Complex Regional Pain Syndromes (Reflex Sympathetic Dystrophy and Causalgia) and Spinal Cord Stimulation

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ABSTRACT

The complex regional pain syndromes (CRPS I and CRPS II), also known as reflex sympathetic dystrophy and causalgia, have been recognized for the past 2,500 years and believed in for the past 150, but they have yet to be understood. These syndromes can be characterized by discrete sensory, motor, and autonomic findings, but many patients with CRPS continue to suffer for years without a diagnosis. The role of the sympathetic nervous system in maintaining these syndromes and its appropriateness as a target for treatment continue to be subjects of enduring controversy. As might be expected in a group of disorders that we still have trouble naming, much less diagnosing, it has been very difficult to reach a consensus on how to treat people afflicted with the CRPS. Recent insights into how the nervous system responds to injury are beginning to explain some of the “impossible” neurological findings that are characteristic of CRPS. These research findings may soon be translated into specific therapies targeted at the processes of neural inflammation that appear to play an important role in these syndromes. Using currently available techniques of quantitative sensory testing should allow us to improve our approach to diagnosing our patients and monitoring their responses to treatment. Incorporating these diagnostic techniques into clinical studies now promises to improve the utility of clinical research in this field. Case-series studies suggest that spinal cord stimulation is a safe and effective treatment for many people with advanced CRPS who have not obtained adequate relief with other treatments.

Key Words. Complex Regional Pain Syndrome; Reflex Sympathetic Dystrophy; Causalgia; Spinal Cord Stimulation; Multiple Independent Constant-Current Architecture

Unbelievable Pain

Patients seeking medical care for neuropathic pain syndromes such as reflex sympathetic dystrophy (RSD) or causalgia, now termed “complex regional pain syndromes” (CRPS I and CRPS II), have often been met with confusion, disbelief, and even suspicion [1]. Faced with symptoms out of proportion to injury, anatomically “impossible” patterns of pain and lacking a defined pathogenesis or a set of diagnostic criteria, many physicians...
have been quick to call these pains psychogenic [2]. Eventually, even neurologically “impossible” findings will find an explanation. Recent advances in research into the mechanisms underlying post-traumatic neuropathic pain are causing us to look at the nervous system in a completely new way that will help us explain many of the findings characteristic of CRPS. Advances in treatment already allow us to offer relief to many of our patients who are suffering with the unbelievable pain.

Believers in the Unbelievable

Until recently, many investigators attributed CRPS to personality disorders such as hypochondriasis [3,4]. Others, such as Dr. John Bonica, showed that the abnormalities in personality and behavior that were associated with CRPS disappeared after the pain was relieved. This strongly suggested that these abnormalities were the sequelae of the terrible pain and not the cause [5]. Even abnormalities commonly found on psychological testing of patients with pain due to CRPS, such as those on the Minnesota Multiphasic Pain Inventory (MMPI)—which was once thought to be an indelible fingerprint of personality—were found to normalize when the pain was relieved [6]. Despite a large volume of reports and medical articles making declarations to the contrary, there is no evidence that CRPS is a psychogenic condition [7].

Throughout modern history, despite this climate of disbelief, some physicians have steadfastly believed in and supported people who suffered with post-traumatic neuropathic pain. Foremost among them have been the military physicians. Throughout the history of medicine, pain management has been a special concern of military physicians who continue to be at the forefront in advocating for aggressive pain treatment to this day [8,9]. Indeed, one of the earliest descriptions of the different types of pain in Western literature, including neuropathic pain, can be found in a military epic, Homer’s *Iliad*.

Descriptions from Antiquity

In Homer’s ancient writings about war, *algos* is the word most often used to describe the pain inflicted in combat [10]. In its contexts, the use of the term *algos* suggests “to endure, to put up with,” or “to work with” the pain. *Algos* can be said to represent nociceptive pain that maintains a certain distance to traumatic events. This distance is both temporal and psychological. When the hero refers to *algos*

it is to other people’s pains or to pains that he himself no longer suffers. In distinction to this, the term *causos* (the root word of “caustic”) refers to a burning type pain that apparently has no end.

The story of Philocetes, written by Sophocles in the fifth century bc, contains what is apparently the earliest description of RSD. Philocetes describes pain in a foot related to a wound inflicted 10 years earlier. This pain—*causos*—is perceived as an independent being that takes possession of its subject, invading him and taking him over. Mention of this type of pain is often modified by words for “consuming” or “devouring.” The pain becomes a living being that feeds on its victim and gradually grows stronger as the sick person weakens. In describing this pain, the Greeks used the term *apotibatos*, meaning “unapproachable.” The Hippocrates who were cataloging medical knowledge at the time, listed *causos* as a specific illness, characterized by persistent burning pain.

War and Neuropathy

Since those ancient times, wars have continued to be marked by trauma to the limbs of soldiers, many of which resulted in amputation or, when it was possible to save the affected limb, in neuritis due to the presence of an arrow or bullet or the partial destruction of a peripheral nerve. In many instances, it was noted that these soldiers continued to feel awful pain for months or years after their wounds had healed. The most common of these pains were neuralgia, phantom-limb pain, and causalgia, the latter defined as “the impression of intolerable, intense, burning pain.” All military
surgeons who practiced in times of war have become acquainted with these chronic inexplicable pains.

Dr. Mitchell and Nervous Illness

In 1863 Dr. W.A. Hammond, the surgeon-general of the Union Army, directed that all wounded soldiers with “nervous illnesses” be treated under the direction of Dr. Silas Weir Mitchell, who came to be regarded as the father of modern neurology. In addition to being a physician, Dr. Mitchell was also a surgeon who had conducted some of the earliest modern experiments on neurosurgical approaches to pain. One of Dr. Mitchell’s mentors, the surgeon Dr. Henry H. Smith, had taught that some patients required operation “not with a view of curing the patient but simply for the purposes of making life pleasant and death easier” [11]. In those days there was heated debate in medical circles about distinguishing between “real” pain and the “imaginary” after-effects of the trauma of war (anxiety, hallucinations, change in character).

Many contemporary physicians noted that post-traumatic “nervous” pain lasted for a long time after recovery. They tended to interpret this as a psychological problem or as an imaginary illness rather than as real pain. Mitchell linked his clinical findings to anatomic and physiological knowledge and even tried to test the hypotheses derived from his clinical observations by experimenting on animals. In reference to the Hippocrates, Mitchell coined the term “causalgia” to describe painful post-traumatic neuropathies and noted that, in these patients, “everything which excites the circulation heightens the pain and exacerbates the suffering. This last fact is so constant that absolute rest is a vital part of the treatment” [12].

Mitchell found that one of the few useful treatments for the wounded soldiers under his care was injections of morphine. He wrote that, “this mode of treatment with narcotics has come into current use today and one cannot have too great a confidence in it. In our work at the military hospital for nervous diseases, resident surgeons went into the wards with the injection apparatus two or three times per day finding themselves faced with anguish and pain and afterwards they left behind them well-being and sometimes a smile. This picture is not exaggerated, as few hospitals have seen as much suffering and torture as ours. There were times when each assistant gave between 60 and 80 hypodermic injections per day and per night.”

Mitchell noted that causalgia typically appeared later than the wound itself and tended to be localized to the hand or foot. Those afflicted with causalgia were sensitive to the smallest external stimulus—“a breath of air, the lightest caress or even vibrations caused by walking” [12]. In order to avoid these triggers, Mitchell enveloped the affected limbs in thick bandages or kept them immersed in water. Mitchell recorded his patients’ reports of the pain, which they likened to “... a burn. Or to the action of a very hot mustard plaster, or to the effect of a red-hot file abrading their skin which often takes on a glossy appearance” [12]. Mitchell said that in cases of causalgia it was valuable to inject morphine directly into the painful extremity while for other painful conditions the site of injection was unimportant. Of note, local anesthesia did not come into use until more than 15 years after the end of the Civil War.

Advances in the First World War

The next surge of scholarly work on the diagnosis and treatment of post-traumatic neuralgia came during World War I and was directly based on the works of Dr. Mitchell [13]. Some of the military surgeons of that time, recognizing the peculiar characteristics of the post-traumatic neuralgias, advocated replacing the term causalgia with “thermalgia” or “reflekschmerz” (reflex pain). They described the associations with glossy skin and hypertrichosis.

In 1916 a French military surgeon, Rene Leriche, noted that the limbs of patients with causalgia showed features that were consistent with
vascular insufficiency and proposed that the pain might be alleviated by sympathectomy [14]. Leriche went on to confirm his hypothesis by relieving arm pain by stripping 12 cm of adventitia from the brachial artery of a patient with causalgia. Based on this experience, Leriche went on to promote resection of the inferior cervical ganglia for the treatment of cardiac angina [15]. Although Leriche later retracted his hypothesis, the sympathetic component became ingrained in concepts of RSD and causalgia for nearly 100 years [1].

In his writings, Leriche noted that one of his formative experiences as a physician came in caring for a patient with causalgia who had attempted suicide several times. Leriche was prescient in his early advocacy of the concept of “pain disorders” that he defined as “certain little-understood conditions whose determinant factors remain unknown but that are frequent and in which pain is the entire, or almost the entire, disorder itself. This pain is so overwhelming that the rest of the symptoms are quite secondary. It is virtually continual or comes in recurrent closely spaced paroxysms or in terrifying bursts of sharp stabbing pain. It is to this type of pain, a disorder in itself rather than a symptom that I am referring. Often it has no specifically determined anatomical cause and it is frequently not transmitted by a lesion affecting an organ. The disorder and its expression are confined within the nervous system. Localized in appearance, it affects virtually the whole individual. Its origins and its apparent causes seem at times to be virtually intrinsic. In fact, everything about it is strictly internal” [15].

**Defining RSD and Causalgia**

Inflammatory causes of RSD and causalgia, an exciting focus of current research (see below), were considered over 100 years ago when these syndromes were classified as “pseudoinflammatory conditions” [16]. This was supported by findings of associated periarticular inflammation [17]. The term “reflex sympathetic dystrophy” was introduced shortly after World War II by Evans [18] to describe a condition similar to causalgia but without major nerve injury. Evans, and many others who followed, strongly felt that this condition was driven by the sympathetic nervous system. In 1986, the International Association for the Study of Pain (IASP) defined RSD as “continuous pain in a portion of an extremity after trauma which may include fracture but does not involve a major nerve.”

**What’s in a Name?**

The growing awareness that many cases of RSD did not have a demonstrable relationship with the sympathetic nervous system led to a revision of the taxonomy [19,20]. In 1994, the terminology was revised and IASP renamed RSD “Complex Regional Pain Syndrome I (CRPS I).” The term causalgia was replaced with “CRPS II.” The IASP’s definition of CRPS I is a “syndrome that usually 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 edema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia.” Type II CRPS is the term used for the painful condition associated with a peripheral nerve injury. The term CRPS is not widely known outside subspecialty circles and many physicians continue to use the terms RSD and causalgia. While these two syndromes are still not defined by concrete clinical criteria, they do have typical clinical characteristics that allow them to be distinguished and clinically diagnosed.
The Epidemiology of CRPS

There are few data on the epidemiology of the CRPS. Factors that confound epidemiologic studies in pain syndromes include difficulty establishing the point of initial onset, differentiating initial episodes from recurrences, and the lack of reliable methods to enable researchers to distinguish between clinically significant and nonsignificant episodes [21]. CRPS I shows a normal age distribution with a peak at 50 years. In most studies, females outnumber males. Both CRPS I and II have been reported with increasing frequency in both children and the elderly [22]. There appears to be a genetic predisposition to developing CRPS in patients who carry the HLA-DQ1 antigen [23]. There have been anecdotal reports suggesting that disuse of an affected extremity per se may contribute to the onset or persistence of these syndromes.

A retrospective study of patients with CRPS followed at a large pain clinic found that patients had seen an average of five physicians and had undergone an average of five different kinds of pain treatment for their pain prior to referral to a pain clinic [24]. The mean duration of CRPS prior to evaluation at the pain center was 30 months. Forty percent of these patients had undergone a bone scan, but only half of these studies had been correctly interpreted as being consistent with CRPS. A large population-based study of CRPS I conducted at Mayo Clinic [25] showed an incidence rate of 5.46 per 100,000 person-years at risk and a period prevalence of 20.57 per 100,000. The female:male ratio was 4:1 with a median age of onset of 46 years. All cases reported an antecedent triggering event, with fracture being the most common (46%). Triple-phase bone scan and autonomic testing diagnosed the condition in over 80% of cases. Seventy-four percent of patients eventually reported resolution that was often spontaneous.

The Clinical Picture of CRPS I (RSD)

In most case series, CRPS I (RSD) is preceded by a noxious event affecting an extremity. Upper extremities are generally twice as likely to be affected as lower extremities. The inciting events can include minor trauma, sprains, bone fractures, surgery (e.g., carpal tunnel, Dupuytren’s contracture), and other lesions such as shoulder trauma, myocardial infarction, or even contralateral stroke [22]. Some studies of CRPS I have reported no identifiable inciting event in up to 35% of cases [26]. Of note, many of the clinical features of CRPS I can be transiently produced in healthy individuals by immobilizing a limb for 1 month [27]. The symptoms of CRPS I are typically disproportionate to the inciting event.

The site of injury on the affected extremity does not determine the location of the symptoms. The signs and symptoms of CRPS I are not confined to the innervation zone of an individual nerve and show a distally generalized distribution [28]. Symptoms are present in tissues that were not affected by the preceding lesion in 95% of patients. In some cases, CRPS I can spread proximally or even involve the entire extremity. A triad of sensory, motor and autonomic symptoms is present in 90% of cases of CRPS I but there appear to be no fixed combinations (see Table 1).

Even before the onset of diagnosable CRPS I, pain is often felt inside the area of the precipitating lesion. With the onset of signs of CRPS I the pain becomes diffuse and deep inside the distal extremity and swelling of the distal limb becomes generalized. By this time, the initial pain may have already disappeared. Spontaneous diffuse pain may not be present with the onset of CRPS I but may appear later. Aggravating factors for symptoms of CRPS I often include physical load, painful stimuli, movement (e.g., physical therapy) environmental or local temperature changes, and increases in hydrostatic pressure (orthostatic changes). The symptom of swelling is usually critically dependent on aggravating stimuli.

Sensory Changes in CRPS I

The sensory changes of CRPS I often have an acute onset. The cardinal symptoms typically

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<tr>
<th>Table 1</th>
<th>Clinical features of CRPS (modified from Schott 1999 [29])</th>
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<tr>
<td>Allodynia</td>
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<td>Altered sweating (absent, excessive, or reduced)</td>
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<td>Atrophy of skin with loss of wrinkles (glossiness of skin)</td>
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<td>Color changes of skin (cyanotic, erythematous, pale, or blotchy)</td>
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<td>Detrusor and urinary sphincter dysfunction</td>
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<td>Dupuytren’s and other contractures</td>
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<td>Hair changes (excessive or reduced growth, and/or fineness instead of coarse)</td>
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<td>Inappropriate warmth or coldness</td>
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<td>Involuntary movements: tremor, dystonia, spasms</td>
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<td>Joint stiffness (acute or chronic arthritic changes)</td>
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<td>Muscle wasting and/or weakness</td>
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<td>Nails (brittle or clubbed; curved, thin, ridged)</td>
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<tr>
<td>Osteoporosis: spotty, localized, or widespread</td>
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<td>Pigmentation changes</td>
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<td>Subcutaneous atrophy or thickening</td>
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<td>Swelling</td>
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occur within hours or days of the injury. At the time of onset, the prominent symptoms are spontaneous pain, generalized swelling, and systematic side differences of skin temperature. These early symptoms often develop in areas and tissues that are not affected by the preceding lesion. Approximately 30% of patients have truly intermittent symptoms [22].

The spontaneous pain in CRPS I is typically described as burning, throbbing, pressing, shooting, or aching. In nearly all cases, the continuous pain is felt deeply inside the distal part of the affected extremity. It always shows a diffuse distribution that is unrelated to territories of individual nerves. The pain typically decreases with elevation of the limb and increases when it is lowered (orthostatic component). Abnormal evoked sensations in CRPS I can include mechanical allodynia in skin; hyperpathia (pain elicited by painful stimuli that appears with a delay, outlasts the stimulus, spreads beyond the area of the stimulus), hyperalgesia (increased response to a stimulus that is normally painful) or hypoalgesia (diminished pain in response to a normally painful stimulus), and hyperesthesia (increased sensitivity to non-noxious stimulation [including touch and thermal sensation without pain]) or hypoesthesia (decreased sensitivity to non-noxious stimulation). All of these sensory abnormalities will have a diffuse distribution with no spatial relationship to the site of precipitating injury or individual nerve territories. These abnormalities are typically more pronounced on the palmar/plantar aspect of the extremity than on the dorsum of the hand or foot. Allodynia is often more prominent at the fingertips and pain is often elicited by movement or pressure at the finger/hand or toe/foot joints.

Autonomic Changes in CRPS I

Autonomic symptoms are common in CRPS I. It is the autonomic changes that give rise to the characteristic appearance of the CRPS patient (see Figure 1). Blood flow to the skin is usually abnormal, with the skin often appearing marbled/reddish or bluish/pale. Most patients with CRPS I have temperature differences of palmar/plantar surfaces, fingertips or toe-tips (warmer or colder). In these cases, all of the fingers or toes in the affected extremity are typically different from their counterparts (average 2.5°C difference). These differences are dynamic, becoming more or less pronounced with changes in ambient temperature. Because of this, it is important to note the ambient temperature when temperature changes in the extremities are assessed. The palmar or plantar aspects of the affected extremities are often hyper- or hypohidrotic. Cutaneous and subcutaneous edema is a common sign of CRPS I. Nearly all patients describe swelling of the distal part of the affected limb that can worsen with stimuli that aggravate the pain. The edema is often accompanied by shiny skin and loss of skin folds [22].

Skeletal Motor Findings in CRPS I

In 90% of cases of CRPS I, active muscular strength of the affected extremity is decreased. This often involves all of the muscles of the distal extremity, especially those involved with hand grip. No abnormalities are found in the tendon reflexes. Complex movements of the affected distal extremity are considerably reduced—in particular the ability to close the fist and to appose the tips of thumb and fifth finger. Tremor (postural or action) is present in about half the patients in the affected extremity. Motor symptoms are more apparent in the upper than lower extremity. In some cases, dystonias can develop in the affected extremity [30]. Impairment of muscle strength appears to be mediated by central motor neurons. Tremor is also centrally mediated.

Trophic Changes in CRPS I

More than 30% of patients with CRPS I have associated trophic skin changes. These include disturbed nail growth, increased or decreased hair growth, palmar/plantar fibrosis, thinned glossy skin, and hyperkeratosis. Skin changes associated with RSD are more diverse than commonly appreciated and can include a wide variety of inflammatory lesions and nonimmune bullous eruptions [31]. Trophic changes are usually not observable in earliest phases of the syndrome.

Joint stiffness is common in CRPS I and may be related to trophic changes in joints or tendons. Over 100 years ago, Sudeck first demonstrated the association between CRPS I and underlying patchy bone demineralization [32]. Plain radiographs often show a diffuse and spotty distal distribution of demineralization of small bones with a periartricular dominance at the longer bones (see Figure 2). These radiologic findings (which are called “Sudeck's dystrophy”) are generally not evident until the syndrome has been established for several months.
In contrast to this, triple-phase bone scanning often shows early changes in bone metabolism in CRPS I with high specificity and sensitivity. The three phases of the uptake of contrast: arterial, soft tissue, and mineral, each shows a characteristic uptake pattern in CRPS I. A diffuse increase in tracer is found in periarticular soft tissue around distal joints on the affected side [33] (see Figure 3). Vasoactive intestinal peptide containing nerve fibers have been found innervating the cortex-periosteum zone, which provides a biochemical basis for regional hyperemia and consequent bone resorption that is observed in CRPS [34]. Nuclear medicine studies show extravasation of plasma into bone [35]. On the basis of his radiologic findings, Sudeck was one of the first to propose an inflammatory etiology for CRPS I. The acute phase has signs and symptoms indicative of inflammation: rubor, calor, dolor, tumor, and functio laesa are present. Moreover, some patients can respond to steroids at this phase [36].

The Clinical Course of CRPS I (RSD)

In CRPS I, the pain expands along the limb or migrates to other body parts in nearly 70% of patients. The pain becomes bilateral producing a “mirror image” of pain in up to 50% of cases [37]. In rare cases, the pain can even encompass the entire body [38,39].

Bonica delineated three stages of CRPS I [40]. The first or acute stage featured pain, edema, warm skin, and increased sweating. The second or dystrophic stage was marked by cold, dry skin, and trophic changes. The third or atrophic stage was marked by atrophied skeletal muscles and bones, joint contractures, progressive loss of function, and persistent pain. Based on this work, Bonica recommended that the treatment of CRPS I begin...
as early as possible. With the new classification of RSD and causalgia as CRPS, the concept of staging is antiquated, realizing that a patient can enter the syndrome anywhere on a continuum—the key point is rapid and aggressive treatment! Trophic changes, hyperalgesia, and diffuse allodynia all appeared to be signs of “permanence,” however.

**CRPS II (Causalgia)**

Complex regional pain syndrome II is, by definition, always preceded by a partial injury to a peripheral nerve or one of its major branches. This syndrome is not always progressive and can persist for years without any clinical changes. The symptoms of CRPS II are generally somewhat less complex than the clinical picture seen in CRPS I. Typical cardinal symptoms are spontaneous burning pain, hyperalgesia, and mechanical and cold allodynia. These symptoms are characteristically most intense in the territory of the affected peripheral nerve and the tendency to spread is less apparent than in CRPS I. The pain may be exacerbated by temperature or movement, stress, or emotional stimuli. Both the spontaneous and evoked components of pain in CRPS II are typically felt superficially and not deep inside the extremity. In contrast to CRPS I, the pain in CRPS II generally does not have an orthostatic component (i.e., no change with elevation or dependence). The spread of sensory, motor, and autonomic into territories outside that of the lesioned nerve is rare in CRPS II.

Complex regional pain syndrome II is characterized by early vasodilatation and late vasoconstriction. This may be due to disruption and then regeneration of sympathetic vasoconstrictor fibers following the injury and subsequent hyper-reactivity of blood vessels to circulating catecholamines, due to “denervation hypersensitivity.” CRPS II usually involves some impairment of motor function. Swelling and dystrophic changes are often present but are more discrete than those seen in CRPS I. Typically, no changes in bone metabolism are evident on radiographs or nuclear medicine studies. Some patients have been described with combined elements of CRPS I and II and some in whom the manifestations of the two syndromes occurred serially [41].

**Parsing the Pain of CRPS**

One of the most important advances in characterizing the CRPS has come with the understanding

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**Figure 2** Demineralization of bone in CRPS. Diminished microcirculation leads to demineralization of bone (trophic change) described by Sudeck. Demineralization begins at the ends of the bones and progresses to become homogenous. This is also known as Sudeck’s dystrophy, Sudeck’s syndrome, Sudeck’s atrophy, Kienböck’s syndrome, Kienböck’s atrophy, Sudeck–Kienböck’s syndrome, Sudeck–Leriche syndrome, Sudeck’s porosis, Kienböck–Meisel disease, Kienböck–Knochenstoffwechsel, Leriche’s syndrome, Sudeck’s post-traumatic syndrome, and Sudeck’s disease among other names.
Figure 3  Triple-phase bone scan in CRPS. The triple-phase bone scan is a nuclear imaging study often utilized as part of the evaluation in CRPS. It is not diagnostic for CRPS as it can be “positive” in other disease states, but can assist in the diagnosis (note: there are no diagnostic tests that are definitive for CRPS). Bone imaging is accomplished by radionuclide scintigraphy after administration of 99m Tc-labeled organic polyphosphates. The osseous accumulation of these radiopharmaceuticals is dependent on bone blood flow and their extraction by the mineral component of bone. Bone tissue is normally in a dynamic state of equilibrium, as it is constantly being broken down and replaced; it is the replacement of bone turnover that is correlated with the uptake of radiopharmaceuticals. After injection, the radiopharmaceutical rapidly equilibrates in the extracellular fluid space; it is cleared simultaneously by renal excretion and bone uptake. Fifty percent of the administered dose is excreted in the urine by 2–4 h after injection. Seventy percent is excreted by 24 h, with the remainder of the radiopharmaceutical remaining in the bone. Bone scintigraphy is routinely performed 2–4 h after injection (this allows for decrease in soft tissue activity). The phases are: Phase I (radionucleotide angiogram)—can show increased or decreased uptake depending on degree of vasoconstriction in the extremity at the time of the examination; Phase II (blood pool), usually with periarticular uptake “hot” zones if syndrome has been associated with long-standing vasoconstriction, and Phase III (delayed bone phase), which periarticular uptake (i.e., “hot” zones), again present if long-standing vasoconstriction. The triple-phase study includes: 1) rapid sequential imaging of vascular filling; 2) immediate static images of regional blood volume; and 3) bone scintigraphy.
that there are different types of pain and that they are often temporally and spatially distinct. The different types of pain probably relate to different mechanisms of illness. In an extremity affected by CRPS I a “zone of primary hyperalgesia” can be identified. This is an area surrounding the tissue injury that shows increased sensitivity to heat and a variety of mechanical and chemical stimuli. This is surrounded by a halo of painful uninjured tissue, “the zone of secondary hyperalgesia.” In this area there is hyperalgesia to mechanical stimuli and often to cold [42].

Several subtypes of mechanical hyperalgesia can be identified in extremities affected with CRPS I [43]. Brush-evoked pain is mediated by A-beta fibers that normally respond to vibration. This can occur in either the primary or secondary zone. Although it is dependent on central plasticity it is maintained by peripheral nociceptor activity. Hyperalgesia to pinprick is mediated by nociceptive C-fibers and A-delta fibers. Hyperalgesia to blunt pressure is generally restricted to the primary zone and is mediated by C-fibers, although it can spread with peripheral recruitment of nociceptors. Hyperalgesia to impact stimuli (e.g., dropping a weight on the area) is also generally found in primary zone. Heightened pain responses to the application of capsaicin or mustard oil are usually characteristic of the primary zone. There are different forms of cold hyperalgesia. In the primary zone it is mediated by C-fibers after central disinhibition and in the secondary zone it is conveyed by specific “cold” receptors. In areas where there is hyperalgesia to cold, mild cooling of the affected area typically elicits burning pain [44].

**Sympathetically Maintained Pain**

Over 100 years ago, the observation that there was an overlap of body regions exhibiting pain and autonomic dysfunction (sweating, temperature, and blood flow abnormalities) led to the hypothesis that chronic pain was a disorder of the sympathetic nervous system [45]. The idea that the pain of the CRPS I and II was driven by the sympathetic nervous system has been one of the most controversial issues in the management of these syndromes. The concept gained adherents over 100 years ago and eventually was incorporated into the name “reflex sympathetic dystrophy.” Recently, the term “sympathetically maintained pain” (SMP) [46] has come into use to describe a group of specific symptoms that may be associated with certain cases of RSD and causalgia but do not constitute a separate clinical entity, or of itself diagnose the syndrome [47]. The types of pains most commonly related to SMP are constant burning pain, touch-evoked allodynia, and cold allodynia. Numbness, dysesthesia, paroxysmal pain, and heat-evoked allodynia are generally not associated with SMP.

Operationally, SMP is defined as pain that is relieved with sympathetic blocks, regional application of guanethidine [48], or intravenous phentolamine [49]. Guanethidine injected intravenously into an extremity affected by SMP initially elicits transient pain generated by norepinephrine release [50]. One group reported the successful treatment of RSD with oral guanethidine [51]. Pain relieved by sympatholytic treatment can often be rekindled when alpha-agonists are locally applied via iontophoresis or subcutaneous injection [52]. An early approach to SMP was surgical resection of sympathetic ganglia. A study showed that pain that was relieved in this manner could be rekindled by stimulating surgically decentralized thoracic sympathetic ganglia [53]. In an animal study of CRPS, sympathectomy not only relieved pain in the affected limb, it also relieved mirror-image pain [54].

**Mechanisms of SMP**

One possible mechanism for SMP depends on changes in primary nocceptors. Under normal circumstances, nociceptors do not generate pain signals in response to sympathetic stimulation or to application of catecholamines. In fact, in the absence of local inflammation, sympathetic outflow suppresses C-nociceptor responses to brief noxious stimuli. This is apparently mediated by beta-2 receptors, which are the main catecholamine receptors expressed by normal C-fibers. Most primary nociceptors can develop heightened sensitivity to catecholamines after an injury [55]. Nerve lesions can also evoke de novo expression of alpha-2 receptors in a subset of dorsal root ganglion (DRG) cells [56].

A neuroinflammatory mechanism for SMP postulates that nerve damage can induce signals transmitted retrograde up sympathetic fibers into the DRG causing activation [57] and proliferation of glial cells [58]. Macrophages are then recruited into the DRG [59]. These glial cells and macrophages release proinflammatory cytokines into the extracellular space of the DRG that stimulate the growth of sympathetic fibers. These sympathetic fibers form basketlike terminals around the satellite cells that surround neuronal cell bodies.
Activation of alpha-2 adrenergic receptors on these sympathetic terminals triggers the synthesis of prostaglandins by the satellite cells. Prostaglandins then sensitize nociceptor terminals that become sensitive to norepinephrine.

Under normal conditions catecholamines are anti-inflammatory in the skin, acting via beta-2 adrenergic receptors on immune cells and inhibiting the production and release of proinflammatory cytokines. These cells do not express alpha-1 receptors under basal conditions. In states of chronic inflammation, however, immune cells downregulate beta receptors and express alpha-1 receptors. With increased expression of alpha-1 receptors on immune-competent cells (e.g., synoviocytes, endothelium, Langerhans, fibroblasts), sympathetic activity promotes sustained inflammation in the skin and soft tissues. Studies show that there is increased alpha-1 expression in skin regions affected by CRPS. This norepinephrine responsiveness generally disappears when the local inflammation resolves.

Some investigators have interpreted the initial increase in local blood flow that is seen in the early stages of CRPS I and II as a sign of reduced sympathetic activity due to the nerve damage that precipitated the syndrome. In that light, SMP may really be an expression of denervation hypersensitivity. In animal experiments, sympathectomy can induce SMP and responsiveness to norepinephrine in intact C-fibers but not A-delta fibers. Over time, after a sympathectomy, more and more C-fibers will acquire noradrenergic reactivity. There is no proof that sympathetic activity per se is increased in patients with CRPS. Denervation hypersensitivity does not explain the hyperhidrosis that is often associated with the early stages of CRPS I and II as sweat glands do not develop denervation supersensitivity. The increased sweating may be generated by an increase in activity of sympathetic sudomotor neurons of central origin.

Sympathetically maintained pain is not specific for CRPS I or II and can be seen in other syndromes. For example, injection of epinephrine around chronic nerve-end neuromas can elicit pain. SMP can also be demonstrated in some cases of herpes zoster, metabolic neuropathies, and phantom limb pain.

These studies have typically been small uncontrolled case series. In one study, surgical sympathectomy gave permanent relief to RSD patients especially if the symptoms had been noted for less than 12 months. A large case series reported data on 73 patients with documented SMP who underwent cervical or lumbar sympathectomy for CRPS I. The investigators reported that 1 year after surgery 25% of patients had significant pain relief and that an additional 50% reported some reduction in their pain. Transient (<3 months) postsurgical sympathalgia developed in 33% of patients who underwent cervical sympathectomy and 20% who underwent lumbar sympathectomy. At 3 months after procedure, 10% of patients reported no reduction in pain or disability and 7% of patients developed new regional pain or sweating disorders. Tasker reviewed outcome data for sympathectomy for CRPS I, however, and found that long-term positive outcomes were poor.

Some recent retrospective studies suggest that sympathetic blocks give “the majority of [CRPS] patients transient or no significant pain relief” [78]. A meta-analysis of trials and case series that involved 1,144 patients showed that the benefit of sympathetic block with local anesthetics was “indistinguishable from that of placebo” [79]. Concerns have been raised that permanent sympatholytic procedures can cause “post-sympathectomy pain syndromes” [80]. Studies with regional intravenous guanethidine show it is no better than placebo [81]. There is a growing impression that there is little evidence that sympatholytic procedures are better than placebo for patients with CRPS I and II. One review of the research concludes that “interrupting the sympathetic nervous system in practice seems futile for obtaining long-term relief of pain in these patients” [82]. One investigator has gone as far as to state that, “it is a lie that sympatholysis may specifically cure patients with unqualified reflex sympathetic dystrophy” [83].

Sympatholytic Treatments for CRPS

Numerous studies have reported clinical benefits of sympatholytic treatments in CRPS I and II. This is What Is in a Name

A major advance in modern pain management is the move from empiric therapies to a mechanism-based approach to treatment. In order to support this, it is vital that physicians make accurate and meaningful diagnoses. The reorganization of the taxonomy of pain has to be seen as an important first step toward designing targeted therapies for the different pain syndromes,
despite the fact that many practitioners are reluctant to accept the loss of familiar names [85]. We have to understand that the traditional anatomical classifications are artificial and of limited diagnostic value and may actually divert our patients from useful treatments.

**Modern Approach to Diagnosis in CRPS**

Modern pain assessment will have to include qualitative and quantitative sensory testing to improve subgroup analysis and support an evidence-based approach to the treatment of CRPS. When faced with a patient with a complex neuropathic pain syndrome, the physician should be asking “which nerve cells and neurochemicals are involved with the pain?” rather than just “where does it hurt?” For starters, peripheral neuropathic pain can be classified as either stimulus-evoked pain or stimulus-independent (spontaneous) pain. The former can be precisely measured by quantitative sensory testing. These tests need to be used, validated, and correlated with responses to treatment.

Once clinically distinct symptoms are delineated, these can be linked to changes in the nervous system that follow peripheral nerve injury. Because most patients with CRPS suffer with a variety of symptoms, it should be possible to identify which neuropathic mechanisms are active in a given individual and to develop a symptom-centered approach to treatment [86]. For example, it is reasonable to think that the treatment for heat-induced hyperalgesia will not be effective for most cases of mechanical allodynia.

There are many useful findings in patients with CRPS I and II that can be precisely assessed and monitored using currently available techniques of quantitative sensory testing [87]. For example, *dynamic mechanical allodynia*, pain elicited by lightly stroking the skin, can be assessed using a brush or tuning fork. *Static allodynia* is a painful response to firm pressure without movement and is measured using a pressure algometer. Other salient endpoints to measure in quantitative sensory testing of patients with CRPS I or II include *mechanical hyperalgesia* (evoked with a pinprick or calibrated stimulator), *mechanical summation* (measured by applying a dynamic stimulus every 2–3 s for three to six times), *heat allodynia, heat hyperalgesia, cold allodynia* (all assessed by gauging the response to measured heating or cooling elements placed on the skin), and *touch sensitivity*.

**Additional Diagnostic Testing in CRPS**

Triple-phase bone scans can demonstrate early changes in bone metabolism in CRPS I with high specificity and sensitivity [88]. Affected extremities show increased uptake of contrast in periarticular areas and specific radiographic findings may relate to prognosis [89]. By using labeled immunoglobulins, scintigraphy can demonstrate intraossary plasma extravasation. Bone scanning should be considered early on in the assessment of an orthopedic injury that has given rise to unusually persistent or intense pain (e.g., an ankle sprain, minor fractures).

Sudomotor function in CRPS can be evaluated through tests of temperature differences between affected and unaffected extremities, unstimulated resting sweat output, and quantitative sudomotor reflex test in which several components of the reflex arc involved in sweating are activated by different stimuli (e.g., acetylcholine, electrical stimulation) [90]. Several brain-imaging modalities may soon become useful in the assessment of CRPS including SPECT scanning that generally shows perfusion changes in the contralateral thalamus in patients with CRPS I [1].

**Diagnostic Tests for SMP**

The tests to assess SMP essentially involve trials of sympatholytic treatment. Sympathetic blocks are performed by injecting local anesthetic medications into the stellate ganglion or lumbar sympathetic ganglia [91]. A complete block has been obtained when the finger- or toe-tip temperature increases to >35°C. Temporary relief of pain indicates that sympathetic activity is involved in the generation of pain. The guanethidine test involves intravenous injection of guanethidine into the affected extremity distal to a supersystolic cuff [92]. The test is positive if the injection is followed by short-lasting burning pain or by a sensation of pressure or heat that has the same distribution as the patient's spontaneous pain. The spontaneous pain is typically relieved after the opening of the cuff 15 min after injection. Guanethidine is first taken up by noradrenergic varicosities of postganglionic axons and depletes norepinephrine from its stores, which leads to excitation of nociceptors. Its second action prevents further release of norepinephrine from the depleted postganglionic axons, conferring pain relief for up to 1 or 2 days.

Phentolamine is a mixed alpha-1 and alpha-2 antagonist that can reduce SMP when adminis-
tered by intravenous infusion [93]. In the “ischemia test” an Esmarch bandage is wrapped around the affected extremity from distal to proximal to reduce the blood volume of distal extremity. A supersystolic cuff is then inflated immediately proximal to the bandage. In SMP, this should suppress or reduce deep pain within 1–2 min [94]. Pain relief in this test apparently predicts the success of sympatholytic interventions. The ischemia test is usually negative in CRPS II and in other forms nonsympathetic neuropathic pain (e.g., diabetic neuropathy). The test may work by decreasing intravascular filling, thus reducing the activity of small-diameter deep somatic afferents.

Etiology of CRPS: Neural Mechanisms

Dysfunction of several types of nerve cells can account for many of the signs and symptoms of CRPS. Nociceptors are peripheral afferent nerves that normally carry pain signals. These include unmyelinated C-fibers and lightly myelinated A-delta fibers. In addition to carrying signals to the spinal cord, these cells are capable of releasing inflammatory mediators into peripheral tissues from their dendritic ends. These include substance P, calcitonin gene-related peptide, and other chemical mediators that can cause capillary leak and activation of inflammatory cells in peripheral tissue triggering a process referred to as neurogenic inflammation.

For most patients, the stimulus-independent burning pain in CRPS I and II is mediated by nociceptive primary afferents. This pain significantly is reduced or abolished by local anesthetic block of the damaged nerves [95]. Some forms of stimulus-induced pain sensations will persist during a differential nerve fiber block that selectively eliminates conduction in myelinated non-nociceptive afferents, also implicating nociceptors in this process [96].

Lesioned afferent axons may generate spontaneous and evoked ectopic impulses that may drive pain and swelling. In one study of patients with mechanical and thermal hyperalgesia, allodynia, and cutaneous vasodilation all had evidence of small-fiber polyneuropathy, which is indicative of a primary dysfunction of nociceptors [97]. Different forms of hyperexcitability were detected by microneurography in both common polymodal and mechanically insensitive C-nociceptors, which can explain many of the somatosensory abnormalities seen in CRPS I and II. Signs of hyperexcitability include reduced receptor threshold (accounting for mechanical and heat alldynias), spontaneous C nociceptor discharge (explaining spontaneous “burning” pain and antidromic vasodilation), and multiplied nociceptor responses to stimulation (accounting for hyperalgesia). The similarity of these findings to the effects of applying capsaicin to the skin and the striking heat dependence of the spontaneous pain suggest that a common feature could be altered expression or modulation of vanilloid-1 receptors provoking abnormal nociceptor discharges.

Localized inflammation of nociceptor axons due to the inciting injury may also play a role in generating the pain associated with CRPS I. In cases where an initial injury is identified, the site is usually reported to be very sore from the outset. If the injury is followed by immobilization this might reduce the tactile inputs to the spinal cord that would otherwise modulate the pain [98]. In an animal model that reflects clinical findings, neuritis at the mid-portion of nociceptor axons can cause distal pain and hyperalgesia [99].

There are several mechanisms by which nociceptors can generate ectopic discharges, thereby signaling pain without the need for a painful stimulus. After nerve injury, afferent fibers can express novel sodium channels that reduce their thresholds for firing [100]. They can also increase their responsiveness to their usual neurotransmitters. For example, the most important chemical trigger for nociceptive firing is bradykinin. Usually only 50% of nonmyelinated cutaneous nociceptors are responsive to bradykinin, but tissue inflammation can induce responsiveness in up to 100%. These inflammatory activators include protons, prostaglandins, and serotonin [101]. The bradykinin receptors induced by inflammation are structurally different and more sensitive than the receptors found in normal nerve cells [102]. Contact with the products of degeneration and demyelination from damaged nerve fibers can also provoke spontaneous activity in intact nociceptors that are running through the same nerve bundle [103].

Disturbance of tactile afferent nerves, which are the large myelinated A-beta fibers that normally carry the sense of touch and vibration, can give rise to some of the sensory abnormalities that are associated with the CRPS. Non-nociceptive afferent inputs from the skin and deep somatic tissues may gain access to the nociceptive system resulting in pain elicited by the stimulation of these non-nociceptive afferents [104]. One mechanism for this is sprouting of nerve endings that can connect
to the “pain-receiving” layers of the dorsal horn of the spinal cord. Allodynia to light touch is probably mediated by mechanoceptors with large myelinated axons that normally encode nonpainful tactile events. This type of pain can be abolished by selectively blocking myelinated fibers in peripheral tissue [105].

Abnormal interactions between nociceptors and tactile fibers can also generate abnormal pain after nerve injury. In many patients, RSD develops after trauma that is comparatively minor and damages only small nerves. Abnormal connections called epbapes may form between the axons of nociceptors and tactile fibers that will cause the nociceptor to fire whenever the tactile fiber is stimulated, thus establishing allodynia. This type of allodynia can also be mediated centrally through re-routing of mechanosensitive A-beta fibers. There must be a role for nociceptive inputs because this symptom can be quickly relieved with nociceptive blocks or transiently worsened with topical application of capsaicin [106].

In addition to nociceptive and tactile afferents, the skin and soft tissues contain thin, afferent fibers that are normally silent. These silent, mechanosensitive fibers can become activated by inflammation and change the transmission characteristics of other peripheral nerves. This is the proposed mechanism for pinprick hyperalgesia, which has a different spatial and temporal profile than brush-evoked pain. In CRPS, pinprick hyperalgesia typically subserves an area is larger than brush-evoked pain and lasts longer after capsaicin is applied [107]. These silent afferents are unmyelinated fibers that are dormant in healthy tissue but respond vigorously when the surrounding tissue is inflamed. They have a delayed onset of activation and will stay activated for hours after the stimulus is removed. These nerve fibers may also mediate hyperalgesia to pressure [108].

Afferent nerve cells in the central nervous system—for example, in the DRG, cord, and brain—also play a role in mediating the pain and other changes seen in CRPS. Sensitization of dorsal horn neurons can lead to hyperalgesia and allodynia [109]. This can turn nonpainful inputs into pain signals. We know that activation of a nociceptor does not always translate into pain as painless stimuli can sometimes trigger nociceptors. For example, polymodal C-fibers (mechano-heat-sensitive units) in humans have firing thresholds at skin temperatures of 41–43°C but the psychophysical heat–pain threshold is higher [110]. Both temporal and spatial summation in a population of nociceptors, which is, in essence, the way that receiving cells in the spinal cord interpret the incoming signals, are important for encoding the magnitude of pain. Hypersensitivity of cells in the DRG or spinal cord can turn nonpainful signals into painful ones. Injured nerves can signal DRG cells to upregulate vanilloid-1 receptor expression that can cause heat hyperalgesia. DRG cells can also release brain-derived neurotrophic factor that phosphorylates spinal n-methyl-D-aspartate (NMDA) receptors causing maintenance of central sensitization. When DRG cells are damaged they can release a factor causing mechanical allodynia (but not thermal allodynia) in undamaged spinal nerves [111].

The Role of Glia in CRPS

The most exciting recent insights into the mechanisms of CRPS relate to the role played by glial cells, a group of non-neural cells that are vital to the maintenance, growth, and repair of the nervous system. There are three major types of glial cells in the central nervous system, astrocytes, microglia, and oligodendrocytes. Astrocytes surround synapses and can sense synaptic activity. They regulate the utilization of neurotransmitters and glucose at the synapse. Microglia are mediators of central nervous system inflammation and are a rich source of proinflammatory cytokines. Oligodendrocytes are myelin-forming cells that ensheath nerve axons.

Each neuronal cell body in the DRG is encapsulated by a layer of glial cells with a basement lamina separating neighboring glially encapsulated neuronal cell bodies [112]. Glial cells regulate neuronal activity in the DRG and the availability of extracellular glutamate, aspartate, and the glutamate-precursor glutamine [113,114]. The glial cells can communicate with each other via gap junctions [115]. They can release proinflammatory cytokines and growth factors when stimulated by peripheral nerve injury. The glia’s ability to respond to neurotransmitters allows them to continuously monitor the physiological integrity of their microenvironment and react rapidly in the event of disturbances.

Injury to the central nervous system often results in the degeneration of neurons and oligodendrocytes [116]. The destruction of oligodendrocytes and the resultant demyelination after trauma both appear to be mediated by the activation of NMDA receptors on these cells [117]. Trauma to neural tissue also causes postlesional
inhibition of oligodendrocyte growth and replication [118].

In contrast, trauma within the nervous systems triggers the growth of astrocytes and microglia in a process termed reactive gliosis, which is analogous to the post-traumatic inflammation seen in peripheral tissues that are subject to injury. Reactive gliosis is a prominent consequence of most pathological processes in the central nervous system and has been associated with the promotion of abnormal pain. The hyperalgesia, the allodynia, and many of the “anatomically impossible” features of CRPS become explicable when seen as part of a neuroinflammatory process mediated by glial cells.

Astrocytes

Astrocytes surround synapses and regulate synaptic activity by adjusting the concentration of neurotransmitters in the synaptic clefts. Under normal conditions, astrocytes remove excess glutamate and aspartate from synaptic spaces and store it. Astrocytes are similar to nerve cells in that they have receptors for neurotransmitters and that they communicate with each other and with neural cells via intercellular gap junctions. In a sense, astrocytes form a second nervous system serving the neural nervous system [119].

One of the most important functions of astrocytes is to integrate neuronal inputs and regulate the neurotransmitters that modulate synaptic sensitivity. Under certain conditions, astrocytes can release their stored neurotransmitters into the synapse, initiating or amplifying a pain signal. Astrocytes have their own α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) and NMDA receptors for glutamate and stimulation of these receptors or sensitization of the cell by prostaglandins will trigger the release of stored neurotransmitters [120].

Astrocytes enwrap pre- and postsynaptic terminals. A single astrocyte can have contact with and be depolarized by multiple neurons [121]. The excitability of astrocytes is mediated by calcium fluxes. Stimulation of astrocytes by glutamate [122], norepinephrine [123], histamine, or other inflammatory mediators can trigger the propagation of a “calcium wave.” Calcium waves can pass between disconnected astrocytes as long as the gap between them does not exceed 120 µm. These gap junctions are regulated by a number of mediators including glutamate, interleukin (IL)-1, and alpha-1 adrenergic agonists [124–128]. These calcium oscillations can be transmitted to distant astrocytes via gap junctions causing distant glial cells to release glutamate and aspartate [129] depolarizing neurons in a different dermatome [130]. This can result in a pain signal that appears to be coming from a nontraumatized area.

Microglia

Microglia mediate the response to injury in the central nervous system as the resident immunocompetent and phagocytic cells. The term “microglia” was coined by Dr. Pio del Rio Hortega in 1919 [131] who found that these cells were of a distinct cell type apart from astrocytes and oligodendrocytes [132]. There was a 20-year period of widespread doubt in the scientific community about the nature and even the existence of microglia in the mid-20th century. Since that time these cells have been found to play important roles in a variety of neurological illnesses including Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis [133].

Microglia, the nervous system’s immune cells, are the most important mediators of central nervous system inflammation and are a rich source of proinflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF). TNF can increase neuronal excitability by inserting into lipid membranes to form a porelike region that becomes a novel voltage-dependent sodium channel [134,135]. TNF can also interact with endogenous sodium and calcium channels on nerve membranes to increase membrane conductance [136,137]. IL-1 and IL-6 can enhance conduction of these ion channels [138–140]. TNF also acts on neuronal TNFR1 receptors to increase exposure of glutamate receptors, thus increasing excitatory synaptic strength. TNF also causes endocytosis of neuronal gamma-aminobutyric acid (GABA) agonist receptors, desensitizing these cells to pain-relieving inputs [141]. In addition TNF also reduces glutamate uptake activity by astrocytes [142].

Interleukin-1 and IL-6 can also cause hyperexcitability of nociceptors and release of inflammatory mediators such as substance P and histamine from immune cells in peripheral tissues. Injection of IL-1 and IL-6 into the limb of an animal can cause patchy osteoporosis much like that seen in CRPS I [143,144]. In addition to cytokines, microglial cells can release short-lived cytotoxic factors such as nitric oxide and superoxide radicals [145].
Chemokines

Components of the nerve cell itself can promote neural inflammation. Strong neuronal activation can release fractaline from the neuron’s external surface [146]. Fractaline is a member of the immune-related family of proinflammatory proteins called chemokines that activate glial cells and other immune cells. Fractaline receptors are expressed by glial cells in the dorsal horn of the spinal cord. Blocking these fractaline receptors can block nerve damage-induced ipsilateral and mirror-image allodynia. Intrathecal injections of fractaline can induce mechanical allodynia. Fractaline cleavage can be induced by glutamate [147]. The finding that fractaline is expressed on neurons and sensory afferents and that its receptor is predominantly expressed on microglia imply that fractaline plays a role in neuron-to-glia communication [148].

Evidence of Neural Inflammation in CRPS

Peripheral nerve lesions can cause activation of mitogen-associated protein kinases (p38 MAPK) in microglia in the spinal cord, leading to the elaboration of inflammatory mediators that sensitize dorsal horn neurons. Activity of dorsal horn neurons, in turn, enhances activation of spinal glia. This positive feedback mechanism can enhance and prolong neuropathic pain even in the absence of ongoing peripheral external stimulation or injury [149]. Abnormal neuronal-glial signaling in neuropathic pain may result in the increased sensitivity to pain that patients with CRPS experience in body regions other than those originally affected by the inciting injury. It may also mediate the “mental fatigue” that affects many patients with chronic pain [150].

Both human and animal studies provide evidence of prolonged localized release of proinflammatory cytokines in body regions affected by CRPS [151]. One study showed that IL-1 and IL-6 (but not TNF) were increased in the spinal fluid of patients with CRPS. Subjects with other forms of chronic pain had normal IL-1 and IL-6 levels, consistent with a pathogenesis of CRPS that is due to central neuroimmune activation [152]. In animal models of CRPS I, blockade of IL-1 [153] or TNF [154] after nerve injury reduces thermal hyperalgesia and mechanical allodynia.

Mirror-Image Pain

One clinical feature of many cases of CRPS I that is relatively specific for this syndrome is “mirror-image pain” [155]. Mirror-image pain arises from the healthy body region contralateral to the actual site of trauma or inflammation. Mirror-image pain is generally characterized as mechanical allodynia [156] and does not involve contralateral nociceptor activity. Rather, it arises from altered spinal processing of incoming sensory information [157].

An animal model for mirror-image allodynia is sciatic inflammatory neuropathy, which develops after microinjection of immune activators around one healthy sciatic nerve at the mid-thigh level in rats. Low-level immune activation produces unilateral ipsilateral allodynia. More intense immune activation produces bilateral allodynia. Allodynia of both sides can be reversed by intrathecal injection of fluorocitrate, a glial metabolic inhibitor. Allodynia and other signs of CRPS I can also be prevented and reversed by intrathecal injection of CNI-1493, an inhibitor of p38 MAPK kinase, or by intrathecal injection of cytokine antagonists specific for IL-1, IL-6, or TNF. These will reverse both the ipsilateral and contralateral allodynia, even if the inflammatory stimulus to the sciatic nerve is maintained.

Animal studies provide important evidence that ipsilateral and mirror-image allodynia are mediated through the actions of glial cells and proinflammatory cytokines. In one study, IL-1 antagonist was able to relieve mirror-image pain that had been established for 2 weeks, suggesting that spinal proinflammatory cytokines not only trigger pathological pain, but that they are critical for its maintenance as well [158]. In a separate study carbenoxolone, a chemical that disrupts gap junctions reversed mirror-image pain in the same animal model of CRPS I [159]. Mirror-image allodynia is not affected by inhibitors to NMDA or dynorphin.

There is, however, a separate syndrome of mirror-image thermal hyperalgesia that is mediated by substance P, NMDA receptors, non-NMDA receptors, and dynorphin [160,161].

Treatment of CRPS

As might be expected from an illness that we still have trouble naming, it has been very difficult to come up with a consensus on how to approach the treatment of CRPS. There are no scientifically well-established treatments for CRPS [162]. Because of the lack of accepted diagnostic criteria and ignorance of precise endpoints (i.e., previous use of staging, and various standards of assessment), different studies of CRPS probably inad-
vertently admix different syndromes. The lack of epidemiologic data makes many clinical studies of CRPS difficult to compare with one another.

Some clinical studies document a greater than 95% spontaneous remission in CRPS I while others document persistent, disabling symptoms despite aggressive treatment [163]. With the growing use of objective indicators, ranging from quantitative sensory testing to cytokine levels, we should soon be able to evaluate and compare various treatments. One way to hasten this would be to establish specialized referral centers for the evaluation and treatment of patients with CRPS analogous to the multidisciplinary research centers dedicated to cancer treatment. Another would be to establish reference labs for specialized laboratory testing. In light of the fact that many patients with severe CRPS do not even get referred to a pain specialist, this appears rather unlikely.

The experience with sympatheolytic procedures in the treatment of CRPS should serve as a cautionary example of how a potentially destructive treatment can become widely accepted based on poorly designed studies. Despite the 90-year legacy of reports in the medical literature promoting sympathectomies for CRPS, we still have no reliable evidence that there is a long-term benefit of these procedures; we are faced with mounting accounts of their harm. This illustrates one feature that CRPS seems to share with other poorly understood chronic pain syndromes (i.e., transformed “migraine” headache, interstitial cystitis); a history of neurodestructive treatments that have been found to make the illness worse. Our growing knowledge of the neurophysiology of pain suggests that most chronic pain is generated by an overexuberant (and probably inflammatory) response to neural injury. This should reinforce our growing understanding that cutting or otherwise injuring nerves might not be part of a useful strategy to limit the nervous system’s reaction to injury.

In 2002, a multidisciplinary panel published a revised consensus statement on the treatment of CRPS promoting “conservative” over “invasive” approaches [164]. Consistent with previous consensus statements [165], this report put physical therapy at the forefront of treatment with the aim of maximizing functional rehabilitation. Physical therapy in CRPS has not been subjected to clinical trial and may not change the overall course of CRPS [166]. Cognitive and behavioral therapies are also strongly advocated. While these are certainly useful for some of the psychological sequelae of chronic pain, such as anxiety and depression, there is no evidence that they influence overall clinical outcomes [167]. While physical and cognitive therapies per se appear to be safe approaches, they could present a risk to patients with rapidly progressive neurological disease if they delay useful medical therapies or facilitate therapeutic nihilism.

A wide variety of medications has been used to treat the pain of CRPS and similar neuropathic pain syndromes. These range from nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and opioid analgesics to drugs aimed at reducing nerve excitability or central hypersensitivity such as anticonvulsants, tricyclic antidepressants, and membrane-stabilizing drugs (reviewed in [162]). While nearly all of these have provided relief to some people with CRPS, none has been accepted as a standard treatment. In addition, there have been many single reports of success with unusual treatments ranging from calcitonin to electroconvulsive therapy that have yet to be replicated [168,169].

Delivering analgesic medications intrathecally (e.g., morphine, baclofen) may increase their effectiveness for the pain of CRPS. Intrathecal delivery can also allow the use of medications that have prohibitive side-effects if delivered in comparable doses by other routes (e.g., clonidine, ziconitide) [170]. One study has suggested that intrathecal baclofen and clonidine may be specifically useful for treating the pain of established CRPS I [171]. Antagonists of neural hypersensitivity such as drugs that antagonize NMDA receptors (e.g., ketamine) or NK-1 receptors (e.g., aprepitant) are currently available and could be adapted for use in CRPS in the near future.

Recent findings on the role of glial cells in the kindling and maintenance of neuropathic pain suggest that the ideal medications for CRPS might target inflammatory cells and their mediators rather than neurons. These could include some of the cytokine antagonists that are currently used in controlling inflammatory illnesses such as rheumatoid arthritis and inflammatory bowel disease. Another pharmaceutical strategy could be to upregulate the production of anti-nociceptive cytokines, such as IL-2 or cytokines that are anti-inflammatory, such as IL-10 that antagonizes the actions of the proinflammatory cytokines. Recent studies show that there are over 20 pharmaceutical agents in current use that trigger increased IL-10 secretion including some of the traditional
“immunosuppressive” drugs that are used to treat chronic inflammatory diseases [172].

**Spinal Cord Stimulation for CRPS**

A moderate numbness eliminates pain. Hippocrates Aphorismes V, 25

Many specialists have regarded pain in and of itself as the prime indication for spinal cord stimulation (SCS) in CRPS. However, restoration and sustainability of blood flow (microcirculation) to the affected end-organ (which in most cases is the extremity) is as important. There are, in fact, reports of CRPS without pain as a presenting symptom, and in these cases, re-establishment of blood flow (and secondarily preservation of muscle and soft tissue), quiescence of tremor, and cessation of mirrored effects are the paramount endpoints of therapy to maximize function.

Spinal cord stimulation is a restorative therapy that currently offers the best chances of obtaining long-term pain relief in CRPS patients with pain that has not responded to physical therapy or analgesic medications [173], while at the same time re-establishing and sustaining blood flow.

One of the main criticisms of the SCS literature has arisen from the possible role of placebo. Because a patient cannot be blinded to SCS, this issue of placebo is used to discount the outcome, despite objective findings being replicated from center to center (i.e., absence of hyperpathia to pinwheel, normalization of capillary filling, normalization and sustainability of temperature over time)—few well-controlled studies have been undertaken to determine the effects of placebo in SCS therapy.

Harke and colleagues recently conducted a prospective study looking at SCS treatment applied to CRPS patients who had SMP (i.e., their pain responded to blockade of sympathetic efferents) [174]. All 29 patients they studied had chronic CRPS (i.e., mean duration of 5.4 years). Sixteen patients had cervical quadripolar arrays, and 13 patients had thoracic quatrapolar arrays; all patients had constant-voltage, fixed-channel system (reference Chapter 3—The Technology: The Anatomy of a Spinal Cord and Nerve Root Stimulator: The Lead and the Power Source). Patients were followed for changes in visual analog scale (VAS) for deep pain and allodynia as well as for changes in Pain Disability Index to quantify impairments to activities in daily living, and for reduction in pain medications (including opioids). Despite the simplicity of the electrode array used and the older technology employed, all of the patients had complete ablation of allodynia when examined at 12 months; 70% showed >50% reduction in Pain Disability Index scoring and 58.6% stopped all pain medications. It is important to point out, however, that 55.2% needed replacement of their battery sources secondary to exhaustion (it should be noted that devices exist that are rechargeable for both constant-voltage and constant-current systems). An additional 41.4% underwent surgical revision of the lead (the authors did not specify whether these were cervical or thoracic) secondary to uncomfortable stimulation. It should be noted, however, that Harke and colleagues did not place the electrodes over the dorsal columns, but in the lateral aspects of the canal (their rationale was to conserve energy), which may, in part, have led to dysesthesias by recruitment of the nerve root. Even with the complications encountered, the effectiveness of SCS in CRPS of SMP type is impressive. This study is added to a recent survey by Bennett and Cameron.

In 1999 Oakley and Weiner reported on 19 patients prospectively [178]. Sixteen were available at follow-up; 11 were still utilizing their devices (2 patients had stopped using the system reporting “no pain”; 1 died unrelated to the device), 2 were unresponsive to therapy. Eight of the 11 patients obtained at least 50% pain relief. There was a significant change in the VAS score from pre- to
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<td>&gt;5 mm reduction VAS (deep pain); allodynia was abolished ($P &lt; 0.01$). Back to work rate was 70% with Pain Disability Index scores decreasing &gt;50% ($P &lt; 0.01$). 58.6% stopped all pain medications after SCS therapy</td>
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<td>Prospective studies with no controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calvillo et al. 1998 [176]</td>
<td>Upper extremity CRPS</td>
<td>31</td>
<td>36 months</td>
<td>Y</td>
<td>Changes in VAS scores, analgesic consumption</td>
<td>VAS statistically significant improvements ($P &lt; 0.0001$); 44.4% reduced narcotic use by 50%</td>
</tr>
<tr>
<td>Ebel et al. 2000 [177]</td>
<td>CRPS I (N = 1) and II (N = 1), phantom limb</td>
<td>3 (2)</td>
<td>36 months</td>
<td>Y</td>
<td>Changes in VAS scores, analgesic consumption</td>
<td>100% success, &lt;50% reduction in VAS, no analgesics required</td>
</tr>
<tr>
<td>Oakley and Weiner 1999 [178]</td>
<td>CRPS</td>
<td>16</td>
<td>7.9 months</td>
<td>Y</td>
<td>Changes in VAS scores; overall benefit (4-point scale)</td>
<td>80% success (overall benefit); VAS statistically significant improvements ($P &lt; 0.05$)</td>
</tr>
<tr>
<td>Retrospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barolat et al. 1989 [179]</td>
<td>RSD</td>
<td>15</td>
<td>14 months</td>
<td>Y</td>
<td>Benefit (4-point scale: none, minimal, moderate, good)</td>
<td>73% success</td>
</tr>
<tr>
<td>Studies</td>
<td>Patient diagnosis</td>
<td>Implantated patient No.</td>
<td>Mean follow-up</td>
<td>Complications listed</td>
<td>Success outcomes</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------------------</td>
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<td>----------------------------------------------</td>
</tr>
<tr>
<td>Bennett et al. 1999 [180]</td>
<td>CRPS I (RSD)</td>
<td>101</td>
<td>18.7/23.5 months</td>
<td>Y</td>
<td>Changes in VAS scores; overall satisfaction</td>
<td>70% quadrupolar/91% octopolar success; VAS improved significant to baseline ($P &lt; 0.0001$)</td>
</tr>
<tr>
<td>Broseta et al. 1982 [181]</td>
<td>Causalgia</td>
<td>11</td>
<td>13 months</td>
<td>Y</td>
<td>Four categories: excellent, good, fair, and poor</td>
<td>72% had excellent or good results</td>
</tr>
<tr>
<td>Devulder et al. 1990 [182]</td>
<td>Phantom limb pain, failed back surgery (FBSS), polyneuropathy causalgia</td>
<td>45 (6)</td>
<td>Not available</td>
<td>Y</td>
<td>Four-point pain scale</td>
<td>83% had good pain relief, no narcotic analgesics</td>
</tr>
<tr>
<td>Hassenbusch et al. 1995 [183]</td>
<td>Intractable low back and leg pain, RSD</td>
<td>42 (9)</td>
<td>25 months</td>
<td>Y</td>
<td>Changes in VDS scores and &gt;50% reduction in pain (3-point scale)</td>
<td>VDS statistical significance from baseline $P &lt; 0.001$; 67% patients had &gt;50% pain relief</td>
</tr>
<tr>
<td>Kemler et al. 1999 [184]</td>
<td>CRPS I (RSD)</td>
<td>18</td>
<td>32 months</td>
<td>Y</td>
<td>Changes in VAS scores and global perceived effect (GPE)</td>
<td>VAS statistical significant improvement from baseline $P &lt; 0.001$; 72% success GPE</td>
</tr>
<tr>
<td>Kumar et al. 1998 [185]</td>
<td>FBSS, peripheral vascular disease, peripheral neuropathy, RSD</td>
<td>189 (13)</td>
<td>66 months</td>
<td>Y</td>
<td>Three-point pain scale</td>
<td>100% had &gt;50% reduction in pain</td>
</tr>
<tr>
<td>Robaina et al. 1989 [186]</td>
<td>RSD</td>
<td>6</td>
<td>23 months</td>
<td>Y</td>
<td>Four-point pain scale</td>
<td>100% had &gt;50% reduction in pain</td>
</tr>
<tr>
<td>Robaina et al. 1989 [187]</td>
<td>Raynaud's syndrome, RSD</td>
<td>11 (8)</td>
<td>27 months</td>
<td>Y</td>
<td>Four-point pain scale</td>
<td>87.5% had &gt;50% reduction in pain</td>
</tr>
<tr>
<td>Sanchez-Ledesma et al. 1989 [188]</td>
<td>Phantom limb pain, postherpetic neuralgia, RSD, Causalgia, stump pain</td>
<td>36 (8/11)</td>
<td>66 months</td>
<td>Y</td>
<td>Four-point pain scale</td>
<td>100% had &gt;50% long-term pain relief, 80% reduced narcotic use</td>
</tr>
</tbody>
</table>

* Studies were included in the survey if they satisfied all of the following criteria: patients were diagnosed as having CRPS; means, percentages, or statistics were available; the effectiveness of SCS was being studied; pain measurements such as the VAS were used as outcomes; and the number of patients studied were listed. Sixteen articles, involving 560 patients, were identified that met the inclusion criteria. These articles were subdivided into three groups that included prospective, randomized, controlled or prospective controlled studies ($N = 2$), prospective studies with no controls ($N = 3$), and retrospective studies ($N = 11$).  
† Incomplete.
postimplant ($P < 0.05$). Complications identified were minor and corrected without adverse effect on stimulation parameters or efficacy.

Kemler and coworkers used a prospective, randomized trial design to examine the effects of SCS on a group of 24 patients diagnosed with RSD [175]. These patients were selected from an initial cohort of 36 patients by trial stimulation, from a group with significant disabilities (10 required wheelchairs, 8 crutches, 13 splints)—this was necessitated secondary to the restrictions placed on the researchers within their system of medicine in The Netherlands.

Patients were included in this study if the disease had lasted for at least six months, affected the entire hand or foot, or if symptoms were restricted to one hand or foot. Patients had also not shown a sustained response to medical or psychological therapies and had a mean pain intensity of at least 5 cm on a 10 cm VAS. The 24 patients were provided with SCS and physical therapy; the control group consisted of 18 patients and was provided with physical therapy only. Outcome measures included: quality of life measurements: the Nottingham Health Profile and Sickness Impact Profile (short version), and pain measurements: VAS and McGill pain questionnaire. Patients were assessed at 1, 3, and 6 months. Data were analyzed on an intention-to-treat basis. At 6 months, the results indicated a significant improvement in the group ($N = 36$) assigned to receive SCS and physical therapy ($P < 0.0001$; mean reduction of pain intensity on VAS = 2.4 cm) compared with the group that received physical therapy alone (mean reduction 0.2 cm). The average reduction for the 24 subjects actually treated with SCS was 3.6 cm.

A significant improvement in the pain component of the Nottingham Health Profile ($P = 0.02$) was also reported in the 24 subjects who were treated with SCS alone. These positive results were demonstrated despite a surgical complication rate of 25% (significantly outlying from reported norms when compared with the literature; see Table 3) (five patients = unsatisfactory positioning of the electrode). Kemler and colleagues concluded that there is a beneficial effect of stimulation in CRPS.

Bennett and Cameron point out [189]:

A criticism of Kemler’s study has been that because all the patients that were selected had previously failed physical therapy, the control group was not given a true alternative therapy. Any permanent deficits secondary to structural surgeries in this patient population (that would preclude functional recovery) were not defined; such deficits would not be expected to respond to SCS. Kemler and his group did propose that better results would have been obtained if optimal lead (i.e., percutaneous vs. paddle, based on anatomy) had been employed at the outset and if multiple stimulation programs had been available (as has been shown retrospectively to be optimal). Nonetheless, Kemler’s study did show that SCS produced improvement in a group of patients where nothing else was effective in reducing pain (39% “much improved” in the global perceived effect with SCS and physical therapy vs. 6% with physical therapy alone); it is logical to predict that in a more favorable group of patients, results would indeed be better.

Calvillo’s group examined 31 patients with CRPS affecting the upper extremity and found a significant ($P < 0.0001$) reduction in VAS scores with SCS compared with baseline [176]. Ebel and colleagues examined the effects of SCS on deafferentation pain syndromes due to peripheral nerve lesions [177]. Three patients, diagnosed with

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of events</th>
<th>Total number of patients</th>
<th>Rate of occurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>531</td>
<td>0.2</td>
</tr>
<tr>
<td>Battery failure</td>
<td>15</td>
<td>460</td>
<td>3.3</td>
</tr>
<tr>
<td>Cerebrospinal fluid leak</td>
<td>4</td>
<td>537</td>
<td>0.7</td>
</tr>
<tr>
<td>Epidural hemorrhage</td>
<td>0</td>
<td>531</td>
<td>0.0*</td>
</tr>
<tr>
<td>Hardware malfunction</td>
<td>11</td>
<td>531</td>
<td>2.1</td>
</tr>
<tr>
<td>Hematoma</td>
<td>2</td>
<td>531</td>
<td>0.4</td>
</tr>
<tr>
<td>Infection</td>
<td>20</td>
<td>531</td>
<td>3.7</td>
</tr>
<tr>
<td>Intermittent stimulation</td>
<td>0</td>
<td>531</td>
<td>0.0</td>
</tr>
<tr>
<td>Lead breakage</td>
<td>17</td>
<td>531</td>
<td>3.2</td>
</tr>
<tr>
<td>Lead migration</td>
<td>97</td>
<td>531</td>
<td>18.0</td>
</tr>
<tr>
<td>Loose connection</td>
<td>8</td>
<td>531</td>
<td>1.5</td>
</tr>
<tr>
<td>Pain over implant</td>
<td>5</td>
<td>531</td>
<td>1.0</td>
</tr>
<tr>
<td>Paralysis</td>
<td>0</td>
<td>531</td>
<td>0.0*</td>
</tr>
<tr>
<td>Seroma</td>
<td>0</td>
<td>531</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin erosion</td>
<td>2</td>
<td>531</td>
<td>0.4</td>
</tr>
<tr>
<td>Undesirable stimulation</td>
<td>13</td>
<td>531</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>531</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* Although no studies in this series reported epidural hematoma or paralysis, it should be noted that the risk for both of these complications exists with the modality.
phantom limb pain, causalgia, and RSD, respectively, were treated with SCS and all three responded positively. The patient with causalgia had a 90% improvement in their VAS score while the patient with RSD had a 70% improvement.

The majority of the published studies are retrospective (Table 2). The overall success rate for patients diagnosed with causalgia, now classified as CRPS type II, was 79% (23/29), while the overall success rate for those patients diagnosed with RSD, now classified as CRPS type I, was 82% (148/180).

Causalgia, now classified as CRPS type II, has been thought to be an indication for SCS for many years. Few studies were found in the survey that examined SCS specifically for this condition. In 1990, Devulder et al. examined the effects of SCS on 45 patients with various chronic pain syndromes [182]. Six of these individuals were identified as having pain due to causalgia. Devulder et al. measured pain relief using a four-point scale: (A) good pain relief, no need for medications; (B) good pain relief, need for non-narcotic analgesics; (C) little pain relief, need for narcotic analgesics; and (D) no longer used the stimulator. At follow-up 83% of patients diagnosed with causalgia were in (A), with good pain relief. These were considered successes without narcotic analgesics.

Broseta and colleagues reported on 11 patients with causalgia with average follow-up of 13 months [181]. Sixty-four percent of the patients reported greater than 75% reduction in pain with only light analgesics—this same group was able to return to work. Finally Sanchez-Ledesma and colleagues reported on 8 people with RSD and 11 with causalgia [188]. With a mean follow-up of 5.5 years, all subjects reported greater than 50% reduction in pain with SCS; 90% of the causalgia patients and 88% of the RSD patients required no analgesics and were able to return to work and an active life.

As found with CRPS II, there is a significantly positive experience reflected in retrospective studies regarding SCS in CRPS I. Kumar and colleagues reported on a 15-year experience of SCS for the treatment of chronic pain (N = 235 of which 189 were successes at trial and permanently implanted with either implantable pulse generator (IPG) or radiofrequency (RF) systems; subjects were examined [mean 66 months]) [183]. Thirteen patients were diagnosed as having RSD; all were found to have long-term satisfactory pain relief (mean 40 months). Barolat reported on 18 patients with RSD; 3 did not experience relief during the trial and were not implanted—the remaining 15 patients underwent internalization with RF or IPG SCS systems [179]. At a follow-up of 14 months, 11 patients (73%) were classified as successes. Barolat et al.'s numbers correspond with Kemler et al.'s: 13 (72%) responded favorably to stimulation, with a significant (P < 0.001) reduction in pain scores (VAS) compared with baseline [184].

In 1989, Robaina's group reported their experience with SCS in treating RSD in two separate articles [186,187]. Their first article described a retrospective examination of the clinical effectiveness of transcutaneous electrical nerve stimulation (TENS) and SCS for the treatment of RSD. Patients were followed for periods of 10–36 months (mean = 23 months). Of the six patients implanted all reported a greater than 50% decrease in pain. In their second article they extended the study of the clinical effectiveness of SCS to eight patients with RSD and three with severe Raynaud's disease of the upper limbs, followed for a mean of 27 months. Of the eight with RSD who were implanted, seven reported a greater than 50% decrease pain.

Hassenbusch and colleagues analyzed patients with intractable midline lower back and unilateral or bilateral leg pain treated with either spinal infusion or SCS [183]. A multidisciplinary group (anesthesiology, neurosurgery, psychiatry, rehabilitation, nursing, orthopedics, etc.) assessed all patients. In nine patients with SCS, the leg pain was attributed to RSD. At the last follow-up, six of nine were found to have greater than 50% pain relief.

Bennett et al. conducted a retrospective study examining the current trends in the use of SCS to treat CRPS I [180]. This study examined the reduction of pain correlating this outcome with the type of stimulation hardware used, setting it apart from the other studies of SCS for CRPS. The study specifically looked for any similarities in patients who were successfully treated with SCS, comparing the results of using single-lead, four-electrode (quadripolar) systems (with an internal battery) (see Figure 4) with those using dual-lead, eight-electrode (octapolar) systems (which at that time required a radiofrequency unit) (see Figure 5). Data were compiled on 101 patients, all meeting the criteria for CRPS I as accepted in the IASP consensus statement [190], and having similar psychological (psychometric testing) findings. Successful outcome was determined by a reduction in the VAS score and by patient satisfaction scoring.
Patients were divided into two groups: those that had single-lead quadripolar systems (N = 30), and those that had dual-lead octapolar systems (N = 71). Each group displayed a significant reduction in VAS pain intensity scores when compared with baseline (P < 0.0001). The overall satisfaction for the group with quadripolar leads was 70%, while those with dual-octapolar leads was 91%. Analysis of variance for improvement in pain score showed a significantly greater improvement (F-value 56.081, P < 0.0001) with dual-octapolar leads. There was a mean pain improvement (ΔVAS) in the quadripolar group of 3.70 ± 0.79; mean pain improvement in the dual-octapolar group was 6.00 ± 1.59.

A significant difference between the two groups was the ability to regain pain control after spontaneous lead movement. In the quadripolar group four patients (3.3%) required surgical revision due to spontaneous lead migration; in the dual-octapolar group no patients required surgical revision due to spontaneous lead migration. The larger number of electrodes available for programming in the dual-octapolar group allowed an increased flexibility when rostral-caudal changes in positioning occurred; patients who experienced movement of their leads were able to recapture their pain coverage with reprogramming alone. This is a significant finding, as further operative intervention was unnecessary.

An unexpected finding of the study was that the dual-octapolar group was also able to use higher frequencies (above 250 Hz) to “recapture” pain control; a subset of patients who had lost pain control in the presence of adequate paresthesia coverage (15.5%) were able to regain control when their stimulation frequency was increased above 250 Hz (mean 455 ± 104.5 Hz). A report by Alo et al. supported this finding by demonstrating an increase in efficacy with the use of frequencies greater than 300 Hz [191]. This 15.5% would have been “failures of stimulation” had a high frequency capability not been available in their system. In addition to the use of higher frequencies, the technology available to the dual-octapolar group allowed the use of multiple programs. This
was considered to be an important factor in the superior outcome in this group. We found that the overall reductions in VAS scores of the dual-octapolar group were comparable with data published by Alo et al. in his prospective study of 80 patients treated with dual-octapolar systems, which included 22 with CRPS [192,193]. The dual-octapolar group in our study used multiple arrays 74.8% of the time to maximize paresthesia coverage, and needed frequencies above 250 Hz 15.5% of the time to maintain pain control. Although both groups reflected statistically significant improvements in pain scores and overall satisfaction when compared with baseline, the dual-octapolar group showed greater improvements. With the use of frequencies greater than 250 Hz, patients were able to regain lost pain control. The percentage of patients that we found benefiting from higher frequencies is similar to that of patients who recently reported paresthesia without pain relief [194].

The current literature suggests a significant benefit in the use of SCS to treat pain due to CRPS I and II when compared with other treatment modalities. Furthermore, there is a low incidence of serious complications (Table 3). Unfortunately, there is a lack of well-controlled studies in this area, which is true, for the most part, of CRPS in general.

Kemler was the only study that compared SCS treatment to a control group, and this study used a control group that was biased toward no improvement as they had previously failed all conservative therapy. All other studies for SCS and CRPS compared outcomes with baseline measurements. Harke is the only prospective study showing ablation of the allodynia, significant diminution in the deep pain, marked improvement in daily living activities, and significant reduction or ablation in the use of pain medications with the application of SCS. That any study showed improvement is extremely encouraging as SCS has been routinely offered as a “last resort” treatment in previous “treatment continuum” thinking, being placed after all more “conservative” treatments have failed (it should be noted that this line of thought has permeated the literature but has no basis in prospective, carefully constructed studies).

Most studies have reported results using stimulation systems with limited capabilities (few electrode contacts and limited output parameters). Recent studies are showing that for the CRPS population a more complex, technically advanced system may be optimal [180,195]. In a recent case series of CRPS I patients using a system delivering a multiple independent constant-current, with electrical field-steering capabilities (the ability to control each electrode’s settings separately and independently [regulating pulse width, amplitude, and frequency]) of other electrodes, Hagen et al. found a consistent ability to capture and maintain paresthesia coverage of all four extremities [195]. They further found that frequency was low (mean 45 ± 5) that appeared to be unique to a multiple independent constant-current, electrical field-steering system, although this phenomenon is now under formal study using a prospective design.

Thus, a more aggressive treatment strategy, which places neuromodulation therapies early on in the treatment progression and the use of more advanced SCS configurations, may prove to be more effective in the two ultimate treatment goals: 1) significant maintained reduction of pain; and 2) significant maintained normalization of blood flow.

The Treatment Paradigm for CRPS and the Role of SCS

In 2003, Bennett proposed a modification to the 2002 consensus statement (and resultant treatment continuum) with a treatment paradigm that realized that rapid treatment that promoted significant and sustained pain relief and, at the same time, produced significant and sustained blood flow was necessary. Knowing the limitations of current medical, psychological, injection, and physical medicine therapies (along with the emerging animal data of stimulation of central/peripheral nerve structures and neuropathic pain and data from SCS and peripheral nerve stimulation and CRPS), he proposed a time-limited course of “traditional” therapy prior to the initiation of electrical neuromodulation. With this, it is hoped that further study in application of electrical neuromodulation as the initial therapy would be performed prospectively. Figure 6 is the treatment paradigm for CRPS, noting slight modifications that reflect a preference for electrical neuromodulation over invasive chemical neuromodulation (intrathecal devices).

There is a need for structured clinical studies comparing early intervention with SCS versus late intervention with SCS, prospective studies comparing electrode arrays against pain patterns with an analysis of programming parameters between the different types of systems (i.e., constant-voltage vs constant-current and electrical field-steering vs fixed-channel). Further complicating
Assess for axis I disorders
· Pain-coping skills
· Biofeedback/relaxation
· Imagery
· Hypnosis
· Relaxation
· Cognitive/behavioral therapy for treatment of axis I disorders and in prevention of overriding depression/anxiety resulting from severe chronic pain
· Expectations
· Motivation control
· Family assistance

If overriding cognitive behavioral issues present then INCREASE frequency of therapy

Adjuvant Therapies
· Acupuncture
· Herbal therapy

1-3 MONTHS

Physical Therapies
· Gentle reactivation
· Desensitization
· Isometrics
· Flexibility
· Edema control
· Peripheral E-Stim
· Treat secondary MFP
· ROM (gentle)
· Stress loading
· Isotonic strengthening
· Aerobic conditioning
· Postural normalization
· Ergonomics
· Movement therapies
· Normalization of use
· Vocational/functional rehabilitation

Medication Management
· NSAIDs
· Tricyclics
· GABA agonists
· A2-agonists
· NMDA antagonists
· Na+ channel blockers
· Opioids
· SSRI/SSNRI
· Other antidepressants

Invasive Techniques
· Peripheral nerve blockade
· DRG blockade
· Sympathetic ganglion blockade
· Epidural blockade

Series of blockade should be limited to pain control for functional return

FAILURE TO PROGRESS

NEUROMODULATION MODALITIES

ELECTRICAL
· Nerve root stimulation
· Spinal cord stimulation
· Peripheral nerve stimulation

CHEMICAL
· Intrathecal pump
· Programmable
· Constant flow

FAILURE TO PROGRESS

LONG-TERM DISABILITY MANAGEMENT

Physiical Therapy
Psychotherapy
Pain Control
Consider neurodestructive modalities if SMP
Ganglionectomy, RF sympathectomy, surgical sympathectomy IF pain has seriously affected ability to perform ADLs
this is the need to better define the study groups; in particular, by given behavioral or cognitive subtype (i.e., comparison of individuals can only be performed once they are stratified as similar psychologically).

It is rational to treat patients who present with CRPS using a multimodal approach. What has not been given competing credence in consensus statements is the place of electrical (and chemical) neuromodulation therapies in CRPS. While other therapies have been proposed as “more conservative” and therefore “initial” therapies, this rationale is not supported with favorable long-term outcome data (i.e., a change in the course of the condition or significant long-term diminution of pain and sequelae of the syndrome). Thus, a time-oriented construct, which relies on the concept that timely reduction of pain with normalization of blood flow should provide the best environment for functional recovery, is proposed.

**Cost versus Benefit of SCS in CRPS**

Kemler and Furnee looked at the economics of “conventional” treatment versus SCS for the treatment of CRPS [196]. They found that during the first year of therapy SCS was higher in cost than non-SCS therapy. However, in the lifetime analysis SCS was more effective than conventional therapy and was less expensive. The findings of Kemler and Furnee are similar to a recent study by Kumar and colleagues that compared conventional chronic pain therapies versus SCS in 104 patients with “Failed Back Surgery Syndrome” (another complex symptom entity) [197]. Treatment costs with SCS were higher for the first 2.5 years; thereafter they were approximately one third lower; 15% of the SCS-treated group returned to work.

**Conclusion**

The CRPS are neurological illnesses with distinct measurable sensory, motor, and autonomic components that probably relate to abnormal reactions to neural injury. Some of the anatomically “impossible” findings that are commonly associated with these syndromes can be explained by recent research discoveries concerning the role of glia in mediating the nervous system’s reaction to injury. As we progress in defining these syndromes by their neurological mechanisms, we should be able to develop better means of diagnosis and assessment. Although no one modality of therapy has been proven to be totally effective for CRPS, studies of SCS show that it holds the greatest promise, thus far, as a safe and effective treatment. To those that do not respond to a coordinated interdisciplinary effort in the first several months, this therapy should seriously be considered.

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