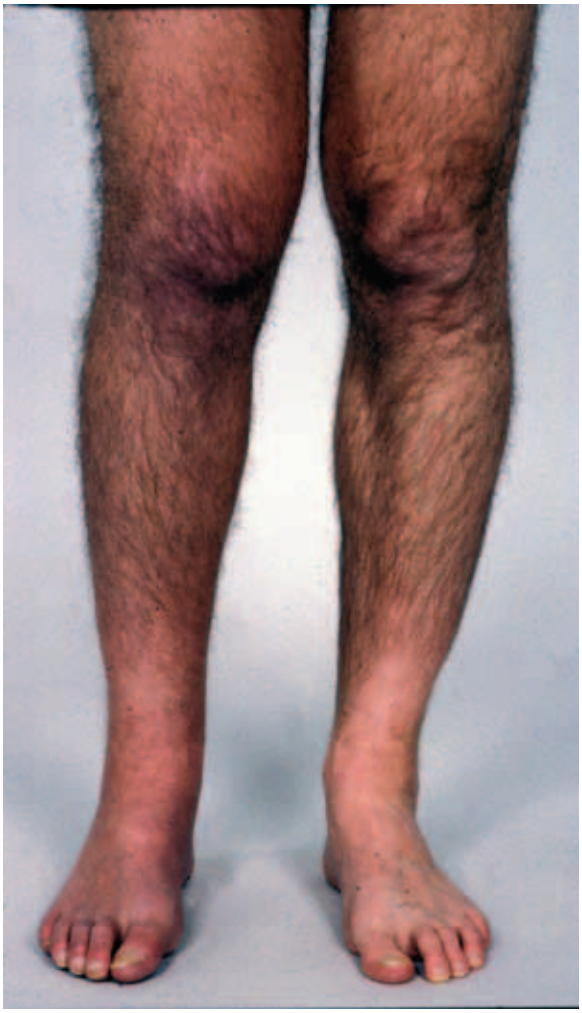


FIGURE 23-1 A patient with early complex regional pain syndrome type 1 affecting the leg. Note the swelling of the leg and the discoloration of the shin.

while others are vasoconstricted with no history of vasodilatation.[13,21,157,175]

In the early phase of CRPS, edema is marked, particularly where the distal part of the limb is affected. Initially, the edema is simple tissue swelling and may be overcome by physical therapy and elevation, if the patient will permit. With time, however (in the classic description, passing from stage 1 to stage 2), the edema becomes more fixed and indurated with coalescence of tissue planes and structures.

Initially, in the early phase of CRPS, loss of joint mobility is caused by swelling and pain combined with an apparent inability to initiate movement or state of neglect or denial with respect to the limb.[27–29,61,62] Weakness, dystonia, spasms, tremor, and myoclonus have also been reported[15,56,106,137]; however, these are not usually prominent within an orthopaedic context. As the early phase progresses, loss of joint mobility will increasingly be the result of the development of contracture. Only if the disease can be halted in the early phase before fixed contracture has occurred can complete resolution occur.

Late Phase of Complex Regional Pain Syndrome

Passing into the late phase, VMI recedes, edema resolves, and atrophy of the limb occurs (Fig. 23-2), which affects every tissue. The skin is thinned and joint creases and subcutaneous fat disappear. Hairs become fragile, uneven, and curled, while nails are pitted, ridged, brittle, and discolored brown. Palmar and plantar fascias thicken and contract simulating Dupuytren's disease.[106] Tendon sheaths become constricted, causing triggering and increased resistance to movement. Muscle contracture combined with tendon adherence leads to reduced tendon excursion. Joint capsules and collateral ligaments become shortened, thickened, and adherent, causing joint contracture.

It is important to restate that the progression of CRPS is very variable. Within orthopaedic practice, the large majority of patients who demonstrate the features of the early phase of CRPS after trauma will not go on to develop severe late phase contracture, although a significant proportion will show chronic subclinical contracture.[106]

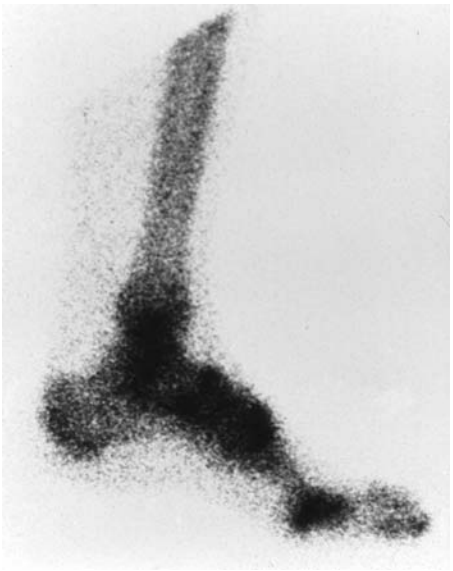
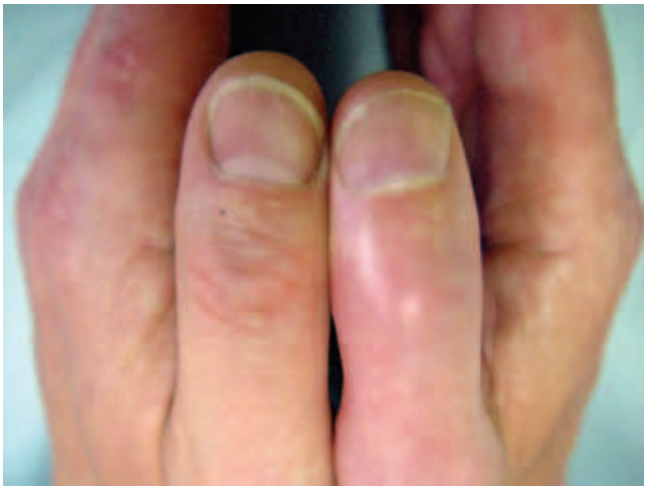


FIGURE 23-3 Bone scan changes in complex regional pain syndrome (CRPS). The delayed phase of a bone scan of a patient with early CRPS type 1 of the lower leg. There is increased uptake throughout the affected region. The bone scan will usually revert to normal after 6 months.

Bone Changes

Bone involvement is universal with increased uptake on bone scanning in early CRPS (Fig. 23-3). This was originally thought to be peri-articular, suggesting arthralgia[84,97,110]; however, CRPS does not cause arthritis and more recent studies have shown generalized hyperfixation,[5,34,40] confirming the view of Doury et al.[21] Increased uptake is not invariable in children.[167] Later, the bone scan returns to normal and there are radiographic features of rapid bone loss: visible demineralization with



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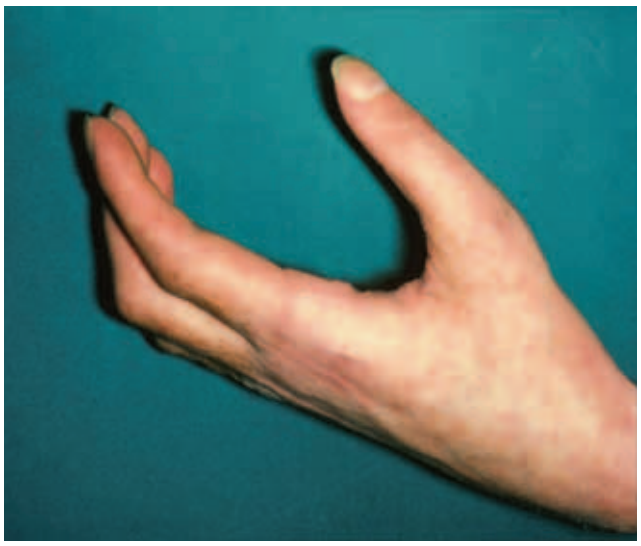
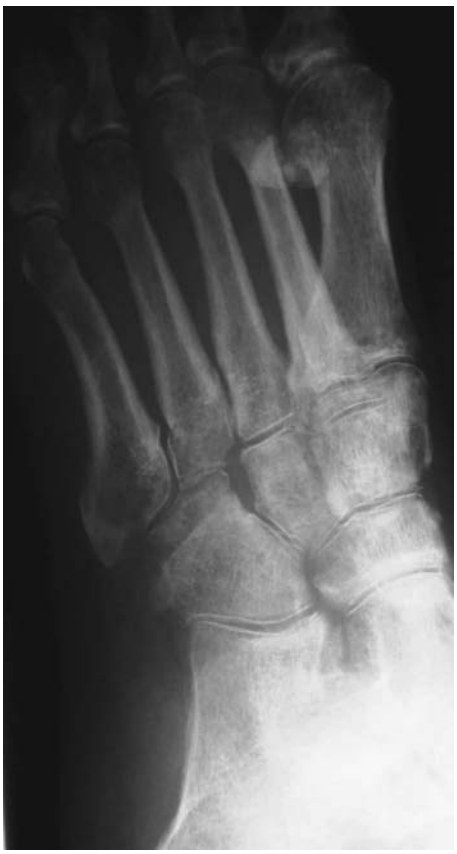


B

FIGURE 23-2 The late phase of complex regional pain syndrome (CRPS). (**A**) Detail of the thumbs of a patient with late CRPS type 1 of the right hand. There is spindling of the digit particularly distally. The nail is excessively ridged and is discolored. (**B**) The hand of a patient with late CRPS type 1. The patient is trying to make a fist. Note the digital spindling and extension contractures with loss of joint creases



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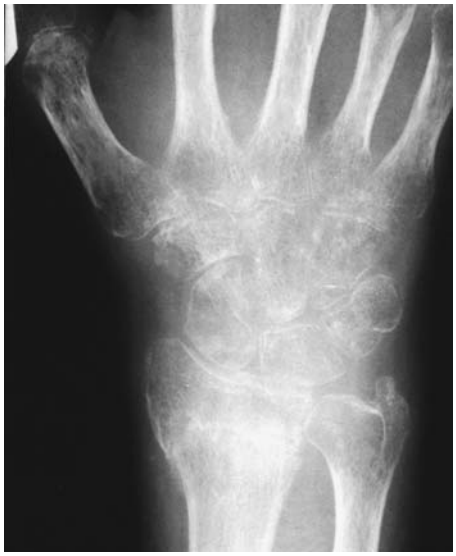

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FIGURE 23-4 Radiographic features of complex regional pain syndrome (CRPS). (**A**) Oblique radiograph of a patient with CRPS type 1 of the foot. There is patchy osteoporosis with accentuation of the osteoporosis beneath the joints. (**B**) Profound osteoporosis in a patient with late severe CRPS type 1 affecting the hand.

patchy, subchondral or subperiosteal osteoporosis, metaphyseal banding, and profound bone loss[98] (Fig. 23-4). Despite the osteoporosis, fracture is uncommon, presumably because the patients protect the painful limb very effectively.

Incidence

It is the common experience of orthopaedic surgeons that patients, as shown in Figure 23-2, are extremely rare. Thus, severe, chronic CRPS associated with severe contracture is uncommon with a reported prevalence of less than 2% in retrospective series.[8,75,102,108,129] In contrast, prospective studies designed to look specifically for the early features of CRPS show that they occur after 30% to 40% of every fracture and surgical trauma (e.g., total knee replacement),[2,3,7,13,14,51,81,135,139] where the features of CRPS have been actively sought. Furthermore, statistically, the features tend to occur together.[3] These common early cases of CRPS are usually not specifically diagnosed.[139] They resolve substantially either spontaneously or with standard treatment by physical therapy and analgesia within 1 year.[13,14,105,139] Some features, particularly stiffness, may remain suggesting that CRPS may be responsible for significant long-term morbidity even when mild.[5,18] The truly intriguing question is, if CRPS is so common, why is it not a universal finding after trauma or orthopaedic surgery?

Etiology

CRPS may occur after any particular trauma while an identical stimulus in a different limb does not cause it. The incidence is not changed by treatment method and open anatomic reduction and rigid internal fixation does not abolish it.[135] It is unclear whether injury severity or quality of fracture reduction alters the incidence.[3,14] There is, however, an association with excessively tight casts[55] and there may be a genetic predilection.[41,94,96,111,112] The following etiologies have been proposed:

PSYCHOLOGICAL ABNORMALITIES

A psychological cause for chronic pain was first suggested by Freud,[19] and historically, it has been suggested that CRPS may be purely a psychological problem.[33] Most orthopaedic clinicians immediately recognize a "Sudecky" patient—that is, broadly speaking, a patient who appears to the clinician to be somebody who is likely to fare poorly after surgical intervention or trauma, perhaps because of to their inability to cooperate fully with physical therapy. In fact, the literature fails to identify this sort of patient and the evidence does not support the notion that CRPS is primarily psychological.[25] Studies of premorbid personality show no consistent abnormality.[122,172] Most patients are psychologically normal,[158] although emotional lability, low pain threshold,[39] hysteria,[127] and depression[144] have been reported. There is an association with antecedent psychological stress,[20,25,63–65,156] which probably exacerbates pain in CRPS, as in other diseases.[23] It seems likely that the severe chronic pain of CRPS causes depression and that a "Sudecky" type of patient who develops CRPS is at risk of a poor outcome because they will not mobilize in the face of pain.

Abnormal (Neuropathic) Pain

CRPS is characterized by excessive and abnormal pain. Pain is usually caused when an intense noxious stimulus activates high-

threshold nociceptors, thus preventing tissue damage. Neuropathic pain in CRPS occurs without appropriate stimulus and has no protective function. However, injured peripheral nerve fibers undergo cellular changes, which cause usually innocuous tactile inputs to stimulate the dorsal horn cells via A-β fibers from low-threshold mechanoreceptors, causing allodynia in CRPS 2.[92,167] Similar C-nociceptor dysfunction explains causalgia. Furthermore, axonal injury prevents nerve growth factor transport, which is essential for normal nerve function.[104,168] In CRPS 1, covert nerve lesions with artificial synapses have been postulated.[43] These "ephases" have not been demonstrated and are unnecessary since inflammatory mediators released by the initial trauma (and possibly retained due to a failure of free radical clearance), can sensitize nociceptors to respond to normally innocuous stimuli.[168]

Sympathetic Nervous System Abnormalities

That CRPS is associated with apparent abnormalities in the SNS is obvious—hence, the popularity of the eponym *reflex sympathetic dystrophy*. Furthermore, since Leriche's early studies,[99,100] generations of therapists have treated CRPS with sympathetic manipulation, noting an acute change in the clinical features,[31,70,76–78,86] although recent studies cast some doubt on whether sympathetic manipulation improves the long-term outcome of the condition.[87,105]

The features of CRPS that suggest SNS dysfunction include abnormalities in skin blood flow, temperature regulation and sweating, and edema. However, SNS activity is not usually painful.[88,89] In CRPS, however, some pain (termed *sympathetically maintained pain* [SMP][141]) is SNS dependent. This accounts for spontaneous pain and allodynia, which may therefore be relieved by stellate ganglion blockade[130] and then restored by noradrenalin injection.[1,148] Furthermore, there is an abnormal difference in cutaneous sensory threshold between the limbs, which is reversed by sympathetic blockade,[54,57,131,132] while increasing sympathetic activity worsens pain.[90]

What, then, is the cause of SMP in CRPS? It is due to the body's reaction to injury. After partial nerve division, injured and uninjured somatic axons express α-adrenergic receptors[30] and sympathetic axons come to surround sensory neuron cell bodies in dorsal root ganglia.[117,161,168] These changes, which may be temporary,[148,159,160] make the somatic sensory nervous system sensitive to circulating catecholamines and norepinephrine released from postganglionic sympathetic terminals.

Abnormal Inflammation

Superficially, CRPS resembles an inflammatory state leading to gross scarring. For this reason, the major differential diagnoses within an orthopaedic context are occult causes of inflammation such as soft tissue infection or stress fracture. Indeed, CRPS is associated with inflammatory changes including macromolecule extravasation[125] and reduced oxygen consumption.[71,149] In animals, infusion of free radical donors causes a CRPS-like state,[150] and amputated human specimens with CRPS show basement membrane thickening consistent with overexposure to free radicals.[151] These considerations suggest that CRPS is an exaggerated local inflammatory response to injury.[72,73] In other words, on this hypothesis, CRPS represents a local form of the systemic free radical disease that causes adult respiratory distress syndrome and multiple organ failure after severe trauma. This concept is supported by evidence that the free radical scavenger vitamin C is effective prophylaxis against post-traumatic CRPS.[170,171]

An alternative explanation for the apparent inflammatory changes in early CRPS is a primary capillary imbalance causing stasis, extravasation, and consequent local tissue anoxia.[48,49,114,134]

Failure to Use the Affected Limb

The popular French term for CRPS, *algodystrophy,* means "painful disuse."[44] It is a common clinical observation that patients who appear to be at risk of developing CRPS are unable or unwilling to cooperate with physical therapy to mobilize their limb after trauma or orthopaedic surgery. Indeed, undue immobilization has traditionally been believed to be at least an important contributory factor in the generation of CRPS or even the sole cause.[9,47,121,163]

CRPS obviously involves a significant abnormality of afferent sensory perception but only recently has the possibility of abnormal efferent motor function been systematically explored. Classically, it was believed that the "immobile RSD limb" was guarded by the patient to prevent inadvertent painful movement or sensory contact.[44,60] In fact, CRPS is associated with an abnormality of motor function that is often overlooked partially because of patient embarrassment and partly because in the past it has been labeled as "hysterical."[33,152] In 1990, Schwartzman and Kerrigan[137] reported a subgroup of CRPS patients with a variety of motor disorders and a minority of patients with CRPS demonstrate obvious dystonia or spasms.[10,45,110,113] A prospective study of 829 CRPS patients showed that abnormalities of motor function were reported by 95%, varying from weakness to incoordination and tremor.[30] Objective testing in small numbers of patients shows that CRPS patients have impaired grip force coordination, target reaching, and grasping.[136,164]

Interviews with patients suggest further possible reasons for the lack of movement in CRPS. Patients demonstrate evidence of "neglect" of the affected limb, similar to that seen after parietal lobe stroke. When asked about moving the limb, statements are made such as "my limb feels disconnected from my body" and "I need to focus all my mental attention and look at the limb in order for it to move the way I want. . . ."[59] Another study revealed bizarre perceptions about a body part including a desperate desire for amputation. There was a mismatch between limb sensation and appearance with mental erasure of the affected part. These authors suggested the term "body perception disturbance" rather than "neglect" to describe this phenomenon.[101] There appears to be a central sensory confusion, in that when a non-noxious stimulus is provided that the patient finds painful due to allodynia, the patient is unable to determine whether it is truly painful, and by impairing integration between sensory input and motor output, movement is impaired.[83,115]

Overall, in CRPS, patients tend to ignore their affected limb and find it difficult to initiate or accurately direct movement and there is a mismatch between sensation, perception, and movement.[29,60,152] Failure to use the limb appears to relate to this rather than the traditional view of learned pain avoidance behavior in response to allodynia. Whatever the exact cause, failure of mobilization may be central to the etiology of CRPS because all the features of phase 1 CRPS, except pain, are produced in volunteers after a period of cast immobilization.[27–29] This may be explained by the fact that activity-dependent gene function is common in the nervous system.[168] and normal tactile and proprioceptive input are necessary for correct central nerve signal processing.[103]

A study of the treatment with mirror visual feedback (MVF) supports the central role of movement disorder in CRPS.[116] The rationale for MVF is restoration of the congruence between sensory and motor information, and it was originally used for the treatment of phantom limb pain.[133] The patients are instructed to exercise both the unaffected and the affected limb. However, a mirror is placed so that they cannot see the affected limb, and when they think they are looking at it, they are actually observing the mirror image of their normal limb. As might be expected, MVF resulted in improvement in range of movement; however, in addition in early CRPS, MVF also abolished or substantially improved pain and vasomotor instability.[150]

MAKING A DIAGNOSIS

Considerable confusion has been generated by a failure to understand the recent work from the IASP. In 1994, when the IASP produced the new diagnostic entity of CRPS, it was descriptive, and general and based on a consensus.[119] Deliberately, it did not imply any etiology or pathology (including any direct role for the SNS). The intention was to provide an officially endorsed set of standardized diagnostic criteria to improve clinical communication and facilitate research.[118] In other words, this was intended as a starting point from which individual researchers could move forward. It was not thought of as a mature clinical diagnostic device.

Since their original publication, the diagnostic criteria have been validated, refined, and developed. The validation studies suggest that the original criteria are adequately sensitive *within the context of a pain clinic* (i.e., they rarely miss a case of actual CRPS); however, the criteria cause problems of overdiagnosis because of poor specificity.[58,80] Comparison of CRPS patients to other proved pain states, such as chronic diabetic patients with ascending symmetric pain, whose neuropathy is confirmed by nerve conduction studies, also show that the criteria are very sensitive but have low specificity, so that a diagnosis of CRPS may be erroneous in up to 60% of cases.[22]

Other problems are evident. For example, the criteria assume that any sign or symptom of vasomotor, sudomotor, and edema-related change is sufficient to justify the diagnosis and there is no possibility of providing greater diagnostic or prognostic accuracy by observing more than one of these features. An additional weakness is the failure to include motor or trophic signs and symptoms. Numerous studies have described various signs of motor dysfunction (e.g., dystonia, tremor) as important characteristics of this disorder, and trophic changes have frequently been mentioned in historical clinical descriptions.[26,28] These differentiate CRPS from other pain syndromes.[58,138] Finally, the wording of the criteria permits diagnosis based solely on patient-reported historical symptoms. This may be inappropriate in the context of litigation.

Factor analysis of 123 CRPS patients has indicated that the features cluster into four statistically distinct subgroups.[80]

1. A set of signs and symptoms indicating abnormalities in pain processing (e.g., allodynia, hyperalgesia, hyperpathia)
2. Skin color and temperature changes, indicating vasomotor dysfunction
3. Edema and abnormalities of sweating
4. Motor and trophic signs and symptoms

The statistical separation of edema and sudomotor dysfunction from vasomotor instability and the finding of motor and trophic abnormalities are at variance with the original IASP criteria, which were therefore modified[22,58,80] (Table 23-3). The important changes are inclusion of clinical signs, their separation from symptoms, and the inclusion of features of motor abnormalities and trophic changes. Intriguingly, these subgroups are virtually identical to those suggested by our group a decade earlier.[3]

Statistical analysis has been undertaken to investigate sensitivity and specificity of decision rules for diagnosis of CRPS compared to neuropathic pain of a proved non-CRPS cause using these criteria[22] (Table 23-4). These propose different diagnostic criteria depending on the clinical circumstances. Thus, for purely clinical diagnosis, the criteria provide a sensitivity of 0.85 and a specificity of 0.69, whereas for research diagnosis, the criteria provide a sensitivity of 0.70 and specificity of 0.94, because, in the former circumstance, one wishes to avoid failing to offer treatment to a possible candidate while in the latter situation one is more concerned to be investigating a homogeneous group in whom the diagnosis cannot be in doubt.

It is critical to understand that the Bruehl modification of the original IASP criteria[24] given in Table 23-3 apply to the diagnosis of CRPS *within a pain clinic setting* and are therefore intended to differentiate CRPS from other causes of chronic pain within that setting. They do not apply directly to the diagnosis of CRPS within the context of an orthopaedic practice. The reason for this apparent conundrum is that the precise nature of CRPS remains unclear and it is therefore a diagnosis of exclusion. Conditions from which CRPS must be distinguished in a pain clinic (e.g., neuropathic pain in association with diabetic neuropathy) are different from those which apply in an orthopaedic or fracture clinic (e.g., soft tissue infection or stress fracture). Therefore, the diagnostic criteria must be slightly different, just as slightly different criteria are required within a pain clinic for diagnosis of CRPS depending on whether the diagnosis is being made for clinical or research purposes.

Atkins et al.[2–4] proposed a set of diagnostic criteria for CRPS specifically in an orthopaedic context(Table 23-5). These were derived empirically from a less-formal but similar process to the IASP consensus approach. The criteria were designed as far as possible to be objective, but the patient's veracity was assumed, so no attempt was made to separate reports of vasomotor or sudomotor abnormalities from observation of them. A number of the criteria are quantifiable,[2,3,51] which allows their powerful use to investigate treatment.[53,54,105] The original criteria were developed in the context of CRPS of the hand following Colles' fracture of the wrist, but they have subsequently been generalized for use in the diagnosis of CRPS in other orthopaedic scenarios and in the lower limb.[13,135] Diagnosis by these criteria, when used after Colles' fracture, maps virtually exactly with the Bruehl criteria, suggesting their reliability.[147]

Clinical Diagnosis in an Orthopaedic Setting

1. **Pain**
   A history of excessive pain is elicited. Abnormalities of pain perception are examined in comparison with the opposite normal side. Excessive tenderness is found by squeezing digits in the affected part between thumb and fingers. This may be quantitated using dolorimetry but this is usually a research tool.[4,6] Allodynia is demonstrated by fine touch and hyperalgesia using a pin. Hyperpathia is examined by serial fine touch or pin prick.

TABLE 23-3 Modified International Association for the Study of Pain Diagnostic Criteria for Complex Regional Pain Syndrome (CRPS)

General definition of the syndrome

CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the *clinical* diagnosis, the following criteria must be met (sensitivity of 0.85 specificity of 0.69)

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
   - **Sensory**
     Reports of hyperesthesia and/or allodynia
   - **Vasomotor**
     Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - **Sudomotor/edema**
     Reports of edema and/or sweating changes and/or sweating asymmetry
   - **Motor/trophic**
     Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign **at time of evaluation** in *two or more* of the following categories
   - **Sensory**
     Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   - **Vasomotor**
     Evidence of temperature asymmetry (>1° C) and/or skin color changes and/or asymmetry
   - **Sudomotor/edema**
     Evidence of oedema and/or sweating changes and/or sweating asymmetry
   - **Motor/trophic**
     Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms.

For *research* purposes, diagnostic decision rule should be at least one symptom ***in all four*** symptom categories and at least one sign (observed at evaluation) in two or more sign categories (sensitivity of 0.70, specificity of 0.94).

From Bruehl et al.[22] and Harden et al.[80]

2a. Vasomotor instability

Vasomotor is often transitory and so it may not be present at the time of examination. If the patient is reliable, then a history confirms its presence. Visual inspection is the usual means of diagnosis.

Thermography can be used to quantitate temperature difference between the limbs. This is greater in CRPS than other pain syndromes,[128,162] and this can be used to distinguish CRPS from other causes of neuropathic pain. However, thermography has not been validated within an orthopaedic context and must therefore be used with caution. It is not usually used in an orthopaedic context.

2b. Abnormal sweating

Whether this feature should be considered with vasomotor instability as proposed by Atkins et al.[3,6] or should be with edema as suggested recently by Harden et al.[80] is not yet clear. As for vasomotor instability, the feature is inconstant and it may be necessary to rely on history. Excessive sweating is usually clinically obvious. In a doubtful case, the resistance to a biro or pencil gently stroked across the limb is useful. The extent of sweating can be quantified by iontophoresis but this is rarely undertaken.

3. Edema and swelling

This is usually obvious on inspection. In the hand, it may be quantified by hand volume measurement. Similarly, skinfold thickness and digital circumference may be measured.[3,6]

4. Loss of joint mobility and atrophy

Loss of joint mobility is usually diagnosed by standard clinical examination. The range of finger joint movement may be accurately quantified.[3,6,51] As outlined here, atrophy will affect every tissue within the limb.

5. Bone changes

Radiographic appearances and bone scans are discussed earlier. CRPS does not cause arthritis and joint space is preserved. Sudeck's technique of assessing bone density by radiographing two extremities on one plate[120,145] remains

TABLE 23-4 Diagnostic Sensitivity and Specificity for the International Association for the Study of Pain Modified Criteria (see Table 23-3) in Distinguishing Patients With &Complex Regional Pain Syndrome (CRPS) From Patients With Neuropathic Pain From a Documented Non-CRPS Cause

Decision rule	Sensitivity	Specificity
2+ sign categories and 2+ symptom categories	0.94	0.36
2+ sign categories and 3+ symptom categories	0.85	0.69
2+ sign categories and 4 symptom categories	0.70	0.94
3+ sign categories and 2+ symptom categories	0.76	0.81
3+ sign categories and 3+ symptom categories	0.70	0.83
3+ sign categories and 4 symptom categories	0.86	0.75

From Bruehl et al.[22]

useful but densitometry is not usually helpful.[156] A normal bone scan without radiographic osteoporosis virtually excludes adult CRPS.

Other Clinical Examinations

Making a diagnosis of "neglect"-like phenomena is relatively easy clinically but may not as yet be useful. Sensory neglect can be elucidated either by history or direct sensory examination with the patient watching or looking away from the affected limb. Motor neglect is examined by asking the patient to undertake a simple task initially while looking away and then while watching the limb. In the upper limb, this can be repetitively opening the closing the fingers or, in the lower limb, tapping the foot. If there is a significant improvement when the patient is watching the limb, a degree of motor neglect is present.[61]

TABLE 23-5 Suggested Criteria for the Diagnosis of Complex Regional Pain Syndrome (CRPS) Within an Orthopaedic Setting

The diagnosis is made clinically by the finding of the following associated sets of abnormalities:

1. Neuropathic pain. Nondermatomal, without cause, burning, with associated allodynia and hyperpathia
2. Vasomotor instability and abnormalities of sweating. Warm red and dry, cool blue and clammy or an increase in temperature sensitivity. Associated with an abnormal temperature difference between the limbs
3. Swelling
4. Loss of joint mobility with associated joint and soft tissue contracture, including skin thinning and ahri and nail dystrophy

These clinical findings are backed up by

1. Increased uptake on delayed bone scintigraphy early in CRPS
2. Radiographic evidence of osteoporosis after 3 months

The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of dysfunction.

Modified from Atkins et al.[2,3]

Investigations

CRPS is a clinical diagnosis and there is no single diagnostic test. The classic case is obvious and direct effects of trauma, fracture, cellulitis, arthritis, and malignancy are common alternative diagnoses. The patient is systemically well with normal general clinical examination, biochemical markers, and infection indices.

Magnetic resonance imaging (MRI) shows early bone and soft tissue edema with late atrophy and fibrosis but is not diagnostic. However, in CRPS 2, MRI may be useful to demonstrate nerve thinning with poststenotic dilatation caused by compression and may even demonstrate a fibrous band causing the compression. It may also demonstrate neuroma formation, although many neuromas are too small to be adequately shown.

Computed tomography (CT) scanning may also be useful in demonstrating a bony compressing lesion. Electromyographic and nerve conduction studies are normal in CRPS 1 but may demonstrate a nerve lesion in CRPS 2.

Differential Diagnosis

Pain, swelling, and vasomotor instability are common associations of trauma and orthopaedic surgery. The following are common differential diagnoses.

1. *Soft tissue infection.* The clinical features are usually clear. The patient is systemically unwell with raised inflammatory markers.
2. *"Mechanical" problems.* Classic examples are incorrect sizing of a total knee replacement causing pain, swelling, and stiffness; overlong screws impinging on a joint; or malreduction of an intra-articular fracture (Fig. 23-5). In accordance with category 4 of the original IASP criteria for CRPS, all mechanical causes for the symptoms and signs must be excluded before making a diagnosis of CRPS. However, it must be borne in mind that the chronic pain of a mechanical problem can itself be the precipitating cause of CRPS.
3. *Conscious exaggeration of symptoms.* This is usually seen in the context of litigation, but the secondary gain from exaggeration may also relate to complex and pathological interpersonal relationships. This problem has been accidentally made more acute and severe by the IASP criteria for CRPS

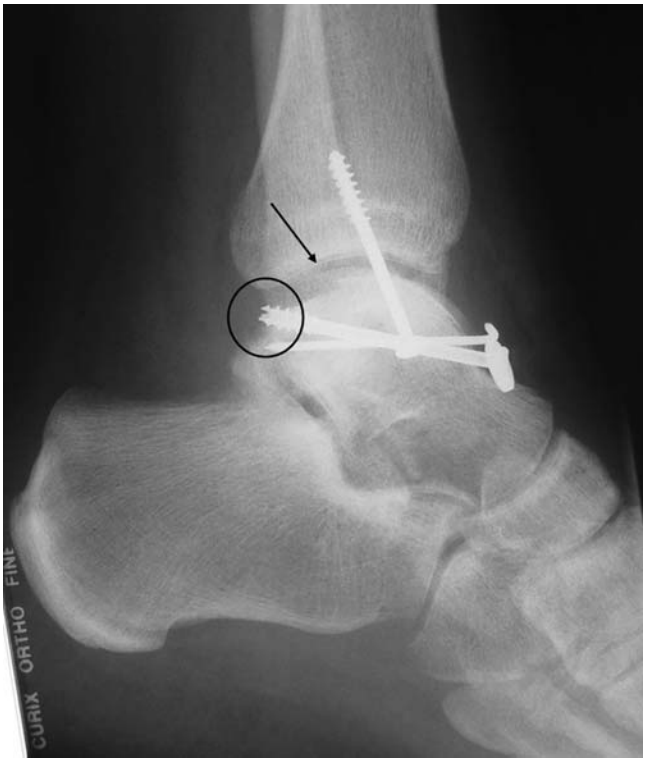

FIGURE 23-5 A patient referred with a diagnosis of complex regional pain syndrome (CRPS). This patient with severe pain in his foot was referred some years after internal fixation of a talar body fracture. He has severe pain and dysfunction. The lateral radiograph shows no evidence of significant osteoporosis, which is inconsistent with the diagnosis. The talar body fracture is not reduced (*arrow*), which renders the ankle and subtalar joints incongruous. Furthermore, the screws are overlong (*circle*) and impinge on the ankle joint. This patient does not have CRPS; he has a mechanical cause for his severe pain, which was resolved by talar osteotomy, anatomic reduction, and refixation. It is important to exclude mechanical causes for pain before invoking the diagnosis of CRPS.

diagnosis. The original criteria (Table 23-2) are readily mimicked by a patient determined to deceive the examining clinician. Unfortunately, the modified criteria may also provide a diagnosis of CRPS in a deceitful patient. Categories 1 and 2 are simple. The patient merely has to report these problems. Category 3 refers to objective criteria. However, sensory abnormalities rely on the patient's subjective response to stimulus. Skin color change can be caused by deliberate dependency and immobility of the limb. Loss of joint range of movement can be caused by conscious resistant to movement, and dystonia, tremor, and weakness can likewise be produced artifactually. The rise of the Internet means that any reasonably determined patient can have very great knowledge of the features of CRPS and the diagnostic criteria. The solution to this problem is to remember that the IASP criteria are designed to differentiate CRPS from other chronically painful conditions. They are not intended to deal with a patient whose veracity is open to question. CRPS is a condition that inevitably leads to dystrophy,[21,44,58,138] and in a patient who has suffered from significant CRPS for any significant length, objective features of dystrophy, such as nail or hair dystrophy, skin and subcutaneous tissue atrophy, fixed joint contracture, and radiographic features of significant osteoporosis with abnormalities of bone scanning, should be present. If the patient's veracity is in doubt, the astute clinician will give only limited or no credence to those features that can be mimicked and look for incontrovertible physical signs.

4. *Psychiatric disease.* Separate from the conscious exaggeration described earlier, psychiatric disease may cause a patient unconsciously to exaggerate the level or impact of physical disease. Somatoform disorders describe conditions in which patients unconsciously exaggerate physical symptoms, and conversion disorders refer to unconscious exaggeration of physical signs. These patients are often psychologically fragile, they may have a history of an unusually severe reaction to multiple minor medical problems, and they may show a tendency to "catastrophize" life events. In addition to this direct influence on a diagnosis of CRPS, patients with CRPS may be depressed because of chronic pain and psychiatric disease may play an indirect part in the condition. It is often very useful to obtain formal psychiatric or psychological opinion and treatment.[156]
5. *Neuropathic pain.* This has been defined and discussed. Neuropathic pain is part of CRPS, but a patient may have neuropathic pain without having CRPS. However, neuropathic pain may give rise to CRPS.
6. *Chronic pain state.* Patients with long-lasting and unremitting pain may become depressed, particularly when there is a neuropathic element. They learn to avoid activities that cause pain, and their relatives and carers act to protect them from perceived injury. This generates a complex psychosocial situation that may require psychological, psychiatric, pain therapeutic, and orthopaedic combined management.

Management

A bewildering array of treatments have been proposed, but proper scientifically constructed prospectively randomized blinded studies are few,[95] and uncontrolled investigations are particularly unreliable in CRPS because of the variety of symptoms and the trend toward self-resolution in the majority of cases. This is well illustrated by a series of publications investigating the treatment of early CRPS after Colles' fracture with intravenous regional guanethidine blockade (IVRGB). An initial investigation showed that IVRGB caused improvement in objective criteria of CRPS severity.[54] A subsequent pilot study appeared to confirm the immediate improvement induced by IVRGB was associated with sustained symptomatic improvement.[53] However, a full prospectively randomized double-blind controlled study demonstrated that IVRGB actually seemed to worsen the condition.[105] The lesson is that these potentially fragile patients must be approached with caution.

This chapter has presented evidence that CRPS is very common in orthopaedic trauma practice. Most sufferers are sensible people, concerned about the development of inexplicable pain, but the occasional "Sudecky" patient fares poorly and should be treated vigorously. Early treatment, begun before contractures occur, gives optimal results, so a high index of clinical suspicion must be maintained. It is not reprehensible to have caused a case of CRPS through surgery or nonoperative management of injury. However, delay in diagnosis and treatment may contribute to a poor outcome.

Modern CRPS treatment emphasizes functional rehabilitation of the limb to break the vicious cycle of disuse,[79,82,141]

rather than SNS manipulation.[26] Initial treatment from the orthopaedic surgeon is with reassurance, excellent analgesia, and intensive, careful physical therapy avoiding exacerbation of pain.[66] Nonsteroidal anti-inflammatory drugs may give better pain relief than opiates, and a centrally acting analgesic such as amitriptyline is often useful even at this early stage. Immobilization and splintage should generally be avoided but, if used, joints must be placed in a safe position and splintage is a temporary adjunct to mobilization. It seems sensible to give the patients vitamin C in view of the early evidence of its efficacy.[170,171]

Abnormalities of pain sensation will often respond to desensitization. The patient is asked to stroke the area of allodynia, where stroking is painful. They are reminded that simple stroking cannot by definition be painful and they are instructed to stroke the affected part repetitively while looking at it and repeatedly saying "this does not hurt, it is merely a gentle touch." The earlier this is begun, the more effective it is. A similar attitude can be taken with early loss of joint mobility due to perceived pain rather than contracture.

The use of mirror virtual therapy is an exciting new concept that is as yet unproved in an orthopaedic context.[116,133]

If the patient does not respond rapidly, a pain specialist should be involved and treatment continued on a shared basis. Psychological or psychiatric input may be important.[25] Second-line treatment is often unsuccessful and many patients are left with pain and disability. Further treatments include centrally acting analgesic medications such as amitriptyline, gabapentin, or carbamazepine; regional anesthesia; calcitonin; the use of membrane-stabilizing drugs such as mexilitene; sympathetic blockade and manipulation; desensitization of peripheral nerve receptors with capsaicin; or transcutaneous nerve stimulation or an implanted dorsal column stimulator.[109,124,142] Behavioral therapy may be necessary in children.[165–167] Where the knee is affected, epidural anesthesia and continuous passive motion may be appropriate.[35,36]

The role of surgery is limited and hazardous. While there is debate within pain therapy circles as to the utility of separating CRPS type 1 from type 2 (although there is evidence that they are symptomatically different[21]), within orthopaedic practice, it is extremely useful. The wording of the IASP criteria is not surgically precise (Table 23-2). However, if one substitutes surgically correctable nerve lesion, in cases of CRPS type 2, treatment should be directed at curing the nerve lesion. Occult nerve compression should be sought and dealt with. For example, decompression of a median nerve at the wrist that is causing CRPS of the hand may abort the CRPS and should be undertaken cautiously in the presence of active disease.

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Surgery is rarely indicated to treat fixed contractures, which usually involve all of the soft tissues. Surgical release must therefore be radical and expectations limited. Surgery for contracture should be delayed until the active phase of CRPS has completely passed, and ideally there should be a gap of at least 1 year since the patient last experienced pain and swelling.

Amputation of a limb affected by severe CRPS should be approached with great caution. Dielissen et al.[42] reported a series of 28 patients who underwent 34 amputations in 31 limbs. Surgery was usually performed for recurrent infection or to improve residual function. Pain relief was rare and unpredictable, and neither was infection always cured nor function universally improved. CRPS often recurred in the stump, especially if the amputation level was symptomatic at the time of surgery. For this reason, only two patients wore a prosthesis.

Generally, surgery represents a painful stimulus that may exacerbate CRPS or precipitate a new attack. This risk must be balanced carefully against the proposed benefit. The risk of surgically precipitated recurrence is greatest when the same site is operated on in a patient with abnormal psychology in the presence of active disease and lowest when these conditions do not apply. Surgery must be performed carefully with minimal trauma with excellent and complete postoperative analgesia. The surgery may be covered by gabapentin. Ideally, the anesthetist will have a particular interest in the treatment of CRPS.

CONCLUSION

This chapter has presented the proposal that CRPS in a mild form, which is often not formally diagnosed, is very common but not universal in an orthopaedic trauma practice. Although the majority of cases will resolve with simple management, CRPS is responsible for significant acute disability and may cause long-term problems.

REFERENCES

1. Ali Z, Raja SN, Wesselmann U, et al. Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. Pain 2000;88:161–168.
2. Atkins RM, Duckworth T, Kanis JA. Algodystrophy following Colles' fracture. J Hand Surg [Br] 1989;14:161–164.
3. Atkins RM, Duckworth T, Kanis JA. Features of algodystrophy after Colles' fracture. J Bone Joint Surg Br 1990;72:105–110.
4. Atkins RM, Kanis JA. The use of dolorimetry in the assessment of post-traumatic algodystrophy of the hand. Br J Rheumatol 1989;28:404–409.
5. Atkins RM, Tindale W, Bickerstaff D, et al. Quantitative bone scintigraphy in reflex sympathetic dystrophy. Br J Rheumatol 1993;32:41–45.
6. Atkins RM. Algodystrophy. Oxford: University of Oxford; 1989.
7. Aubert PG. Etude sur le risque algodystrophique. [These pour le doctorat en medecin diplome d'etat.] Paris: University of Paris, Val de Marne; 1980.
8. Bacorn R, Kurtz J. Colles' fracture: a study of 2000 cases from the New York State Workmen's Compensation Board. J Bone Joint Surg Am 1953;35A:643–658.
9. Bernstein BH, Singsen BH, Kent JT, et al. Reflex neurovascular dystrophy in childhood. J Pediatr 1978;93:211–215.
10. Bhatia KP, Bhatt MH, Marsden CD. The causalgia-dystonia syndrome. Brain 1993;116: 843–851.
11. Bhatia KP, Marsden CD. Reflex sympathetic dystrophy may be accompanied by involuntary movements. BMJ 1995;311:811–812.
12. Bickerstaff DR, Charlesworth D, Kanis JA. Changes in cortical and trabecular bone in algodystrophy. Br J Rheumatol 1993;32:46–51.
13. Bickerstaff DR, Kanis JA. Algodystrophy: an under-recognized complication of minor trauma. Br J Rheumatol 1994;33:240–248.
14. Bickerstaff DR. The natural history of post traumatic algodystrophy. Sheffield, UK: University of Sheffield; 1990.
15. Birklein F, Riedl B, Sieweke N, et al. Neurological findings in complex regional pain syndromes—analysis of 145 cases. Acta Neurol Scand 2000;101:262–269.
16. Boas R. Complex regional pain syndromes: symptoms, signs and differential diagnosis. In: Janig W, Stanton-Hicks M, eds. Reflex sympathetic dystrophy: a reappraisal. Seattle, WA: IASP Press; 1996:79–92.
17. Bonica JJ. Causalgia and other reflex sympathetic dystrophies. In: Bonica JJ, ed. Management of pain. Philadelphia: Lea & Febiger; 1990:220–243.
18. Bonica JJ. The management of pain. Philadelphia: Lea & Febiger; 1953.
19. Breuer J, Freud S. Studies in hysteria. Translated and edited by J. Strachey with the collaboration of A. Freud. New York: Basic Books; 1982.
20. Bruehl S, Carlson CR. Predisposing psychological factors in the development of reflex sympathetic dystrophy. A review of the empirical evidence. Clin J Pain 1992;8: 287–299.
21. Bruehl S, Harden RN, Galer BS, et al. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain 2002;95:119–124.
22. Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. Pain 1999;81:147–154.
23. Bruehl S, Husfeldt B, Lubenow TR, et al. Psychological differences between reflex sympathetic dystrophy and non-RSD chronic pain patients. Pain 1996;67:107–114.
24. Bruehl S. Do psychological factors play a role in the onset and maintenance of CRPS-1? In: Harden RN, Baron R, et al, eds. Complex regional pain syndrome. Seattle, WA: IASP Press; 2001.
25. Bruehl S. Psychological interventions. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:201–216.
26. Burton AW, Lubenow TR, Prithvi Raj P. Traditional interventional therapies. In: Wilson

P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and treatment. Seattle, WA: IASP Press; 2005:217–233.
27. Butler SH, Galer BS, Benirsche S. Disuse as a cause of signs and symptoms of CRPS. Abstracts: 8th World Congress on Pain. Seattle, WA: IASP Press; 1996:401.
28. Butler SH, Nyman M, Gordh T, editors. Immobility in volunteers produces signs and symptoms of CRPS and a neglect-like state. Abstracts: 9th World Congress on Pain; 1999. Seattle, WA: IASP Press.
29. Butler SH. Disuse and CRPS. In: Harden RN, Baron R, Janig W, eds. Complex regional pain syndrome. Seattle, WA: IASP Press; 2001:141–150.
30. Campbell J, Raga S, Meyer R. Painful sequelae of nerve injury. In: Dubner R, Gebhart G, Bond M, eds. Proceedings of the 5th World Congress on Pain. Amsterdam: Elsevier Science Publishers; 1988:135–143.
31. Casale R, Glynn CJ, Buonocore M. Autonomic variations after stellate ganglion block: are they evidence of an autonomic afference? Funct Neurol 1990;5:245–246.
32. Channon GN, Lloyd GJ. The investigation of hand stiffness using Doppler ultrasound, radionuclide scanning and thermography. J Bone Joint Surg Br 1979;61B:519.
33. Charcot JM. Two cases of hysterical contracture of traumatic origin (Lectures VII and VIII). Lectures on Diseases of the Nervous System. Nijmegen: Arts and Boeve; 1889: 84–106.
34. Constantinesco A, Brunot B, Demangeat JL, et al. Three phase bone scanning as an aid to early diagnosis in reflex sympathetic dystrophy of the hand. A study of eighty-nine cases. Ann Chir Main 1986;5:93–104.
35. Cooper DE, DeLee JC. Reflex sympathetic dystrophy of the knee. J Am Acad Orthop Surg 1994;2:79–86.
36. Cooper DE, DeLee JC, Ramamurthy S. Reflex sympathetic dystrophy of the knee. Treatment using continuous epidural anesthesia. J Bone Joint Surg Am 1989;71A:365–369.
37. De Takats G. Causalgic states in peace and war. JAMA 1945;128:699–704.
38. De Takats G. Reflex dystrophy of the extremities. Arch Surg 1937;34:939–956.
39. De Takats G. The nature of painful vasodilatation in causalgic states. Arch Neurol 1943; 53:318–326.
40. Demangeat JL, Constantinesco A, Brunot B, et al. Three-phase bone scanning in reflex sympathetic dystrophy of the hand. J Nucl Med 1988;29:26–32.
41. Devor M, Raber P. Heritability of symptoms in an experimental model of neuropathic pain. Pain 1990;42:51–67.
42. Dielissen PW, Claassen AT, Veldman PH, et al. Amputation for reflex sympathetic dystrophy. J Bone Joint Surg Br 1995;77B:270–273.
43. Doupe J, Cullen C, Chance G. Post traumatic pain and causalgic syndrome. J Neurol Neurosurg Psychiatry 1944;7:33–35.
44. Doury P, Dirheimer Y, Pattin S. Algodystrophy: diagnosis and therapy of a frequent disease of the locomotor apparatus. Berlin: Springer Verlag; 1981.
45. Dressler D, Thompson PD, Gledhill RF, et al. The syndrome of painful legs and moving toes. Mov Disord 1994;9:13–21.
AQ6 46. Evans JA. Reflex sympathetic dystrophy. Surg Clin N Am
47. Fam AG, Stein J. Disappearance of chondrocalcinosis following reflex sympathetic dystrophy syndrome. Arthritis Rheum 1981;24:747–749.
48. Ficat P, Arlet J, Lartigue G, et al. [Post-injury reflex algo-dystrophies. Hemodynamic and anatomopathological study]. Rev Chir Orthop Reparatrice Appar Mot 1973;59: 401–414.
49. Ficat P, Arlet J, Pujol M, et al. [Injury, reflex dystrophy and osteonecrosis of the femoral head]. Ann Chir 1971;25:911–917.
50. Field J. Measurement of finger stiffness in algodystrophy. Hand Clin 2003;19:511–515.
51. Field J, Atkins RM. Algodystrophy is an early complication of Colles' fracture. What are the implications? J Hand Surg [Br] 1997;22:178–182.
52. Field J, Atkins RM. Effect of guanethidine on the natural history of post-traumatic algodystrophy. Ann Rheum Dis 1993;52:467–469.
53. Field J, Gardner FV. Psychological distress associated with algodystrophy. J Hand Surg [Br] 1997;22:100–101.
54. Field J, Monk C, Atkins RM. Objective improvements in algodystrophy following regional intravenous guanethidine. J Hand Surg [Br] 1993;18:339–342.
55. Field J, Protheroe DL, Atkins RM. Algodystrophy after Colles fractures is associated with secondary tightness of casts. J Bone Joint Surg Br 1994;76B:901–905.
56. Field J, Warwick D, Bannister GC. Features of algodystrophy ten years after Colles' fracture. J Hand Surg [Br] 1992;17:318–320.
57. Francini F, Zoppi M, Maresca M, et al. Skin potential and EMG changes induced by electrical stimulation. 1. Normal man in arousing and non-arousing environment. Appl Neurophysiol 1979;42:113–124.
58. Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. International Association for the Study of Pain. Clin J Pain 1998;14:48–54.
59. Galer BS, Butler S, Jensen MP. Case reports and hypothesis: a neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy (complex regional pain syndrome-1). J Pain Symptom Manage 1995;10:385–391.
60. Galer BS, Harden N. Motor abnormalities in CRPS: A neglected but key component. In: Harden N, Baron R, et al, eds. Complex regional pain syndrome. Seattle, WA: IASP Press; 2001.
61. Galer BS, Harden RN. Motor abnormalities in CRPS: A neglected but key component. In: Harden RN, Baron R, Janig W, editors. Complex regional pain syndrome. Seattle, WA: IASP Press; 2001:135–140.
62. Galer BS, Jensen M. Neglect-like symptoms in complex regional pain syndrome: results of a self-administered survey. J Pain Symptom Manage 1999;18:213–217.
63. Geertzen JH, de Bruijn H, de Bruijn-Kofman AT, et al. Reflex sympathetic dystrophy: early treatment and psychological aspects. Arch Phys Med Rehabil 1994;75:442–446.
64. Geertzen JH, de Bruijn-Kofman AT, de Bruijn HP, et al. Stressful life events and psychological dysfunction in complex regional pain syndrome type I. Clin J Pain 1998;14: 143–147.
65. Geertzen JH, Dijkstra PU, Groothoff JW, et al. Reflex sympathetic dystrophy of the upper extremity—a 5.5-year follow-up. Part II. Social life events, general health and changes in occupation. Acta Orthop Scand Suppl 1998;279:19–23.
66. Geertzen JH, Harden RN. Physical and occupational therapies. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:173–179.
67. Gibbons JJ, Wilson PR. RSD score: criteria for the diagnosis of reflex sympathetic dystrophy and causalgia. Clin J Pain 1992;8:260–263.
68. Glick EN. Reflex dystrophy (algoneurodystrophy): results of treatment by corticosteroids. Rheumatol Rehabil 1973;12:84.
69. Glick EN, Helal B. Post-traumatic neurodystrophy. Treatment by corticosteroids. Hand 1976;8:45–47.
70. Glynn CJ, Basedow RW, Walsh JA. Pain relief following post-ganglionic sympathetic blockade with I.V. guanethidine. Br J Anaesth 1981;53:1297–1302.
71. Goris RJ. Conditions associated with impaired oxygen extraction. In: Gutierrez G, Vincent JL, eds. Tissue oxygen utilisation. Berlin: Springer Verlag; 1991:350–369.
72. Goris RJ. Treatment of reflex sympathetic dystrophy with hydroxyl radical scavengers. Unfallchirurg 1985;88:330–332.
73. Goris RJ, Dongen LM, Winters HA. Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy? Free Radic Res Commun 1987;3:13–18.
74. Green JT, Gay FH. Colles' fracture residual disability. Am J Surg 1956;91:636–646.
75. Hannington-Kiff JG. Hyperadrenergic-effected limb causalgia: relief by IV pharmacologic norepinephrine blockade. Am Heart J 1982;103:152–153.
76. Hannington-Kiff JG. Pharmacological target blocks in hand surgery and rehabilitation. J Hand Surg [Br] 1984;9:29–36.
77. Hannington-Kiff JG. Relief of causalgia in limbs by regional intravenous guanethidine. Br Med J 1979;2:367–368.
78. Hannington-Kiff JG. Relief of Sudeck's atrophy by regional intravenous guanethidine. Lancet 1977;1(8022):1132–1133.
79. Harden RN. The rationale for integrated functional restoration. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:163–171.
80. Harden RN, Bruehl S, Galer BS, et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain 1999;83:211–219.
81. Harden RN, Bruehl S, Stanos S, et al. Prospective examination of pain-related and psychological predictors of CRPS-like phenomena following total knee arthroplasty: a preliminary study. Pain 2003;106:393–400.
82. Harden RN, Swan M, King A, et al. Treatment of complex regional pain syndrome: functional restoration. Clin J Pain 2006;22:420–424.
83. Harris AJ. Cortical origin of pathological pain. Lancet 1999;354:1464–1466.
84. Holder LE, Mackinnon SE. Reflex sympathetic dystrophy in the hands: clinical and scintigraphic criteria. Radiology 1984;152:517–522.
85. Homans J. Minor causalgia. A hyperaesthetic neurovascular syndrome. N Engl J Med 1940;222:870–874.
86. Jacquemoud G, Chamay A. Treatment of algodystrophy using intravenous guanethidine regional block. Ann Chir Main 1982;1:57–64.
87. Jadad AR, Carroll D, Glynn CJ, et al. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. J Pain Symptom Manage 1995;10:13–20.
88. Janig W, Koltzenburg M. Possible ways of sympathetic afferent interaction. In: Janig W, Schmidt RF, eds. Reflex sympathetic dystrophy: pathophysiological mechanisms and clinical implications. New York: VCH Verlagsgesellschaft; 1992:213–243.
89. Janig W, Koltzenburg M. What is the interaction between the sympathetic terminal and the primary afferent fibre? In: Basbaum AI, et al, eds. Towards a new pharmacology of pain. Chichester: John Wiley and Sons; 1991:331–352.
90. Janig W. CRPS 1 and CRPS 2: A strategic view. In: Harden RN, Baron R, Janig W, eds. Complex regional pain syndrome. Seattle, WA: IASP Press; 2p. 3–15.
91. Janig W. The sympathetic nervous system in pain: physiology and pathophysiology. In: Stanton-Hicks M, editor. Pain in the sympathetic nervous system. Massachussetts: Kluwer Academic Publishers; 1990:17–89.
92. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 2003;102:1–8.
93. Katz MM, Hungerford DS. Reflex sympathetic dystrophy affecting the knee. J Bone Joint Surg Br 1987;69B:797–803.
94. Kimura T, Komatsu T, Hosoda R, et al. Angiotensin-converting enzyme gene polymorphism in patients with neuropathic pain. In: Devor M, Rowbotham M, Wiesenfeld-Hallin D, eds. Proceedings of the 9th World Conference on Pain. Seattle, WA: IASP Press; 2000:471–476.
95. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain 1997;73:123–139.
96. Knepper R. [Pathogenic evaluation of pain]. Med Welt 1967;35:1994–1996.
97. Kozin F, Genant HK, Bekerman C, et al. The reflex sympathetic dystrophy syndrome. II. Roentgenographic and scintigraphic evidence of bilaterality and of periarticular accentuation. Am J Med 1976;60:332–338.
98. Kozin F, McCarty DJ, Sims J, et al. The reflex sympathetic dystrophy syndrome. I. Clinical and histologic studies: evidence for bilaterality, response to corticosteroids and articular involvement. Am J Med 1976;60:321–331.
99. Leriche R. Oedeme dur aigu post-traumatique de la main avec impotence fonctionelle complete. Transformation soudaine cinq heures apres sympathectomie humerale. Lyon Chir 1923;20:814–818.
100. Leriche R. Traitement par la sympathectomie periarterielle des osteoporoses traumatiques. Bull Mem Soc Chir Paris 1926;52:247–251.
101. Lewis JS, Kersten P, McCabe CS, et al. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). Pain 2007;133:111–119.
102. Lidström A. Fractures of the distal end of radius. A clinical and statistical study of end results. Acta Orthop Scand 1959;suppl 41.
103. Liepert J, Tegenthoff M, Malin JP. Changes of cortical motor area size during immobilization. Electroencephalogr Clin Neurophysiol 1995;97:382–386.
104. Lindsay RM, Harmar AJ. Nerve growth factor regulates expression of neuropeptide genes in adult sensory neurons. Nature 1989;337:362–364.
105. Livingstone JA, Atkins RM. Intravenous regional guanethidine blockade in the treatment of post-traumatic complex regional pain syndrome type 1 (algodystrophy) of the hand. J Bone Joint Surg Br 2002;84B:380–386.
106. Livingstone JA, Field J. Algodystrophy and its association with Dupuytren's disease. J Hand Surg [Br] 1999;24:199–202.
107. LoPinto C, Young WB, Ashkenazi A. Comparison of dynamic (brush) and static (pressure) mechanical allodynia in migraine. Cephalalgia 2006;26:852–856.
108. Louyot P, Gaucher A, Montet Y, et al. [Algodystrophy of the lower extremity]. Rev Rhum Mal Osteoartic 1967;34:733–737.
109. Lubenow TR, Buvanendran A, Stanton-Hicks M. Implanted Therapies. In: Wilson P,

Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:235–253.
110. Mackinnon SE, Holder LE. The use of three-phase radionuclide bone scanning in the diagnosis of reflex sympathetic dystrophy. J Hand Surg [Am] 1984;9:556–563.
111. Mailis A, Wade J. Profile of Caucasian women with possible genetic predisposition to reflex sympathetic dystrophy: a pilot study. Clin J Pain 1994;10:210–217.
112. Mailis A, Wade JA. Genetic considerations in CRPS. In: Harden RN, Baron R, Janig W, eds. Complex regional pain syndrome. IASP Press; 2001:227–238.
113. Marsden CD, Obeso JA, Traub MM, et al. Muscle spasms associated with Sudeck's atrophy after injury. Br Med J (Clin Res Ed) 1984;288:173–176.
114. Matsumura H, Jimbo Y, Watanabe K. Haemodynamic changes in early phase reflex sympathetic dystrophy. Scand J Plast Reconstr Surg Hand Surg 1996;30:133–138.
115. McCabe CS, Haigh RC, Halligan PW, et al. Referred sensations in patients with complex regional pain syndrome type 1. Rheumatology (Oxford) 2003;42:1067–1073.
116. McCabe CS, Haigh RC, Ring EF, et al. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology (Oxford) 2003;42:97–101.
117. McLachlan EM, Janig W, Devor M, et al. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. Nature 1993;363:543–546.
118. Merskey H. Essence, investigation, and management of "neuropathic" pains: hopes from acknowledgment of chaos. Muscle Nerve 1995;18:455–456; author reply 8–62.
119. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. 2nd ed. Seattle, WA: IASP Press; 1994.
120. Mitchell SW, Morehouse GG, Keen WW. Gunshot wounds and other injuries of nerves. Philadelphia: JB Lippincott; 1864.
121. Muller ME, Allgower M, Schneider R, et al. Manual of internal fixation. Techniques recommended by the AO group. 2nd ed. London/New York: Springer Verlag; 1979.
122. Nelson DV, Novy DM. Psychological characteristics of reflex sympathetic dystrophy versus myofascial pain syndromes. Reg Anesth 1996;21:202–208.
123. Nonne N. Über die Radiolographische nachweisbare akute und kronische "Knochenatrophie" (Südeck bie Nerven-Erkrankungen). Fortschr Geb Röntgenstr 1901;5: 293–297.
124. Oaklander AL. Evidence-Based Pharmacotherapy for CRPS and Related Conditions. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:181–200.
125. Oyen WJ, Arntz IE, Claessens RM, et al. Reflex sympathetic dystrophy of the hand: an excessive inflammatory response? Pain 1993;55:151–157.
126. Patman RD, Thompson JE, Persson AV. Management of post-traumatic pain syndromes: report of 113 cases. Ann Surg 1973;177:780–787.
127. Pelissier J, Touchon J, Besset A, et al. La personnalite du sujet souvrant d'algodystrophie sympathique reflexe. Etudes Psychometrques par le test MMPI. Rheumatologie 1981; 23:351–354.
128. Perelman RB, Adler D, Humphreys M. Reflex sympathetic dystrophy: electronic thermography as an aid in diagnosis. Orthop Rev 1987;16:561–566.
129. Plewes LW. Sudek's atrophy of the hand. J Bone Joint Surg Br 1956;38B:195–203.
130. Price DD, Long S, Wilsey B, Rafii A. Analysis of peak magnitude and duration of analgesia produced by local anesthetics injected into sympathetic ganglia of complex regional pain syndrome patients. Clin J Pain 1998;14:216–226.
131. Procacci P, Francini F, Maresca M, et al. Skin potential and EMG changes induced by cutaneous electrical stimulation. II. Subjects with reflex sympathetic dystrophies. Appl Neurophysiol 1979;42:125–134.
132. Procacci P, Francini F, Zoppi M, et al. Cutaneous pain threshold changes after sympathetic block in reflex dystrophies. Pain 1975;1:167–175.
133. Ramachandran VS, Roger-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. Proc R Soc Lond B Biol Sci 1996;263:377–386.
134. Renier JC, Moreau R, Bernat M, et al. [Contribution of dynamic isotopic tests in the study of algodystrophies]. Rev Rhum Mal Osteoartic 1979;46:235–241.
135. Sarangi PP, Ward AJ, Smith EJ, et al. Algodystrophy and osteoporosis after tibial fractures. J Bone Joint Surg Br 1993;75B:450–452.
136. Schattschneider J, Wenzelburger R, Deuschl G, et al. Kinematic analysis of the upper extremity in CRPS. In: Harden RN, Baron R, Janig W, editors. Complex regional pain syndrome. Seattle, WA: IASP Press; 2001:119–128.
137. Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology 1990;40:57–61.
138. Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy. A review. Arch Neurol 1987;44:555–561.
139. Stanos SP, Harden RN, Wagner-Raphael L, et al. A prospective clinical model for investigating the development of CRPS. In: Harden RN, Baron R, Janig W, eds. Complex regional pain syndrome. Seattle, WA: IASP Press; 2001:151–164.
140. Stanton-Hicks M, Baron R, Boas R, et al. Complex regional pain syndromes: guidelines for therapy. Clin J Pain 1998;14:155–166.
141. Stanton-Hicks M, Janig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995;63:127–133.
142. Stanton-Hicks M, Rauck R, Hendrickson M, et al. Miscellaneous and experimental therapies. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:255–274.
143. Steinbrocker O. The shoulder-hand syndrome: present perspective. Arch Phys Med Rehabil 1968;49:388–395.
144. Subbarao J, Stillwell GK. Reflex sympathetic dystrophy syndrome of the upper extremity: analysis of total outcome of management of 125 cases. Arch Phys Med Rehabil 1981;62:549–554.
145. Südeck P. Über die akute (reflektorische) Knochenatrophie nach Entzündungen und Verletzungen in den Extremitäten und ihre klinischen Erscheinungen. Fortschr Geb Rontgenstr 1901;5:227–293.
146. Südeck P. Über die Akute (reflektorische) Knochenatrophie. Arch Klin Chir 1900;762: 147–156.
147. Thomson McBride AR, Barnett AJ, Livingstone JA, et al. Complex regional pain syndrome (type 1): a comparison of 2 diagnostic criteria methods. Clin J Pain 2008;24: 637–640.
148. Torebjork E, Wahren L, Wallin G, et al. Noradrenaline-evoked pain in neuralgia. Pain 1995;63:11–20.
149. van der Laan L, Goris RJ. Reflex sympathetic dystrophy. An exaggerated regional inflammatory response? Hand Clin 1997;13:373–385.
150. van der Laan L, Kapitein P, Verhofstad A, et al. Clinical signs and symptoms of acute reflex sympathetic dystrophy in one hindlimb of the rat, induced by infusion of a free-radical donor. Acta Orthop Belg 1998;64:210–217.
151. van der Laan L, ter Laak HJ, Gabreels-Festen A, et al. Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. Neurology 1998;51: 20–25.
152. Van Hilten JJ, Blumberg H, Schwartzman R. Factor IV: Movement disorders and dystrophy. pathophysiology and measurement. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:119–137.
153. van Hilten JJ, van de Beek WJ, Vein AA, et al. Clinical aspects of multifocal or generalized tonic dystonia in reflex sympathetic dystrophy. Neurology 200126;56:1762–1765.
154. Van Houdenhove B, Vasquez G, Onghena P, et al. Etiopathogenesis of reflex sympathetic dystrophy: a review and biopsychosocial hypothesis. Clin J Pain 1992;8: 300–306.
155. Van Houdenhove B. Neuro-algodystrophy: a psychiatrist's view. Clin Rheumatol 1986; 5:399–.
156. Van Houdenhove B, Vasquez G. Is there a relationship between reflex sympathetic dystrophy and helplessness? Case reports and a hypothesis. Gen Hosp Psychiatry 1993; 15:325–329
157. Veldman PH, Reynen HM, Arntz IE, et al. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–1016.
158. Vincent G, Ernst J, Henniaux M, et al. [Attempt at a psychological approach in algoneurodystrophy]. Rev Rhum Mal Osteoartic 1982;49:767–769.
159. Wahren LK, Gordh TJ, Torebjork E. Effects of regional intravenous guanethidine in patients with neuralgia in the hand; a follow-up study over a decade. Pain 1995;62: 379–385.
160. Wall PD. Noradrenaline-evoked pain in neuralgia. Pain 1995;63:1.
161. Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve injured rats. Pain 1983;17:321–339.
162. Wasner G, Schattschneider J, Baron R. Skin temperature side differences—a diagnostic tool for CRPS? Pain 2002;98:19–26.
163. Watson Jones SR. Fractures and joint injuries. 4th ed. Edinburgh, London: ES Livingstone; 1952.
164. Wenzelburger R, Schattschneider J, Wasner G, et al. Grip force coordination in CRPS. In: Harden RN, Baron R, Janig W, eds. Complex regional pain syndrome. Seattle, WA: IASP Press; 2001:129–134.
165. Wilder RT. Management of pediatric patients with complex regional pain syndrome. Clin J Pain 2006;22:443–448.
166. Wilder R, Olsson GL. Management of pediatric patients with CRPS. In: Wilson P, Stanton-Hicks M, Harden RN, eds. CRPS: current diagnosis and therapy. Seattle, WA: IASP Press; 2005:275–289.
167. Wilder RT, Berde CB, Wolohan M, et al. Reflex sympathetic dystrophy in children. Clinical characteristics and follow-up of seventy patients. J Bone Joint Surg Am 1992; 74A:910–919.
168. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353:1959–1964.
169. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000; 288:1765–1768.
170. Zollinger PE, Tuinebreijer WE, Breederveld RS, et al. Can vitamin C prevent complex regional pain syndrome in patients with wrist fractures? A randomized, controlled, multicenter dose-response study. J Bone Joint Surg Am 2007;89A:1424–1431.
171. Zollinger PE, Tuinebreijer WE, Kreis RW, et al. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomised trial. Lancet 1999;354: 2025–2028.
172. Zucchini M, Alberti G, Moretti MP. Algodystrophy and related psychological features. Funct Neurol 1989 Apr-Jun;4:153–156.
173. Zyluk A. [The three-staged evolution of the post-traumatic algodystrophy]. Chir Narzadow Ruchu Ortop Pol 1998;63:479–486.
174. Zyluk A. Results of the treatment of posttraumatic reflex sympathetic dystrophy of the upper extremity with regional intravenous blocks of methylprednisolone and lidocaine. Acta Orthop Belg 1998;64:452–456.
175. Zyluk A. The natural history of post-traumatic reflex sympathetic dystrophy. J Hand Surg [Br] 1998;23:20–23.

AUTHOR QUERIES

AQ1–Please note that all of the references were renumbered so that the reference list would be an alphabetical listing, per book style. Please check numbers in text carefully. Thank you.

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