*Review Article*

# Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy Syndrome): Diagnosis and Therapy—A Review of 824 Patients

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The records of 824 complex regional pain syndrome (CRPS) patients referred in January 1991 to January 1996 are reviewed in this article, and the diagnostic and therapeutic approaches are compared with studies reported in the medical literature. At least two follow-up visits were required to enable a patient to be included in the study. Problems of terminology and over- and underdiagnosis are discussed.

## Background

Complex regional pain syndrome [1], or reflex sympathetic dystrophy, is a complex form of neuropathic pain associated with hyperpathia, neurovascular instability [2], neuroinflammation [3,4], and limbic system dysfunction [5]. It is triggered by stimulation of neurovascular thermoreceptor C fibers sensitized to norepinephrine [6–9]. This afferent sensory impulse leads to CRPS [10–12]. The syndrome involves extremities, head, back [13–15], shoulder [16], and breast [17], as well as viscera [13,18].

The neurovascular dysfunction [2] of CRPS separates this condition from the somatic (unrelated to the sympathetic) system [19,20] pain syndromes. The standard somatic pain is a circumscribed, focalized pain sensation usually not accompanied by neurovascular dysfunction. It does not generate an inflammatory response. In somatic pain, the involved larger myelinated nerve fibers (somatosensory nerve fibers) can be easily detected and studied by nerve-conduction studies. This is in contrast to CRPS [1] pain, which is a disturbance of microcirculation generated by small C fibers in the wall of arterioles [6,19,20], which are not large enough in size to be detected by nerve conduction studies. The afferent somatic (somatosensory) pain fibers terminate in the contralateral parietal sensory neocortex, providing concise and focalized sensation. In contrast, the neuropathic pain of CRPS is regional, and its polysynaptic sensory fibers terminate bilaterally in the limbic system [21]. This explains the

symptoms of insomnia, agitation, irritability and depression in CRPS [5] (Fig. 1).

The disease affects both young and old. It is as common in children as adults [22], usually with good prognosis; but it is not usually diagnosed in time [22–26], if at all.

## Etiology

Complex regional pain syndrome has a long list of etiologies, including trauma. The trauma is usually minor [1,27, 28]. Major trauma is more likely to stimulate somatic (nonsympathetic) nerves, which tend to overshadow the sympathetic type of pain [29], reducing the likelihood of development of CRPS [30]. Certain traumatic events are more common originators of CRPS: repetitive stress injury [31]; an unexpected injury such as stepping off a curb or missing a step; and an injury to the dorsum of the hand or foot [29,32] are some frequent causes.

Selective damage to the unmyelinated C-fiber sensory nerves [6–9] in the wall of the blood vessels may occasionally lead to CRPS in the absence of any major traumatic event. For clinical examples, among our 824 consecutive CRPS patients, the following cases due to microvascular nerve dysfunction were identified: lipid metabolism disturbance in the wall of the arterioles (Fabré Disease), four patients; minor injury to the small blood vessels due to hypermobility of the joints (Ehrler Danlos Syndrome), two patients; electrical injury with passage of electricity through the path of least resistance (arterioles) [33–35] 63 patients; venipuncture CRPS [36–42] due to the rare complication of needle insertion's causing selective damage to unmyelinated small C-fiber nerves in the wall of the venules [6], 17 patients. This selective injury to C-fibers in the absence of simultaneous trauma to the myelinated somatic nerve fibers, leaves the smaller C-fibers uninhibited [19,20], leading to a more severe CRPS [43]. Trauma to the perivascular C-fibers leads to their supersensitization to systemic and circulatory norepinephrine, increasing the C-fibers firing and sensitization of spinal cord [7–9,44].

Due to a fluctuating clinical picture, careful history taking helps identify the warning signs. Complex regional pain

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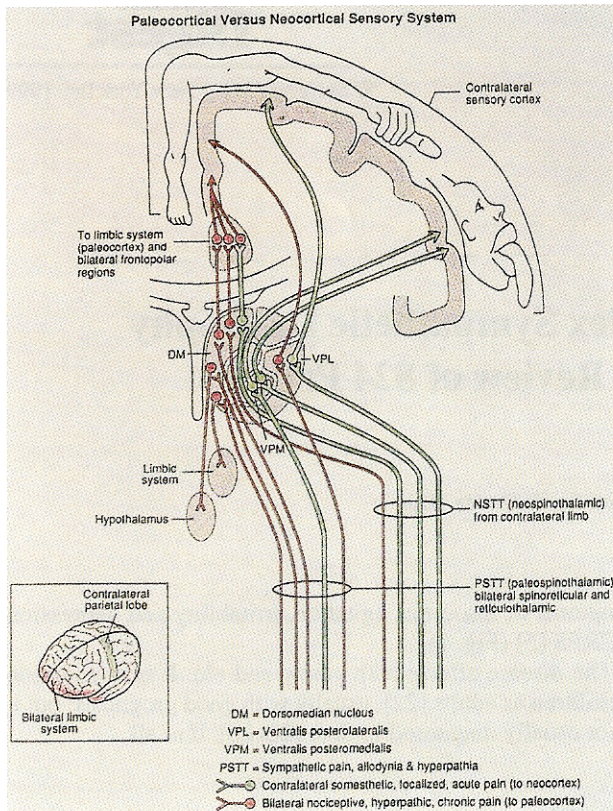[2]E-mail: MHashmi@Pol.net

**Fig. 1.** The afferent somatosensory nerves terminate in the contralateral parietal somatosensory cortex. In contrast, the unmyelinated C-fiber thermosensory nerves through synaptic relays terminate in bilaterally in limbic frontal temporale regions responsible for mood, memory and judgment. This explains the emotional disturbance, and insomnia in CRPS. With permission from CRC Press Publishers [29].

syndrome should be considered whenever a patient is having an unusual problem with excruciating pain, stiffness and inflammation following a minor trauma [16,29]. Instantaneous, severe edema immediately following a minor trauma, in absence of bone, tendon, or ligament injury, is a strong warning sign of onset of CRPS [29]. When the trauma of surgery [45–49], arthroscopy, or application of a cast to an extremity causes acute edema and circulatory disturbance, the diagnosis of CRPS should be considered [16,29]. Persistent pain and swelling of unexplained origin, aggravated by bed rest or on arousal are highly suspicious of CRPS.

Asymmetrical excessive sweating (hyperhydrosis) in a painful extremity is a major warning sign. Other warning signs are the development of hyperpathia and allodynia after ostomy at the elbow, rib, or foot (bunionectomy).

## Terminology

The complex clinical picture of reflex sympathetic dystrophy has eluded simple terminology. Even at the present time, the mere existence of the disease has been denied [50] by those who do not understand it. This flies in the face of documented peripheral and CNS dysfunctions [51] of the disease. Mitchell first labeled the syndrome as *erythromelalgia* and later as *causalgia* [32]. Sudeck reported atrophy [52] and inflammation [3]. The sympathetic role in the development of causalgia was first reported by LeRiche in 1916, who did the first sympathectomy [53]. Other names [34,54–73] have included *trophoneurosis, traumatic angiospasm, traumatic vasospasm* [55], *mimocausalgia* [58], and *minor causalgia* [57]. The French literature usually refers to it as *algodystrophy.*

The latest terminology is CRPS [1], which is more descriptive and inclusive. However, it does not include inflammatory and neuropsychological aspects of the syndrome in its terminology. The definition of CRPS [1] does not exclusively limit the condition to the syndrome of reflex sympathetic dystrophy. As an example, brachial plexus damage due to radiotherapy for cancer of the breast is a CRPS without inflammation and vasomotor dysfunction.

Recently, Galer and colleagues [74] have pointed to a tendency for overdiagnosis of this disorder using CRPS criteria. They noted that 37% of diabetic neuropathy patients met the diagnostic criteria of CRPS, which is an obvious tendency for overdiagnosis.

Complex regional pain syndrome II, which refers to the causalgic form of reflex sympathetic dystrophy, points to the fact that in causalgia there is ectopic [75] and ephaptic [76] nerve damage bypassing the synaptic transmission of electric current in nerve fibers between the adjacent damaged smaller and larger myelinated nerves [63–68]. The term CRPS II is more specific than *causalgia,* which is nonspecific and can be present in conditions other than CRPS [67,68].

## Sympathetically Maintained Pain versus Sympathetically Independent Pain

There has been debate regarding the phenomenon of sympathetically maintained pain [16,77–79], referring to selective diagnostic blockade of pain with α-1 blockers, such as phentolamine [79], and guanethidine [80]. Whereas some [81] have regarded sympathetically maintained pain as a prerequisite for the diagnosis of CRPS, others [16] consider sympathetically maintained pain a separate syndrome; others [77] have questioned and doubted any significance of sympathetically maintained pain (Table 1). In clinical practice, in early phases of CRPS (a few weeks to a few months), the pain is usually successfully blocked with phentolamine α-1 sympathetic blockade [81], confirming the sympathetically maintained nature of the pain. As the disease becomes chronic, and especially as the condition becomes complicated by treatment modalities such as surgery [44] or repetitive application of ice [59,60], the pain changes in nature from sympathetically maintained pain to sympathetically independent pain (Table 1).

In early stages, the disease is characterized by upregulation and supersensitivity of sensory nerves to norepinephrine [6,9]. In chronic stages, the disease is manifested by a dysfunctional rather than an upregulated sympathetic system [10–12] (Table 1). By then, the clinical picture also changes due to the inflammatory nature of the neuropathic pain [3,4] leading to edema, secondary entrapment neuropathies, subcutaneous hemorrhages, or neurodermatitis. In addition, with

**Table 1.** Complex regional pain syndrome (RSD)—sympathetically maintained pain and sympathetically independent pain over time

| Stage | Signs / symptoms | Phentolamine block | Immune system |
|---|---|---|---|
| I: Dysfunction | Hyperpathia, allodynia, muscle weakness, flexor spasms, thermal changes | 79% SMP (50 of 72 patients) | High helper T cells hyperimmune (in 55 of 71 patients) |
| II: Dystrophy | Edema, skin, hair and nail changes | 59% SMP (39 of 66 patients) | Variable |
| III: Atrophy | Muscle atrophy, neurovascular instability, cutaneous rash or skin ulcers | 28% SMP (17 of 62 patients) | Variable |
| IV: Irreversible disturbance of plasticity, autonomic failure | Systemic autonomic failure, visceral edema, irreversible low BP, MRSA (methycillin resistant staph. murena infection), elephantiasis, cancer | 0% SMP (none of 28 patients) | High killer T cells hypoimmune (in 28 of 36 patients) |

SMP = sympathetically maintained pain

passage of time, neurovascular instability [2] develops, pointing to dysfunction and failure of the sympathetic system to protect and sustain normal vasomotor function. This phenomenon, causing fluctuating changes of circulation and color of the extremity in a matter of a few minutes (chameleon sign), reflects lack of sustained normal tonus of arteriolar vasculature normally achieved by intact sympathetic function. The neurovascular instability cannot be expected to be responsive to sympathetic blocks due to instability and random dysfunction of vasomotor tonus. This is one of the factors that explains the sympathetically independent pain nature of CRPS after a few months (Table 1).

There are other types of neuropathic pain with neurovascular dysfunction that are sympathetically maintained in nature but do not have the other characteristics of CRPS. Examples are postherpetic neuralgia, diabetic neuropathy, and neuropathic pain seen in HIV or cancer patients. Thus not every sympathetically maintained pain is synonymous with CRPS. Simple reliance on sympathetic nerve blocks for the diagnosis of reflex sympathetic dystrophy, especially in later stages of the disease, can be misleading. The sympathetically maintained pain–sympathetically independent pain confusion as to whether pain is sympathetically or independently maintained plays a major role in over- and underdiagnosis of CRPS (Table 2).

Lack of response to sympathetic block should spare the patient from excessive repetitive sympathetic ganglion blocks (which traumatize the ganglion cells). Instead, other nerve blocks that suppress both sympathetic and somatic nerves [82], such as regional Bier block [83], brachial plexus block, epidural block, and paravertebral block [84,85], are more effective.

## Mechanism of Development

Leriche [53] first blamed the disease for dysfunction and stimulation of the sympathetic system. However, it has become clear that all CRPS is not sympathetically maintained pain [16,77], ruling out simple stimulation and upregulation of the sympathetic system. Moreover, sympathectomy is usually a failure [29,86–88]. Livingston [89] postulated a "vicious circle" of activated internuncial pools of spinal cord upregulating the efferent spinal cord sympathetic nerves with secondary ischemia (due to vasoconstriction) restimulating the neural pools of the spinal cord. More recent research [9,86] has emphasized the supersensitization of the sensory

**Table 2.** Diagnostic confusion in CRPS and other syndromes

| Overdiagnosed patients | CRPS | Underdiagnosed patients |
|---|---|---|
| Diabetic neuropathy* (54) | | CTS (93) |
| Arachnoiditis (19) | | MFS and FM (21) |
| Nutritional neuropathy (19) | | Thoracic outlet (14) |
| Nerve root contusion (18) | | Rotator cuff injury (12) |
| Repetitive stress injury* (6) | | Morton's neuroma (9) |
| Münchausen syndrome (5) | | Brachial plexitis (5) |
| Disimmune neuropathy (3) | | Diabetic neuropathy* (5) |
| Vasculitis (2) | | Ulnar entrapment (4) |
| MS (2) | | Repetitive stress injury* (4) |
| Meningioma of cord (1) | | Bursitis (3) |
| Syrinx (1) | | Münchausen syndrome (2) |
| | | Cervical disc herniation (1) |
| Subtotal 134*** (16%)*** | Subtotal 651*** | Subtotal 173** (21%)** |
| | Total 824 (100%)** | |

CTS = Carpal Tunnel Syndrome; MFS = Myofascial Syndrome; FM = Fibromyalgia.

*Diabetic neuropathy and repetitive stress injury were in both categories

**651 + 173 = 824 CRPS patients

***The 134 overdiagnosed patients were excluded from this study

afferent alpha adrenoreceptors [6–9], rather than the efferent sympathetic nerves, as the causative factor.

The sympathetic system has three major physiologic roles: regulation of body temperature; regulation of vital signs (BP, pulse, respiration), and regulation of the immune system [5,90,91]. These three functions are aimed at protection of the internal environment of the body (milieu interne) [92]. The complex symptoms and signs of CRPS make more sense by keeping the above physiologic functions in mind, and help the clinician arrive at proper diagnosis of the syndrome based on the following four minimal diagnostic criteria: afferent sensory dysfunction of thermoreceptors, mechanoreceptors, and chemoreceptors (pain); efferent vasomotor response (neurovascular response); control of the immune system [5,90] as a protective stabilizer of "milieu interne" (inflammation); and limbic system modulation of the sympathetic system (emotional disturbance).

## The Four Clinical Principles of CRPS

### Pain

The first of the four principles for the development of CRPS is manifestation of specific types of pain outlined below. The neuropathic pain of CRPS is manifested by one or more of the following pain modalities: hyperpathia (protopathia) [93,94] (see Table 3), allodynia [95], ectopic [75,96] or ephaptic pain [89] of causalgia [32], and inactivity-chemoreceptor-originated deep pain [44,97] (Table 3).

*Hyperpathia* (protopathia). This is an intense, usually persistent, and burning regional pain. The hyperpathic pain was constant in 81% of our 824 patients. Blümberg and Jänig [44] reported the pain constant in 75%, and intermittent in 25% of their patients. The pain is out of proportion to the severity of trauma [98].

Simple tactile stimulation of the involved area originating the hyperpathia may be accompanied by objective signs of rise in pulse and BP [99–103]. In addition, the hyperpathic pain is accompanied by a regional mild hypesthesia to touch and pain (Fig. 2). This hypesthesia is not in the sensory distribution of somatic nerve roots.

By virtue of exclusive function of thermal regulation, these thermal sensory nerve fibers have an affinity to the anatomical structures of arterioles and arteries (heat source). As a result, dysfunction of these sensory nerve fibers does not show a dermatomal, but a thermatomal, sensory nerve distribution [93,95] (Fig. 2). This is a sensory loss usually in the distribution of brachial, femoral, carotid, or mesenteric arteries [29] (Fig. 2).

There are actually three different types of sensory loss: (1) dermatomal, (2) thermatomal, and (3) glove-and-stocking distribution (Fig. 2). The dermatomal sensory loss is seen in radiculopathies, and other forms of somatic sensory nerve damages.

The thermatomal, neuropathic (microvascular) pain distribution is usually seen in CRPS, diabetic neuropathy, and postherpetic neuralgia. This type of thermatomal sensory loss should not be mistaken for the classical glove-and-stocking sensory loss—due to primary or secondary gain (malingering or conversion reaction)—which limits itself to joints such as the wrist, knee, or shoulders (Fig. 2) in a glove-and-stocking distribution. Only a careful examination of touch and pain sensations separates each of these three sensory types [104] (Fig. 2).

### Spread of CRPS

Regional hyperpathia (protopathia) plays a major role in the spread of CRPS. This is mainly due to summation of repetitive stimulation of the thermoreceptors [105], which results in a tendency for spread [43,105–107] of hyperpathia to proximal and distal portions of the extremities [83]. In advanced, complicated cases, it may lead to horizontal and vertical spread [1,106–110] to other extremities. This spread may play a major role in aggravation of CRPS [93, 107,108]. This phenomenon is due to stimulation of the uninhibited C-fibers [43] perpetuating the sensitization of afferent receptor nerves [111] in the spinal cord [112]. Other factors such as sympathectomy (see page 16) and surgical procedures are also instrumental in the spread of CRPS (see page 17).

Activation of thermal C nociceptor sensory pain fibers plays a major role in hyperpathic pain [12,19,20,113–118].

Table 3. Pain modalities in CRPS

| Type of pain | Nerve dysfunction | Aggravating factor |
|---|---|---|
| Hyperpathia | Unmyelinated C-thermoreceptors | Trauma, ice, inactivity, surgery |
| Allodynia | Myelinated A-beta fibers | Ice, inactivity, avoidance of tactile sensory input |
| Deep burning pain | Unmyelinated chemoreceptors | Inactivity, cast application, wheel chair, heavy sedation |
| Causalgia | Ectopic (ephaptic) electric short between myelinated and unmyelinated nerve fibers | Surgery, diagnostic or therapeutic needle injection in the nerve damage area |

The afferent small C-fiber system has a tendency to be inhibited by the larger A-fiber myelinated somatosensory nervous system. Lack of such inhibition (i.e., lack of simple touch or avoidance of tactile contacts due to hyperpathic pain) can result in increased firing of the afferent neuropathic pain fibers with secondary pathological efferent sympathetic discharge, and further sensitization of the layers I and II of the gray matter of the spinal cord [81,119]. This is not a simple upregulation, but a dysfunction of the sympathetic system [11, 12,120]. This dysfunction explains the reason for failure of sympathectomy. Sympathectomy aggravates the already existing sympathetic dysfunction [29, 86–88].

*Allodynia.* Allodynic pain is elicited by a stimulus that usually does not cause pain: eg, a simple breeze, bed sheet contact, and other types of mild tactile stimulation (Table 2). In CRPS, there is a tendency for sensitization of the involved skin surface. Typically, the patient avoids any type of sensory stimulation and protects the allodynic area with the help of wrapping the extremity with a cloth or a glove. In extreme cases, the patient may avoid showering or bathing for months. Mechanoallodynia is usually mediated by A-beta, low-threshold mechanoreceptors, which are small myelinated nerve fibers. They do not respond successfully to pure sympathetic ganglion blocks [112,121–124]. They are more likely to respond to epidural or paravertebral blocks [84,85].

One model of experimental allodynia is application of capsaicin to skin [125,126]. The center of the capsaicin-damaged injection site shows analgesia [125,126] surrounded by an area of hyperpathia most probably mediated through small thermoreceptor C-fibers. This area of hyperpathia is surrounded by an area of mechanoallodynia mediated by A-beta larger fibers [127,128]. The capsaicin-induced damage and mechanoallodynia evokes a CNS sensitization that may manifest by spread of allodynia and hyperpathia beyond the area of nerve damage [129]. This classical model of CRPS damage (in the center) and dysfunction (in the periphery) is identified on infrared thermal imaging as a central hyperthermia, reflecting damage and lack of vasoconstrictive function of sympathetic nerves, surrounded by a margin of hypothermia [104] (Fig. 3).

Application of ice [59,60] exaggerates vasoconstriction, coagulates and damages the myelinated nerve fibers [61, 130,131], aggravates the nerve damage and enlarges the area of mechanoallodynia, resulting in bias toward sympathetically independent pain rather than sympathetically maintained pain [61] (Table 1). Procedures such as carpal tunnel
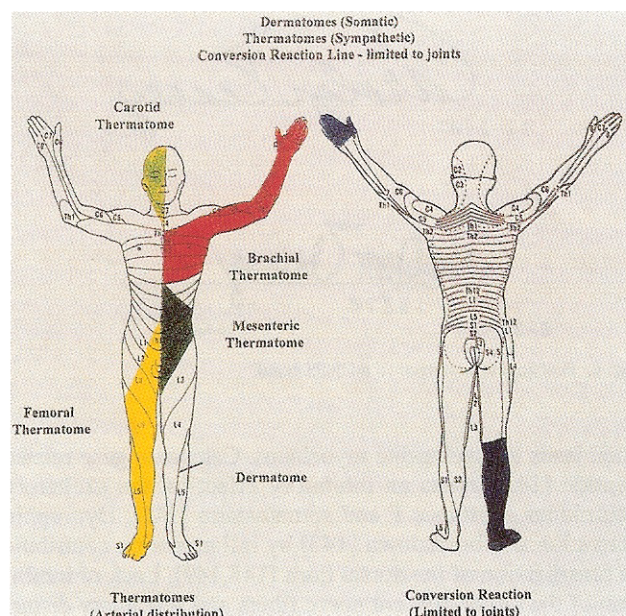
Fig. 2. Sympathetic nerves follow the arteries and arterioles to modulate proper temperature and circulation to the extremities. In CRPS the sensory loss is usually in the thermal distribution of the blood vessels (thermatomes) rather than in the nerve roots distribution of the somatic nerves (dermatomes). The malingering and conversion reaction sensory loss is non-anatomical and usually limited to the joints. With permission from Springer-Verlag New York [104].
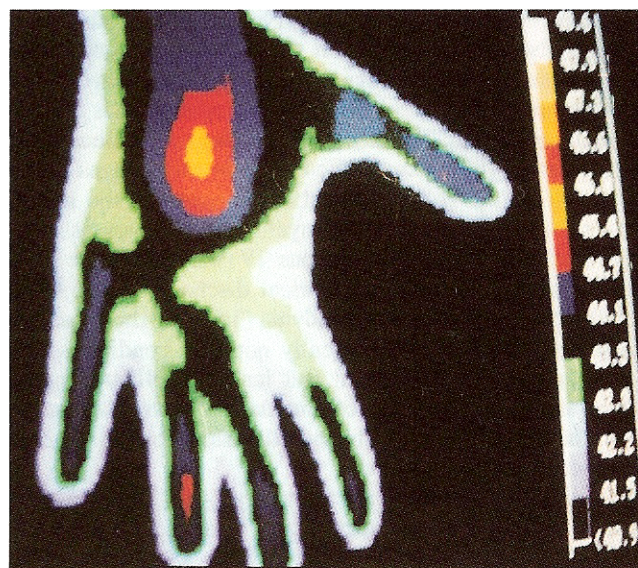


Fig. 3. Complex regional pain syndrome due to electrical injury. Point of entrance is in the palm of the hand. The three concentric thermal changes are typical of sympathetic nerve damage and dysfunction. The central vortex of the damaged area has lost its thermal vasoconstrictor function, resulting in heat leakage. The second circular margin shows less hyperthermia. The third and fourth circular margins are hypothermic (intact sympathetic function).

surgery for inflammation due to CRPS, arthroscopy, or exploratory surgical procedures also aggravate the sensory damage and reproduce a similar allodynic phenomenon. Michaelis and colleagues [132] have reported rapidly increasing mechanoreceptor activity in damaged nerve fibers. Somatic nerve stimulation inhibits the aggravation of allodynia. For this reason, allodynia is best relieved by physiotherapy, massage therapy, exercise, moist heat and mixed somatosympathetic paravertebral and epidural blocks [84,85] with bupivacaine (Marcaine) and Celestone or methylprednisolone (DepoMedrol).

In our study the application of ice for 2 mos or longer resulted in a higher percentage of stage III to IV as compared to no ice or less than 2 mos' treatment ($p$ <0.001) (Table 4). As ice selectively damages and coagulates [59,62,130] the myelinated nerve fibers (which are rich in lipids), the allodynia is gradually transformed to thermatomal hypesthesia augmented by ice-induced hypothermia.

*Causalgic pain.* The causalgic pain in CRPS II syndrome [1] (Table 3), is characterized by attacks of "lightning," "stabbing," "electric shock," "prickling," "deep itching," and "jerking" type of pain. In later stages, the pain is accompanied by myelogenic response of myoclonic jerks of the extremity or of the trunk—as well as atonic (akinetic) falling attacks—due to myelopathic sensitization [111,116,133]. Differential nerve-fiber stimulation studies have shown the importance of the role of large myelinated nerve fibers in ectopic [75], ephaptic [76] (nonsynaptic) causalgic-damaged nerves. This is due to the crossfire (electric short) discharges of the damaged myelinated nerve trunks [63–65] stimulating

Table 4. The influence of treatment on CRPS stages during 2 years or longer follow-up (824 patients)

| Characteristics of treatment (% of 824 patients) | Stage I**** number of patients | Stage II number of patients | Stage III-IV*** number of patients |
|---|---|---|---|
| History of amputation * 11 patients (1.3%) | 0 (0%) | 2 (19%) | 9 (81%) ($p$=0.025) |
| Chemical sympathectomy 13 patients (1.5%) | 0 (0%) | 2 (15.4%) | 11 (84.6%) |
| Surgical sympathectomy 22 patients (2.6%) | 0 (0%) | 3 (13.6%) | 19 (86.4%) |
| Surgical treatment ** 295 patients (36%) | 24(8%) | 106 (36%) | 165 (56%) ($p$<0.001) |
| No surgery 528 patients (64%) | 164 (31%) | 190 (36%) | 174 (33%) ($p$<0.001) |
| Cast application 173 patients (21%) | 4 (2%) | 67 (39%) | 102 (59%) |
| Wheelchair bound 49 patients (6%) | 0 (0%) | 19 (38%) | 30 (62%) |
| Ice Rx>2 mos 226 patients (27.5%) | 16 (7%) | 92 (41%) | 118 (52%) ($p$<0.001) |
| Ice Rx<2 mos 34 patients (4.1%) | 13 (38%) | 11 (32%) | 10 (30%) ($p$<0.001) |
| Age: <21 yrs with surgery 46 patients (5.5%) | 6 (12%) | 19 (42%) | 21 (46%) ($p$<0.001) |
| Age: <21 yrs without surgery 92 patients (11%) | 61 (66%) | 22 (24%) | 9 (10%) ($p$<0.001) |

*Many patients had more than one treatment modality, which changes the total percentage.

**Sympathectomy, rotator cuff, thoracic outlet syndrome, compression neuropathy, exploration, etc.

***Stage I = dysfunction; Stage II= dystrophy; Stage III = atrophy; Stage IV = total autonomic failure

****Due to the nature of treatment, stage III may reverse to stage I and vice versa

the adjacent partially damaged nerve fibers. This abnormal electric discharge may explain the beneficial effect of anticonvulsants. The neuroma-impinged sensory nerve fibers in the amputee stump originate similar spontaneous electrical discharges [76]. The electrical discharges are blocked by phentolamine [66] sympathetic blocks in early stages of the disease [66–70]. This beneficial effect points to the secondary involvement of small unmyelinated C fibers as well. Conversely, injection of intravenous (IV) norepinephrine stimulates and aggravates the electrical discharges [68,69]. In contrast to hyperpathia and allodynia (Table 3), the causalgia (including CRPS II) is frequently noted in conditions that cause damage to both small and larger myelinated nerve fibers, especially in cases of amputation, neuromas, bullet wounds, surgical scars, knife and other sharp-object injuries, electrical injuries, and cancer.

*Deep pain of inactivity.* Recently [44,97,134] a new source of pain has been recognized. It originates from the deep chemoreceptor C fibers in muscle and bone. These chemoreceptors become activated with inactivity [97]. Blümberg and Jänig [44] reported incidence of pain with inactivity in 65% of their patients. The deep spontaneous pain associated with inactivity showed a higher incidence in 75% of their patients [44]. In our series of 824 patients, the deep pain sensation on arousal in the morning (associated with inactivity) was noted in 79% of patients versus pain with activity in 63% of patients. Patients describe this type of pain as deep, itching, and intolerable. With increasing inactivity (e.g., use of a wheelchair), this deep pain arouses the patient 2½ times more frequently than the ambulatory patients. Intermittent walking reduces the incidence of deep pain.

*Efferent (Motor) Response*

The second diagnostic principle is efferent motor dysfunction in the form of vasoconstriction, flexor spasm, and movement disorder including dystonia and tremor. In more advanced cases, myoclonic jerks due to spinal cord sensitization [79,119] and deafferentation [135,136] develop. These myelogenic myoclonic jerks are due to the enlargement of peripheral receptive fields of central pain-projecting neurons in superficial laminae I and II of the dorsal horn [137]. The sensitization and the enlargement of laminae I and II excitatory fields is due to relatively long-term, uninhibited dysfunctional afferent sensory nerve input to the deeper layers 4 and 5 of the dorsal horn of the spinal cord [11]. The deeper layers 4 and 5 exert inhibitory function on superficial laminae I and II excitatory internuncial cells (Table 3) [11,138]. The small granular primary sensory neurons of the superficial layers 1 and 2 normally possess small receptor fields that respond mainly to the C nociceptors and A-delta fibers [138]. These neurons synthesize neuropeptides that are transported through the afferent fibers centrally and peripherally [139,140]. The chronic repetitive stimulation of these sensory nerve fibers is accompanied by release of chemicals such as calcitonin gene-related peptide (CGRP) [141], substance P [142] and nitric oxide [143–146]. Excessive somatostatin and substance P release can potentially damage and reduce the inhibitory function of the granular cells in the deeper layers 4 and 5 of dorsal horn neurons leading to sensitization [147], deafferentation, and aggravation of hyperpathic pain and allodynia. The same phenom-
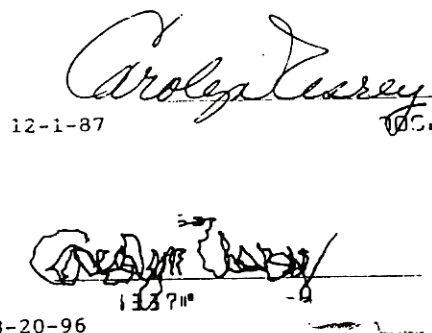


**Fig. 4.** Posttraumatic tremor in a CRPS hand.

enon leads to myelogenic myoclonus. Calcitonin gene-related peptide [141] exerts an inhibitory effect on the excitatory neurokines substance P and somatostatin [141]. Dynorphin activation and breakdown [143] by inflammation contribute to sensitization of the dorsal horn [148,149]. Lack of inhibition of the larger afferent nerve fibers and secondary disturbance of inhibition of wide-dynamic-range [110] function of layers 4 and 5 result in increased excitation of the efferent spinal cord nerve cells. The end result is disturbance of spinal cord plasticity [150,151], deafferentation [135,152], attacks of myelogenic myoclonic jerks, and akinetic attacks, as well as tremor and other forms of movement disorder [93,153] (Fig. 4). Simple somatic peripheral nerve injury is not enough to cause tremor. The above-mentioned central sensitization at the spinal cord level is required to lead to dystonia and tremor [154].

Motor dysfunction may manifest in the form of dystonic flexor spasm, flexor deformity [83], toe walking, and pronation of the hand or foot (equino varus). The dystonic flexor spasm seems to be due to the primitive withdrawal response to the pain source. Tremor is not uncommon. Blümberg and Jänig have reported tremor and other movement disorders in over 80% of CRPS patients [44]. Veldman and coworkers have noted movement disorder in 95% of 829 patients [16]. In our series of 824 patients, the incidence was 78%. Application of a cast causes immobilization and stimulation of the deep mechanoreceptors [97]. These "silent sleeping nociceptors" [97] become activated with rest and inactivity. This, in turn, leads to pain, edema and movement disorder. Cardoso and Jankovic [154] have reported 11 cases of patients suffering from CRPS who developed Parkinsonian-type tremor following application of cast to the extremity [154]. The cast becomes harmful if the extremity is edematous and inflamed due to neuroinflammation [4,93,155] of the original trauma or surgery.

Gowers [156] in 1888 first reported peripheral nerve origin in some of the movement disorders (circa 1888). Practically every form of movement disorder can be observed in peripheral nerve injuries, especially in CRPS patients. These are frequently in the form of dystonic movements and are mistaken for conversion reaction. It is true that any group of movement disorders, including seizure disorder, is contaminated by a minority of conversion reaction patients or malingerers (17% in the case of seizure disorder). This minority incidence does not prove that all movement disorder patients are "functional."

Myoclonic jerks may be a manifestation of deafferentation and sensitization of the spinal cord [137] due to long-term afferent

**Table 5.** Carpal tunnel syndrome somatic versus neuropathic

| Characteristic | A-Somatic | B-CRPS (neuropathic) 98 of 824 cases |
|---|---|---|
| Pain | Proportionate to impingement | Allodynic: (even painful to touch) hyperpathia worse in late stages |
| Trophic changes | Thenar atrophy in late stages | Edema: hair and skin changes; interossei atrophy in late stages |
| Tinel's sign | Limited to carpal tunnel | Indiscriminative: entire wrist hyperpathic |
| Muscle tonus | Weak, atrophic in advanced cases | Dystonic flexor spasm and deformity |
| Nerve conduction velocity | Delayed sensory and motor distal latency | Normal or borderline sensory delay |
| Neurovascular instability: mottling, color changes: (chameleon sign) | None | Present off and on |
| Surgical findings | No inflammation | Edema; osteonecrosis |

**Table 6.** Differential diagnosis of CRPS versus myofascial syndrome and fibromyalgia

| Characteristic | CRPS (824 patients) | Myofascial pain (68 patients) | Fibromyalgia (85 patients) |
|---|---|---|---|
| Allodynia | 97% | — | — |
| Hyperpathia | 98.6% | — | 11% |
| Cold intolerance | 82% | — | 5% |
| Pain | Regional | Focal, discrete | Migratory, variable, nonspecific |
| Dystrophy, atrophy | + | — | — |
| Edema, entrapment neuropathy | +++ | — | — |
| Skin color change | . +++ | — | — |
| Trigger points | + | + + | + + |
| Fatigue | ++++ | + | + |
| Flexor spasm and deformity | + | — | Muscle spasm but no deformity |
| Limbic system dysfunction, (insomnia, memory loss) | ++++ | ± | ± |
| Movement disorder: Tremor, myoclonus | + | — | — |

+ = mild; ++ = moderate; +++ and ++++ = severe; ± = inconsistent; —= absent

cytokines' damage to the inhibitory granular cells in layers I and II. As such, they develop in later stages of the disease. Any form of immobilization (cast, wheelchair, etc.) contributes to this phenomenon. Myoclonic jerks are seen in patients undergoing withdrawal of opioids (rebound phenomenon).

In 38 of our 824 patients suffering from CRPS due to spinal cord injury, myoclonic jerks were invariably noted. In addition, myoclonic jerks were present in 44 of 63 CRPS patients secondary to electrical injury [33,35]. This may be due to electricity going through the path of least resistance (afferent C fibers) and secondarily originating spinal cord dysfunction [29,33]. Myoclonic jerks are a long-term complication of limb amputation (10 of 11 amputees among our 824 patients).

Myoclonic jerks are frequently mistaken for "pseudoseizures" due to the fact that the ictal events originating from the spinal cord are too deep to present themselves on scalp video-EEG monitoring [157]. In more severe cases, such as electrical injury complicated by CRPS [35], a somatosensory evoked potential test [158] identifies the spinal cord dysfunction [33,159] as the originator of this form of myelogenic seizure.

*Disturbance of Immune System (Neurogenic Inflammation)*
The third diagnostic principle is neuroinflammation. Neuropathic pain, including CRPS I, is complicated by inflammation in varying degrees [160]. This inflammation [93,120, 155,161,162] was first reported by Mitchell (1864) [32] as "shiny skin" and, later on, by Sudeck (1942) [3]. The neurogenic inflammation [4,146,163,164] results in bulbous lesions [155], sterile abscess [16], edema and impingement of the nerves at the wrist, elbow, thoracic outlet and ankle areas resulting in the disease's being mistaken for conditions such as carpal tunnel [18,165–167] (Table 5), thoracic outlet, tarsal tunnel syndromes, and myofascial syndrome [168] (Table 6). The well-intended surgical procedure to relieve

such entrapment neuropathies may in turn aggravate the inflammation by virtue of surgical trauma [169], becoming a new source of neuropathic pain.

The inflammation [93,120,155,161,162] is another manifestation of a dysfunctional sympathetic system. The sympathetic system is responsible for immune system regulation [90]. As a result, the patient may develop bouts of unexplained fever, edema, attacks of subcutaneous bleeding, neurodermatitis, bulbous lesions [155], pelvic inflammatory disease, or interstitial cystitis [170]. Inflammation may cause development of subcutaneous skin nodules, pulmonary nodules, laryngitis, difficulty with phonation, attacks of hacking cough and hematemesis. In late stages it can cause elephantiasis, subcutaneous bleeding, bullous [156] and deep ulcerative lesions [162] involving the skin (Fig. 5) as a manifestation of disturbance of the immune system [90]. It can be mistaken for infection, osteomyelitis, dermatitis, and cystitis. Treatment with antibiotics provides no relief.

The inflammation is usually intermittent, and is not consistently present [94]. Only a careful history taking can document previous attacks of inflammation [94]. Frequently, in stage III, the atrophy of the involved limb is masked by edema of inflammation, giving the limb a normal appearance. This phenomenon misleads the examiner to label the disease as stage I. The neuroinflammatory mediators (neurokines) substance P [146, 164,171,172], CGRP [144,146], bradykinin, and other inflammatory substances play a major role in development of inflammation [163,173], as well as movement disorder [153,174–175] in CRPS. Oxidative stress with free radical-mediated lipid peroxidation in the area of nerve damage plays a role in inflammation [176]. Release of nitric oxide and other cytokines at the
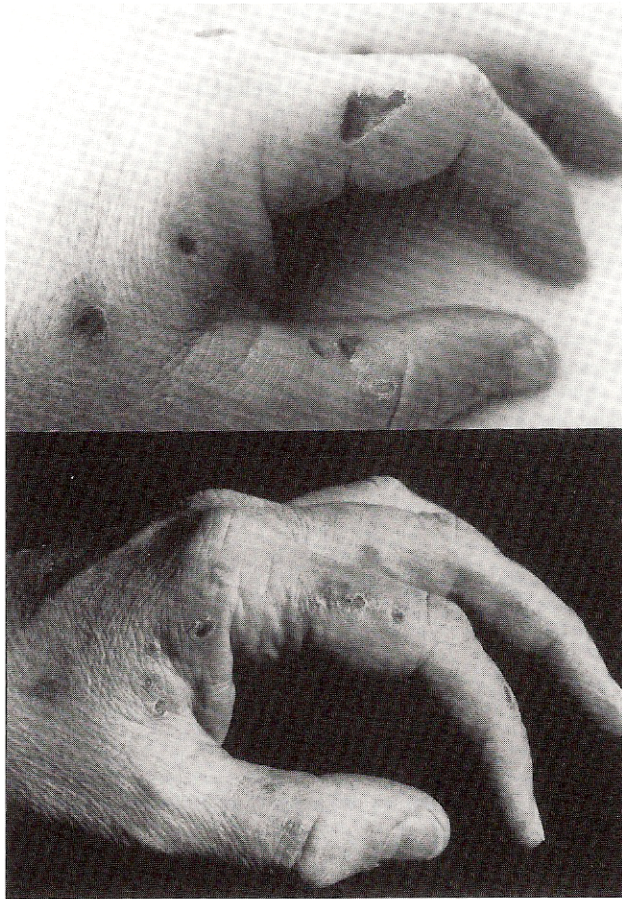
**Fig. 5.** (Top) Ulcerative lesions of left hand 9 mos after antecubital veni-puncture CRPS. This is a sign of immune system dysfunction secondary to CRPS. (Bottom) The same hand after 2 mos of IV Mannitol and gamma globulin therapy.

area of nerve dysfunction plays a major role in inflammation and immune regulation [143–146].

*Emotional Aspects of CRPS*

The final diagnostic principle is emotional disturbance in CRPS. In contrast to somatic sensory nerves, the sensory neuropathic nerve fibers responsible for the development of CRPS do not end up in the contralateral neocortical parietal sensory cortex (Fig. 1). Instead, according to Bennarroch [21], over 90% of these sensory nerve impulses terminate in the limbic system [5,21] (Fig. 1). Moreover, positron emission tomography demonstrates a significant cerebral insular and limbic activation during painful stimulation of neuropathic pain [177]. The vicious circle of chronic neuropathic pain leading to disturbance of plasticity, as well as inflammation, causes further long-term potentiation of pain impulse and nerve stimulation in higher centers in the limbic system. This leads to insomnia, agitation, depression, poor memory and poor judgment [5]. The above neurophysiological observations explain the fact that practically every patient suffering from CRPS demonstrates some degree of limbic system disturbance. In our study of 824 patients, one or more of the limbic system dysfunctions were present in every case except three. These consisted of insomnia (92%), irritability, agitation, anxiety (78%), depression (73%), poor memory and concentration (48%), poor judgment (36%),

and panic attacks (32%). Understanding the nature of emotional components of reflex sympathetic dystrophy spares the patient from misdiagnosis and improper treatment.

Mary Lynch [178], in her comprehensive review of the psychological dysfunctions in CRPS, has found no difference between CRPS patients and the general population. On the other hand DeGood and colleagues [179] found patients suffering from CRPS, when compared to back pain and headache patients, had the highest level of pain intensity, but demonstrated relatively less emotional distress.

**Diagnosis**

The main hurdle in diagnosis is the fact that the majority of physicians do not consider CRPS in their list of differential diagnoses. This syndrome is commonly over- or under-diagnosed. In our series of 824 patients, CRPS was over-diagnosed in 134 (16%) of cases, and under diagnosed in 173 (21%) of cases (Table 2). The 134 overdiagnosed cases have already been excluded from this study.

A syndrome as complex and as potentially variable in symptomatology and temporal course as reflex sympathetic dystrophy cannot be expected to be diagnosed with a single laboratory test. Complex regional pain syndrome is a syndrome and should be diagnosed by inclusion (the above-outlined 4 principles) rather than by exclusion.

Tests used to diagnose CRPS include the following:

1. Scintigraphic triphasic bone scanning [180] has been the popular test of choice for the diagnosis of CRPS in the past three decades. Whereas earlier literature has described the scintigraphic triphasic bone scanning as highly sensitive and specific in establishing the diagnosis of CRPS [181], a recent review of medical literature by Lee and Weeks [182] has shown this test to be positive in approximately 55% of cases, which is quite close to a random statistical yield. Chelimsky and coworkers [94] found this test abnormal in no more than 25% of CRPS patients.

   As the disease becomes more chronic, the bone scan yield becomes more variable [183]. In the early stages, usually the test shows an increased flow and delayed periarticular uptake. Later, the flow normalizes but delayed views remain diffusely intense bilaterally. This lack of lateralization may be due to bilateral spinal cord representation of neurovascular functions in CRPS [162,163, 173]. In more chronic stages, the flow becomes reduced and the scintigraphic triphasic bone scanning images return to normal [183]. Realizing the fact that scintigraphic triphasic bone scanning shows symmetrical uptake in chronic stages, it misleads the clinician to conclude that the patient does not have CRPS. Subsequently, the patient is deprived of proper diagnosis and treatment. Malis and coworkers [184] found scintigraphic triphasic bone scanning changes nonspecific even in post-sympathectomy patients.

2. Diagnostic nerve blocks using phentolamine [79] and guanethidine [80] are usually positive in the early stages and gradually lose their sensitivity (Table 1).

3. Electromyography and nerve conduction velocity cannot be expected to show any abnormality in CRPS I (reflex sympathetic dystrophy), which is due to dysfunction of poorly myelinated or unmyelinated sensory nerve fibers.

Nerve conduction velocity measures the velocity and function of the large myelinated fibers, which are not usually involved in CRPS I. Electromyography/nerve conduction velocity cannot identify disturbance of small sensory or autonomic nerve fibers [185]. Diagnosing CRPS with the help of electromyography and nerve conduction velocity is similar to diagnosing a viral infection with a standard rather than an electron microscope. A nerve conduction velocity study usually yields either normal or confusing borderline delay of distal latency in CRPS (probably due to longstanding vasoconstriction in the region). Multiple electromyography needle insertions in the CRPS extremity may result in further sensitization of $\alpha$-1 receptors [186]. Complex regional pain syndrome II causalgic pain is frequently due to ectopic, ephaptic (nonsynaptic) electrical transmission [63–65,75,78] between damaged myelinated and unmyelinated fibers. Electromyography and nerve conduction velocity findings may be abnormal in a minority of these patients, but such test results do not yield an exclusive diagnostic value for CRPS.

4. Computed tomography and magnetic resonance imaging (MRI) are not expected to detect the damage to the microscopic nerve fibers in the wall of blood vessels [6–9], and usually do not show any abnormalities in CRPS. The MRI may show inflammation in soft tissues and muscles, osteopenia and osteonecrosis; but these are nonspecific changes. At times, due to the presence of unrelated disc bulging, laminectomy is performed in such patients, which may aggravate the inflammation of CRPS. The MRI in patients suffering from CRPS frequently shows bulging discs or small herniation of intervertebral discs due to the longstanding bilateral algogenic paraspinal muscle spasm causing an accordion effect on the spine. If at all possible, nonsurgical treatment is preferred. The stress of a surgical procedure is apt to aggravate the inflammatory and immune disturbances of CRPS [45,48,49,187].

5. The quantitative sudomotor axon reflex test [94] studies the cholinergic sudomotor function of the sympathetic system [188–191]. It does not address the norepinephrine dysfunction. It has a high degree of sensitivity and specificity in detecting postganglionic dysfunction of cholinergic (parasympathetic) sudomotor nerves [191].

6. Infrared thermal imaging has a limited application in neurology [192]. It can be used to study and compare subtle temperature changes in different parts of the body. Like any other test outlined above, it cannot "diagnose" CRPS but can identify areas of damage (hyperthermia) versus irritation (hypothermia) of sympathetic nerves. The infrared thermal imaging is quite sensitive in pointing to the function of skin temperature, which is the exclusive domain of the sympathetic system [190,193]. Cold stress-infrared thermal imaging [194–196] may provide additional useful information. Thermal imaging shows any old or new sympathetic nerve damage or dysfunction, thus confusing the examiner and demanding careful and proper clinical correlation. In addition, as the disease becomes chronic and the sympathetic dysfunction becomes bilateral, the infrared thermal imaging shows identical bilateral temperature changes, causing difficulty in diagnosis. The same phenomenon causes confusion in interpretation of other tests in CRPS. Infrared thermal imaging is useful in identifying the area of maximal damage as follows:

- In the area of original nerve damage (e.g., hand or foot) the hyperthermia points to damage and paralysis of vasoconstrictive function of the sympathetic system (the central hyperthermic area) [104] (Fig. 3). The central hyperthermia usually points to the apex of damaged tissue, resulting in heat leakage as well as accumulation of substance P [197–199] and nitric oxide [145,200]. This is an important therapeutic clue to avoid further trauma. Traumatic procedures such as surgical exploration, nerve blocks, a clonidine patch, capsaicin, or electromyographic needle insertion should not be applied to the damaged hyperthermic area in the extremity, which may lead to further damage and aggravation of the condition [201–203]. In the acute stage, the damaged area is hyperthermic [16,29]. After a few weeks, the hyperthermic area shrinks. In some cases [16] the hyperthermia persists due to permanent damage to sympathetic nerve fibers [104]. This bodes a poor prognosis.
- Hyperthermia in referred pain areas, eg, paravertebral nerves, is due to substance P and nitric oxide [145,172] accumulation but does not necessarily point to the origin of the injury.
- Virtual sympathectomy: (Fig. 6) After more than a dozen stellate or lumbar ganglion nerve blocks, the repetitive needle insertion traumatizes the ganglion enough to result in permanent hyperthermia [104] in the extremity ("virtual sympathectomy"). Infrared imaging identifies this phenomenon and spares the patient from further damage [104].

7. The laser Doppler flow study is a sensitive test for the study of capillary circulation [204]. It studies a small area of the body, limiting its overall extent of information. This test has demonstrated sympathectomy to be ineffective in providing increased circulation in an extremity after exposure to cold [205,206].

8. The quantitative thermal sensory-evoked response test [207] is sensitive and useful in studying the functions of C thermoreceptors and A-beta mechanoreceptors in CRPS [207]. This test identifies the threshold of cold and heat touch and pain sensations. This test may be abnormal in CRPS patients (cold hyperalgesia) and in erythromelalgia (heat hyperalgesia) [207]. The test has been well standardized [204,208].

## Stages

The temporal course of CRPS has been divided into stages. Depending on the nature of the injury, the stages vary in their duration. In the 17 patients suffering from venipuncture CRPS in our series (Fig. 5), deterioration from stage I to stage III was measured in a few weeks up to less than 9 mos. This is in contrast with CRPS in children [108], in whom stages would stagnate, reverse or improve slowly.

Stage I (Table 1) is a sympathetic dysfunction with typical thermatomal distribution of the pain (Fig. 2). The pain may spread in a mirror fashion to a contralateral extremity or to adjacent regions on the same side of the body [106]. In stage I, the pain is usually sympathetically maintained pain (Table 1).
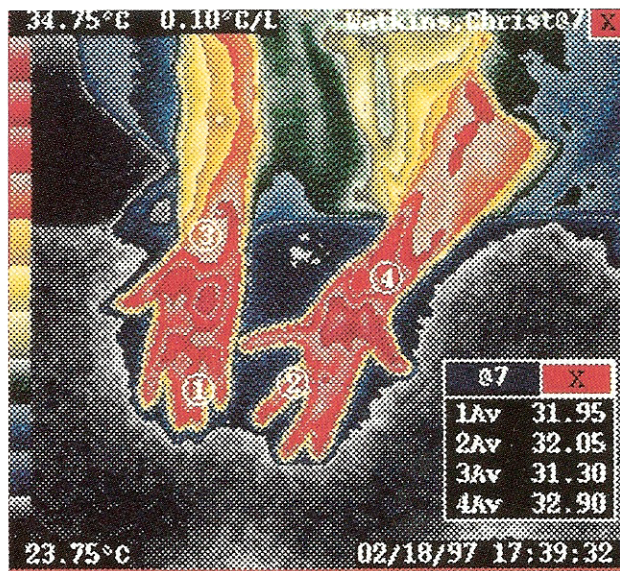
**Fig. 6.** More than two dozen stellate ganglion blocks to each side have damaged enough sympathetic nerves to cause permanent hyperthermia as the manifestation of virtual sympathectomy. Further blocks have no diagnostic or therapeutic value.



**Fig. 7.** Complex regional pain syndrome of 7 yrs' duration due to right hand injury. Two years of unsuccessful operations at right carpal tunnel, and 5 yrs of immobilization of the hand have resulted in "Boxer's hand deformity" and ultimate amputation.

In stage II (Table 1), the dysfunction changes to dystrophy manifested by edema, hyperhidrosis, neurovascular instability with fluctuation of livedo reticularis and cyanosis, causing change of temperature and color of the skin in a matter of minutes. The dystrophic changes also include bouts of hair loss; ridging; dystrophic, brittle and discolored nails; skin rash; subcutaneous bleeding; neurodermatitis; and ulcerative lesions (Fig. 5). Due to the confusing clinical manifestations, the patient may be accused of factitious self-mutilation [209] and Münchausen syndrome. All these dystrophic changes may not be present at the same time [94] in a patient. Careful history taking is important in this regard.

In stage III, the pain is usually no longer sympathetically maintained and is more likely a sympathetically independent pain. Atrophy in different degrees is seen. Frequently, the atrophy is overshadowed by subcutaneous edema. The complex regional pain and inflammation spread to other extremities [94,210,211] in approximately one-third of CRPS patients. At stage II or III it is not at all uncommon for CRPS to spread to other extremities [106–108]. At times, it may become generalized [106]. The generalized CRPS is an infrequent late-stage complication. It is accompanied by sympathetic dysfunction in all four extremities as well as attacks of headache, vertigo, poor memory, and poor concentration. The spread through paravertebral and midline sympathetic nerves may be vertical, horizontal, or both [83,106,107,212]. The original source of CRPS may sensitize the patient to later develop CRPS in another remote part of the body triggered by a trivial injury. The ubiquitous phenomenon of referred pain to remote areas (e.g., from foot or hand to spine) should not be mistaken for the spread of CRPS.

At stage III, inflammation becomes more problematic and release of neuropeptides from C-fiber terminals results in multiple inflammatory and immune dysfunctions. The secondary release of substance P may damage mast cells and destroy muscle cells and fibroblasts [213–216].
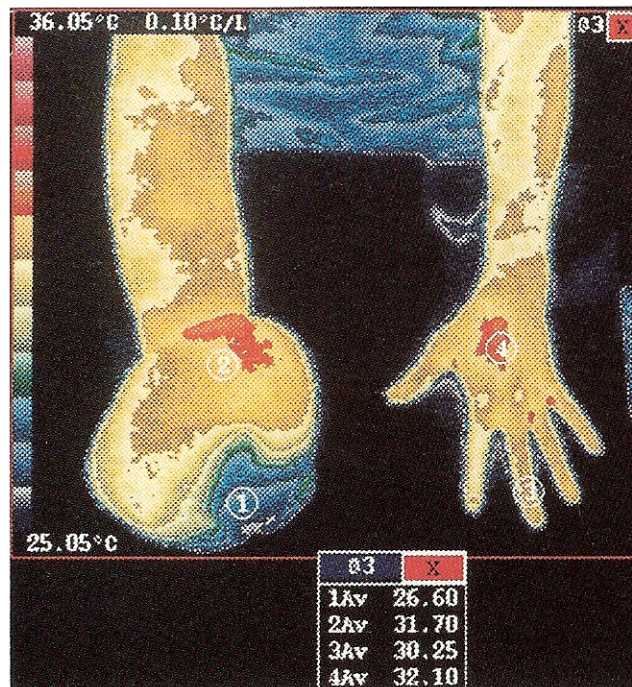
In two patients in our series, the long-term effect of inflammation resulted in spontaneous rupture of biceps muscle and tendon. In stage III (Table 1), sympathetic ganglion nerve blocks usually do not provide enough pain relief because the condition is too advanced and the pain is usually sympathetically independent pain. Repetitive sympathetic nerve blocks at this stage may result in exhaustion of the sympathetic system [104], leading to traumatic "virtual sympathectomy" [29,104] (Fig. 6) and deteriorating the patient's condition. At this stage, epidural and paravertebral nerve blocks [84,85] are more effective.

Stage IV [29] (Table 1) identifies the final stage of CRPS manifested by:

1. Failure of the immune system, reduction of helper T-cell lymphocytes and elevation of killer T-cell lymphocytes (Table 1); this is in contrast to the opposite, up-regulated function of immune system in the early stages (Table 1).
2. Reversal of hypertension to hypotension; the hypertension in early stages due to $\alpha$-1 up-regulation reverses to eventual exhaustion and to the common occurrence of orthostatic hypotension in this late stage (in 24 of our 36 patients in stage IV). The BP changes in this stage are due to autonomic failure, and the failure of the sympathetic system exaggerates the response to drugs that lower or raise the BP [167].
3. Intractable generalized edema involving the abdomen, pelvis, lungs, and extremities due to longstanding disturbance of sodium-potassium and calcium-magnesium pumps usually left untreated for years; the same organs may eventually be subject to multiple abscesses due to failure of immune function.

4. Ulcerative skin lesions [162] (Fig. 5).
5. High risks of cancer and suicide.
6. Multiple surgical procedures seem to be precipitating factors for development of stage IV (Table 4).

Stage IV is almost the flip side of earlier stages and points to exhaustion of autonomic and immune systems. Ganglion blocks in this stage are useless and treatment should be aimed at improving edema and the failing immune system. Sympathetic ganglion blocks and alpha blockers, including clonidine, are contraindicated in stage IV due to hypotension. Instead, medications such as midodrin (Proamantin) [217] are helpful to correct the orthostatic hypotension.

Dogmatic reliance on staging is somewhat artificial in nature. Each patient follows a different course. In children and teenagers [22–26] usually the prognosis is good and stages need not develop due to the fact that their rich cerebral growth hormone, sex hormone and endorphin formation prevent deterioration. The same logic applies to pregnant women. With early treatment, the disease may revert to stage 1. Even patients suffering from stages II or III after proper treatment may revert to stage I and may look quite normal. The reverse is true in patients treated with surgery, immobilization, and ice application, who in a matter of less than 1 yr may end up in stage III (Table 4).

## Treatment

The goal of treatment is reversal of the course, amelioration of suffering, return to work if at all possible, avoidance of surgical procedures (Table 4), and improvement of quality of life. The keys to success are early diagnosis and early assertive treatment. Lack of proper understanding and proper diagnosis lead to improper treatment with poor outcome. There is a desperate need for future research in the treatment of CRPS. Delay in diagnosis is a factor in therapeutic failure. According to Poplawski and colleagues [218], treatment, and its results, are hampered by delay in diagnosis. Early diagnosis (up to 2 yrs) is essential for achieving the goal of successful treatment results [218]. Simple monotherapy with only nerve block, only gabapentin, or otherwise, is not sufficient for management of CRPS. Treatment should be multidisciplinary and simultaneous: effective analgesia, proper antidepressants [219] to prevent pain and insomnia, physiotherapy, nerve blocks, proper diet, channel blockers when indicated, and anticonvulsant [220] therapy should be applied early and simultaneously. Administration of piecemeal, minimal treatments is apt to fail.

### Physical Therapy

Proper physical therapy is at the top of the list for proper treatment. In this regard, in neuropathic pain, "no pain is all gain" rather than the opposite. Any activity that aggravates the neuropathic pain should be avoided. Distress of pain aggravates the sympathetic dysfunction. The patient is instructed to frequently change positions. Usually, the major aggravators of the pain are inactivity [97], distressful overdoing of exercise, or repetitive stress injury [31].

### Ice and Heat Therapy

Basbaum [130], and others [59–62] have demonstrated extensive lesions affecting large myelinated axons secondary to ice exposure. These lesions are in the form of Valerian degeneration and segmental demyelination [59,62,130]. Cold injuries, frostbites and heat burns are common iatrogenic causes of peripheral neuropathic pain [131]. Heat or cold therapy with warm or cold water should not be mistaken for freezing ice or boiling water exposure. Obviously, ice and hot water are damaging and should be avoided. Temporary use of ice is the treatment of choice for acute but not chronic pain. The repetitive application of ice in chronic pain patients causes cold skin due to vasoconstriction followed by vasodilation, usually lasting about 15 min [130]. In our study of 824 patients, 34 patients were exposed to ice treatment for less than 2 mos versus 226 patients exposed to ice treatment for more than 2 mos (Table 4). In the group with over 2 mos' exposure to ice, 52% ended up in Stages III to IV versus 30% in the less than 2 mo exposure to ice ($p <0.001$) (Table 4). Conversely, only 7% of the group with longer exposure were in Stage I versus 38% in the group with shorter exposure ($p <0.001$) (Table 4). Ice and heat challenge may stimulate and aggravate the sympathetic dysfunction. The sympathetic dysfunction in and of itself causes neurovascular instability [2], in the form of mottling and erratic fluctuation of temperature of the extremity, pointing to a dysfunctional sympathetic system. Ice and heat challenge exaggerate this instability. It is important to listen to the patient. If ice causes pain, it should be avoided. The same is true with heat therapy.

### Inactivity

If at all possible, the CRPS patient should not be hospitalized unless it is absolutely necessary (such as for emergency surgery). The usual hospital policy of enforced bed rest aggravates CRPS. The inactivity results in upregulation and activation of the sleeping nociceptors (deep chemoreceptors in bone and muscle) [97], with secondary deep, intolerable pain. The patient is instructed to stay in bed no more than 8 to 9 h a night and to try to walk before going to bed. If sitting or lying down causes pain, the patient is instructed to get up and move around. If walking or any type of exercise causes pain, the patient is to rest frequently. Treatment of osteopenia requires ambulation and weight bearing. The use of a wheelchair, walker and other assistive devices should be discontinued.

The CRPS patients are usually in pain on arousal in the morning due to long hours of inactivity and bed rest. The same phenomenon awakens the patient in early hours of the morning, keeping him or her awake most of the night. The best advice to the patient is to get up and walk. Any excessive exercise is as harmful as inactivity. Aerobic exercise is quite beneficial. Physical therapy should be applied by the patient several times a day, with frequent resting in between. Limiting physical therapy to two to four times a week in the physical therapy department provides a false sense of security and causes a tendency for the patient to become less active the rest of the week. The patient should incorporate therapy into the daily living schedule by trying to change position as often as possible.

### Pain Relief

Adequate pain management is the top priority [45]. It is doubtful if any CRPS patient improves unless the pain is properly under control. According to Bonica, "Pain is never benign" [221]. Proper pain relief ". . . enables the host to resist life-threatening consequences of surgery" [45]. The ideal prophylactic analgesic for this condition is antidepres-

sants [213,219,222]. From a therapeutic standpoint, there are three forms of pain that require three different therapeutic disciplines.

1. Acute pain such as heart attack, surgical procedure, etc. The analgesic of choice for this type of acute pain is opiates.
2. Chronic pain of 6 mos or longer, such as seen in CRPS or failed back syndrome. Surgery usually fails and aggravates the dysfunction [45]. Repetitive ice application is damaging [59–62,130]. The analgesic of choice is the prophylactic use of antidepressants [219] supplemented by analgesics less likely to cause rebound and tolerance.
3. Cancer pain: the body is undergoing acute and chronic destructive pathology complicated by side effects of chemotherapy or radiotherapy. The goal is to keep the patient comfortable and pain free by all means available; surgery and any palliative medication should be applied generously to keep the patient from suffering for the remaining life expectancy of a few months or few years. The same logic cannot be applied to chronic pain patients, such as those with CRPS, whose life expectancy is a few decades. A few decades of opioid agonist treatment leads to rebound pain and tolerance (demanding higher doses), and the risks of depression, suicide, or overdose.

## Opiates

Opioids play a major role in management of pain and inflammation in the peripheral and central nervous system [143]. The endogenous ligands-opioid peptides (endorphins) are expressed by resident immune cells in peripheral tissues [143]. Depriving the patient of proper pain medication can aggravate the immune system dysfunction. The selection of proper opiates for treatment of CRPS is quite critical. Both opioid agonists and mixed opioid agonist-antagonists have been used for treatment of pain in such patients. Opiates are considered effective in the treatment of neuropathic pain [223]. However, due to the complexity and multiple origins of the pain in CRPS, in some patients the opioid agonists are not as effective [224]. Morphine does not consistently reduce the neuropathic pain [82,224]. Morphine (0.1–1 mg/kg IV) may increase the localization threshold of lesioned limb pressure and may decrease the chronic pain score [225,226]. Morphine may decrease mechanoallodynia [112] in the diabetic rat, but the effective doses have to be quite high in the range of 2 to 4 mg/kg IV, which are too high for human application [223]. Long-term use of opioid agonists has the potential of tolerance and dependence [227], impairment of physical function [228], and depression [229,230]. Yet 83% of pain specialists have been reported in 1992 [231] to maintain chronic non-cancer pain patients on these medications. This percentage has grown far higher since then: of 824 patients in this study, only 36 (4.3%) had not received long-term opioid agonists therapy. Moreover, the present trend is for polypharmacy of opioids in high doses. Such high doses exceed the optimal therapeutic window for analgesia.

The therapeutic window refers to the fact that opiates, similar to anticonvulsants, are most effective in their therapeutic range [167]. Above and below this window they are ineffective [222].

## Morphine

Opioid agonists such as morphine, fentanyl, and others have been found ineffective against the abnormally fluctuating reaction to thermal allodynia (neurovascular instability), while retaining antinociceptive activity against painful thermal stimuli (heat hyperalgesia) [112]. Long-term use of morphine suppresses many specific functions of the immune system [152]. Both acute and chronic application of morphine strongly suppresses the T-cell and B-cell immune functions [232]. Morphine may interfere with the development of antibody-antigen immune function [233]. Due to the fact that many cells and organs related to the immune system have been shown to have opiate receptors [143], morphine has the potential of directly affecting and altering many immune processes [143,234]. Morphine may affect and suppress noxious stimulus-evoked fos protein-like immunoreactivity [152]. Morphine and other similar opioid agonists bind to opioid receptors in the limbic system (temporal lobe) [235], affecting memory and mood.

Contrary to the common concept, large doses of opiates usually disrupt the natural sleep pattern. It is true that opiates induce excessive sedation in 24 h. However, the nocturnal sleep pattern is interrupted every few hours due to withdrawal phenomenon, leaving the patient tired and sleepy during the day. The use of proper antidepressants and adherence to the above-mentioned therapeutic window help correct this problem.

## Buprenorphine

The above side effects of long-term treatment with opioid agonists leave the door open to search for more effective opiates. Buprenorphine, an opiate agonist-antagonist, is a strong analgesic [236] without causing dysphoria, or dependence [236–238]. Sublingual buprenorphine has been used successfully for detoxification from cocaine, heroin and methadone dependence [236–238]. Buprenorphine is a Class V narcotic in contrast to morphine, methadone or fentanyl, which are Class II. Within the proper therapeutic window, buprenorphine (2 to 6 mg/day) and butorphanol (up to 14 mg/daily), act as opioid antagonists by occupying only mu and delta receptors. In higher than therapeutic doses, they fill the kappa receptors as well, changing said drugs to pure opioid agonists [239] and resulting in problems of rebound and tolerance [240]. Within 2 to 6 mg per day, buprenorphine occupies mu and delta opioid receptors, but the kappa receptor is not occupied and is capable of receiving endorphins. When all three opioid receptors are occupied, endorphins cannot bind to them. Consequently, endorphin formation is ceased, leading to dependence and tolerance [241].

The Harvard group [242] and others [243,244] have found buprenorphine to act as an antidepressant leading to ". . . clinically striking improvement in both subjective and objective measures of depression" [242]. This is in contrast to the common depressive effect of opioid agonists.

## Antidepressants

Antidepressants, similar to carbamazepine, block the N-methyl-D-aspartate (NMDA) receptors [245] and improve cell membrane function. Antidepressants are important in improving the eventual recovery, immune system function, and reduction of mortality and morbidity in chronic pain patients [246–248].

Antidepressants possess pure analgesic properties [219]. An example is doxepin (Zonalon) topical cream, which is an excellent topical analgesic for neuropathic pain. The analgesic effect of tricyclics is reversed by naloxone [213]. The analgesic property makes the therapeutic use of antidepressants essential for treatment of neuropathic pain [220].

Antidepressants with properly balanced serotonin and norepinephrine reuptake inhibition provide maximal analgesia. Antidepressants, similar to a morphine pump, provide naloxone-reversible, endorphin-type pain relief [213]. Such drugs as desipramine [249], imipramine and trazodone are superior to mainly serotonin inhibitors such as mitrazepine (Remeron) and fluoxetine. Remeron is a good hypnotic, but in our patients it has shown no significant analgesic value. On the other hand, venlafaxine (Effexor) is a weak inhibitor of serotonin and a strong inhibitor of norepinephrine reuptake, aggravating hypertension [250,251] and sympathetic vasoconstriction by augmenting norepinephrine function. Venlafaxine has a high profile of adverse drug interaction with P450 [252] and CYP2D6 [152] isoenzyme inhibitors (which comprise a long list of medications). It is best not to use this drug in CRPS. Buproprion (Wellbutrin) aggravates seizure disorder. Myoclonic jerks, a common complication of CRPS, are aggravated by this drug. Its use is contraindicated in CRPS. Certain antidepressants such as tricyclics and trazodone, increase the synaptic serotonin and norepinephrine concentrations [253]. This balanced phenomenon provides effective analgesia [213], natural sleep, and antidepressant effect. Trazodone [253] provides analgesic effect in less than 24 h, in contrast with 5 to 7 days for the same effective result with tricyclics. Trazodone does not cause weight gain when compared to amitriptyline (see below).

The tricyclics, similar to carbamazepine, block the NMDA receptors by acting as sodium channel blockers [245] similar to mexiletine [254]. The antidepressants are assumed to improve the function of the inhibitory nerve cells in the periaqueductal gray matter and in its descending pathways, achieving better inhibition of pain [131]. This inhibitory enhancement also improves sleep pattern. Desipramine, a by-product of amitriptyline, blocks the $\alpha$-1 adrenergic receptor function and reduces sympathetic efferent activity [249], leading to improvement of cardiac outflow and norepinephrine-related nerve stimulation.

Of the tricyclics, amitriptyline has been the most widely used analgesic; but it has strong anticholinergic and sedative side effects [255], and may cause paranoid and manic symptoms [256]. More importantly, it has a tendency to cause weight gain. In our study of 824 CRPS patients, 612 had already been tried on amitriptyline. In the first year, these patients gained an average of over 7 kg, and, in the following year, an additional 3.6 kg. Trial of desipramine or trazodone did not cause any significant weight gain. Weight gain in a CRPS patient who already has difficulty with ambulation is quite harmful. In addition, tricyclics have adverse cholinergic and muscarinic properties, resulting in complications of orthostatic hypotension and ECG changes.

Desipramine, a byproduct of amitriptyline metabolism, is a "cleaner" tricyclic with fewer side effects [213,257,258]. Nefazodone (Serzone) has no discernible analgesic value. Moreover, it is a very potent inhibitor of serotonin reuptake, which may cause "serotoninergic syndrome" of diarrhea, tremor, and altered mental state [259].

The selective serotonin reuptake inhibitor antidepressants provide varying degrees of analgesia. However, one fifth of the patients on selective serotonin reuptake inhibitors develop loss of libido and significant sexual dysfunction [219,260]. This complication limits the routine application of selective serotonin reuptake inhibitors for analgesic purposes in CRPS. In late stages, and in patients treated with a morphine or hydromorphone pump, the serum level of estrogen and testosterone is at or below the lower limits of normal. The low sex hormones in these patients are often accompanied by edema, fatigue, hot flashes in women, and a tendency for inactivity. Supplementing estrogen or testosterone in such patients counteracts the chronic fatigue and cold extremities, and improves the level of analgesia. Selective serotonin reuptake inhibitors in at least one fifth of patients aggravate these symptoms and preclude their use.

### Anticonvulsants

Anticonvulsant treatment is helpful in CRPS [253,261] for two types of symptoms: (1) in spinal cord sensitization leading to myoclonic and akinetic attacks; and (2) in patients who suffer from ephaptic- or neuroma-type of nerve damage characterized by stabbing, electric shock, or jerking type of pain secondary to damage to the nerve fibers [262]. In such cases, anticonvulsants [220], especially Tegretol (nongeneric) [261,263], valproic acid, gabapentin [264], and Klonopin (nongeneric) [265–267], are quite effective. The ephaptic, causalgic CRPS II is best managed with combination of an effective anticonvulsant, antidepressant, and analgesics.

Clonazepam is effective in the control of myoclonic jerks [265]. Decades of experience with Klonopin and Tegretol in neurology have taught the lesson that these brands are superior to their generic forms (clonazepam and carbamazepine) in controlling epileptic seizures. The American Academy of Neurology has recommended that generic antiepileptic drugs not be prescribed. Gabapentin (Neurontin) [264], which is an adjunctive anticonvulsant, provides relief for burning-type neuropathic pain. Similar to Tegretol, gabapentin is also neuroleptic. Carbamazepine, similar to mexiletine [254,268], is an effective sodium channel blocker. It is far better tolerated than mexiletine.

### Nonsteroidal Anti-inflammatory Drugs

The inflammatory complications of CRPS respond properly to nonsteroidal anti-inflammatory drugs [176,260,269]. The beneficial effects of nonsteroidal anti-inflammatory drugs may be related to correcting the immune inflammatory damages in nerve death, be it neuropathic inflammation of CRPS, nerve death due to Alzheimer's [270,271], or cerebrovascular disease (e.g., benefits from aspirin therapy). In Alzheimer's, immune factors such as "membrane attack complex" [272,273] play a role in nerve death, this may explain the benefits of nonsteroidal anti-inflammatory drugs [274]. Ketorolac (Toradol) can be utilized for pain relief and detoxification from opioid dependence. It should not be used for more than 10 days due to danger of gastrointestinal bleeding. The CRPS inflammation frequently causes joint pain, which is aggravated by a drop in barometric pressure due to exvacuo edema of the synovial membrane containing microneurovascular circulation. Nonsteroidal anti-inflammatory drugs help alleviate this condition.

## Alpha Blockers

The α-1 blockers phenoxybenzamine (Dibenzyline) and tera-zocin (Hytrin) are effective systemic nerve-blocking agents. Forty soldiers suffering from CRPS type II were treated with phenoxybenzamine, with excellent results [275], eliminating the need for sympathectomy. Clonidine [276,277] in oral, intrathecal [278], or cutaneous patch [276] forms is quite effective as an α-2 blocker. Application of clonidine patch to the area of original damage in the extremity may aggravate the pain. It is effective when applied topically to the paraver-tebral area in cervical or lumbar region corresponding to the referred pain of sensory nerve roots. After completion of sympathetic nerve block injection, application of a clonidine patch is a complementary treatment and may prevent the need for further invasive nerve block. Another effective α-2 blocker, yohimbine, is not as potent as α-1 blockers.

## Management of Inflammation and Edema

A common manifestation of inflammation is the disturbance of cell membrane function in the form of edema [44,144, 148,149,154,155,161,162, 180, 279] also known as neurogenic inflammation [163]. This is due to disturbance of sodium-potassium and calcium-magnesium pumps [171].

There are two different forms of edema: (1) extracellular hypervolemia, such as seen with congestive heart failure (this is a pitting edema due to increased plasma volume); and (2) intracellular edema, such as seen with glaucoma and pseudotumor cerebri. This form of edema causes intracel-lular cytoplasmic water retention leading to cerebral edema [280] and indurated edema associated with neurovascular instability (fluctuating rusty, reddish, or pale discoloration). Normally, the perineurium is impenetrable to water [84]. In inflamed tissue the peripheral nerve terminals increase by ("sprouting") [84]. As a result, edema sensitizes the tissue to opioid peptides and to pain. Standard diuretics such as hydrochlorothiazide or furosemide dehydrate and reduce the volume of the extracellular space. They are most effective in cardiovascular diseases. The osmotic diuretics such as man-nitol [280], chlordiazepoxide or magnesium salts [281,282] reduce the intracellular volume and reduce neurogenic edema (Fig. 5). The edema of CRPS due to normal cell membrane dysfunction [185] leads to rise in intracellular $Na^+$ and $Ca^{++}$ [283]. Correction of sodium potassium pump with the help of NMDA inhibitors such as mexiletine [254,284], carbama-zepine [263], and MK801 [285] also help reduce edema.

Magnesium sulfate (epsom salt), in oral, IV, enema, or bathing form, effectively reduces the edema [281,282,286]. It acts similarly to calcium channel blockers [256,286], which are also effective in neuropathic pain and headache. For the complication of neurogenic bladder and interstitial cystitis [170], nifedipine may be helpful [287].

## Treatment of Osteopenia

Osteopenia, usually transient [288], is a common complica-tion of CRPS. Most commonly, it affects the hip, foot, shoulder, and wrist areas. Treatment consists of a combina-tion of weight bearing, mobilization, estrogen replacement, biphosphonates [289–291], and a diet rich in calcium (e.g., cabbage and dairy products). Mobilization is the most indis-pensable form of treatment.

## Hormone Replacement Therapy

According to McEwen and colleagues, "Ovarian steroids produce measurable cognitive effects after ovariectomy and during aging" [274]. Hormone replacement improves the cerebral cognitive functions [274,292]. Estrogen plays a ma-jor role in formation of new excitatory synapses and NMDA regulation both in male and in female formative brains [274, 292]. Realizing that women CRPS patients, regardless of age, have a tendency for menopausal symptoms (hot flashes and excessive sweating), serum estrogen levels were meas-ured in 60 of these patients in this study. The serum estrogen (midcycle estradiol) was in the 87- to 195-PG/ml range as compared to the normal 100- to 395-PG/ml range. Estrogen replacement therapy improved cognitive function and re-duced the tendency for hyperhydrosis in these patients. In 43 patients who underwent infusion-pump therapy for CRPS, a more significant drop in serum estrogen and testosterone levels was noted. Forty-one patients required hormone re-placement therapy, which improved pain reduction by an average of 1.7 (on a basis of 0 to 10) and reduced or cleared up the edema of the lower extremities.

## Management of Referred Pain

Referred pain is a potential source of confusion. The remote manifestation of referred pain misleads the clinician and may cause unnecessary treatment applied to the referred pain area. For example, an ankle injury with referred pain to the lumbar spine region may lead to unnecessary diskectomy for an in-nocuous disc bulging at the L-5/S-1 level due to multiple preg-nancies and deliveries. Or referred pain and inflammation to the wrist due to an elbow injury may be mistaken for carpal tunnel syndrome (Table 5) and may end up with unnecessary surgery. Neurogenic inflammation [163] plays a major role in referral of the pain [163,173]. The primary afferent sensory neuron plays a major role in modulation of excitatory and pro-inflammatory neuropeptides such as substance P [197,198] and CGRP [141], inhibitory hormones such as corticotropin-releasing hormones, and opioid peptides such as Dynorphin [143]. In the late stage, the pain is usually allodynic and has a tendency for referred pain syndrome (e.g., shoulder-hand syndrome, carpal tunnel syndrome) and for involvement of the paravertebral sensory nerves due to peripheral nerve injury. This nerve irritation, mainly due to substance P [197–199] ascending along the pri-mary afferent sensory nerve fibers [142,146,164,171,283,293, 294], manifests itself as neck pain, back pain and occipitofron-tal headache.

The paravertebral nerve irritation in the upper cervical nerve root levels (C1–3) may in turn stimulate the trigemino-vascular nerves [210,211,295] leading to pathogenesis of headaches in CRPS. Substance P is a versatile modulator of the immune system. It upregulates the formation and func-tion of monocytes [143]. It stimulates the release of lym-phocytic cytokines [143]. It ameliorates the neurogenic edema [163,173,296]. Capsaicin does the opposite by depleting sub-stance P [146,164,297,298]. Capsaicin has long been used as an experimental model of neuropathic pain [146,164,297, 298]. Its repetitive use causes a new source of pain.

## Nerve Blocks

Nerve blocks may be diagnostic [121], therapeutic, or both. The two types of blocks are not identical and interchange-

able. The diagnostic nerve blocks with simple local anesthetic injection last a few hours to a few days. Unfortunately diagnostic ganglion nerve blocks are commonly mistaken to be a form of therapy. The metaanalysis studies by Kozin [299], Carr and coworkers [300], and Schott [301], have emphasized such blocks are indistinguishable from placebo. Simple pain relief from blocks sympathetically maintained pain does not prove CRPS [77]. Other conditions such as diabetic neuropathy can also be sympathetically maintained type of pain. Therapeutic blocks such as regional, epidural, or paravertebral usually contain bretylium, guanethidine, or corticosteroid; their effects last up to several weeks.

There are three main forms of diagnostic blocks: (1) sympathetic ganglion block, (2) local anesthetic nerve block, and (3) compression regional block [302]. Diagnostic nerve blocks are hampered by a significant incidence of false-positive and false-negative results, even in the best hands [110]. Ganglion nerve blocks with local anesthetics are mainly diagnostic. The local anesthetic effect doesn't last more than 2 h to a maximum of 1 to 14 days. Ganglion nerve block should be complemented with therapeutic nerve blocks such as brachial plexus, regional, and epidural nerve blocks. Whereas ganglion nerve blocks temporally improve circulation and relieve pain, they do not improve flexor spasm and deformity of the hands and feet. The brachial plexus and regional blocks are more beneficial in correcting such movement disorders.

The relief from epidural, paravertebral, regional and brachial plexus blocks with a combination of bupivacaine and prednisolone lasts about 8 to 12 wks. It is effective for somatic radiculopathy and for neuropathic pain [84,85]. Repeated stellate ganglion blocks can permanently damage the sympathetic nerve cells and result in "virtual sympathectomy" [104]. In addition, such repetitive trauma may be complicated by migraine headaches [303].

## Paravertebral versus Zygoapophyseal Treatments

According to Cheema [304], paravertebral nerve block provides effective pain relief for both sympathetically maintained pain and sympathetically independent pain. This is in contrast with articular facet (zygapophyseal) blocks, which are fraught with painful joint injuries.

The paravertebral nerve blocks are technically similar to zygapophyseal blocks but should not be mistaken for each other. The zygapophyseal blocks invade the zygapophyseal joint. Insertion of needle, or radiofrequency treatment of the zygapophyseal joint is traumatic to the joint, and has the potential of adding new pathology with additional source of pain. Bogduk's team [305], has reported only 40% pain relief in patients undergoing such zygapophyseal joint neurotomy. The paravertebral nerve block does not invade any joint structure and should not be mistaken for zygapophyseal injection or neurotomy.

### Referred Pain and Nerve Blocks

Referred pain as a remote manifestation of neuropathic pain is mainly modulated by substance P [197–199] and nitric oxide [145,200]. The response of substance P and nitric oxide can be identified in paravertebral regions of the spine as neuropathic inflammation and antidromic vasodilation [306]. As the substance P ascends along the primary afferent sensory nerve fibers [142,171,283,293,294], the substance P accumulates in and around paravertebral sensory nerves. Pressure on the paravertebral regions identifies the areas of inflammation. Gentle pressure by the examiner may release a reddish blush over the skin in the referred pain area. This guides the clinician to treat the condition by performing paravertebral nerve blocks. The blocks should be done at proximal paravertebral areas of nerve irritation rather than at the site of the nerve injury in the extremity. Insertion of a needle in the distal extremity area of the nerve damage for nerve block, similar to stress of surgery, may aggravate the inflammation and pain [48,49,307]. Bier, regional blocks [82] with bretylium or guanethidine are an effective diagnostic and therapeutic block. Insertion of the needle should be away from the vortex (see infrared thermography under diagnostic test) of damaged nerve area in the foot or hand.

### Sympathectomy

In our series of 824 CRPS patients, 22 had undergone surgical sympathectomy, with temporary partial relief of 6 days to 38 wks in nine patients, up to 54 wks in 10 patients, and no relief in 3. Chemical sympathectomy was done (prior to referral to our medical center) on 13 patients, with temporary relief of 3 days to 29 wks in four patients, no relief in five, and rapid deterioration of CRPS in four patients. Surgical, radiofrequency and chemical or (neurolytic) [308] sympathectomies [53] have been applied in the treatment of CRPS since 1916 [53]. Sympathectomy may provide temporary pain relief but, after a few weeks to months, it loses its effect [29,86]. The success has been limited to the series that have had short-term patient follow-ups of a few months after surgery [309,310]. Sympathectomy and application of neurolytic agents should be limited to patients with life expectancies measured in weeks or months, eg, cancer and end-stage advanced occlusive vascular disease patients. On the other hand, CRPS patients usually have three to five decades of life expectancy ahead of them. They should not be exposed to aggravation of pain due to sympathectomy.

The sympathectomized patients developed postoperative spread of CRPS in 12 of our 35 patients (37%). This high incidence of spread is in contrast to the 18% incidence in the rest of 824 cases.

Reasons for sympathectomy failure include the following:

1. Laser Doppler-vascular studies [2] have revealed the temporary benefits of vasoconstrictor reflexes lasting no more than 4 wks. The neurovascular instability [2,104] in late-stage reflex sympathetic dystrophy is not expected to respond to sympathectomy. Sympathectomy is aimed at achieving vasodilation. The neurovascular instability refers to vacillation and instability of vasoconstrictive function. This leads to fluctuation of vasoconstriction alternated with vasodilation in an unstable fashion [205]. Following sympathectomy the blood flow and skin temperature on the nonsympathectomized side are significantly lower after exposure to a cold environment [205]. This phenomenon may explain the reason for spread. In the first 4 wks after sympathectomy, the laser Doppler flow study shows an increase of blood flow and temperature of the extremity. Then after 4 wks the skin temperature and vascular perfusion slowly decrease and a high-amplitude vasomotor constric-

tion develops [205], reversing any beneficial effect of surgery.

2. At no time can the sympathectomy be complete—unless it is done at the time of autopsy with complete removal of the chains of sympathetic ganglia.

3. Due to extensive interconnection of chains of sympathetic ganglia, removal of a short chain of sympathetic ganglia is easily compensated by rerouting of the sympathetic impulses through the horizontal and vertical connections of sympathetic nerve fibers in the paraspinal chain of sympathetic ganglia, as well as through the midline connection of sympathetic ganglia via the midline sympathetic plexi such as cardiac plexus, superior mesenteric plexus, etc. (Fig. 6). This is no different than disruption of traffic on a major highway, which is easily compensated by rerouting of the traffic load by available alternate routes (Fig. 6).

4. The wide dynamic range [12] of spread of pain impulse in adjacent levels of spinal cord [72,73] explains the spread of pain to adjacent levels above and below the sympathectomized area [29,43,86].

5. The α-1 adrenoreceptors in the sympathectomized area are hypersensitive to the smallest concentrations of circulatory or adjacent tissue noradrenaline [6–9]. Microneurographic studies in four sympathectomized patients reproduced the original pain in the sympathectomized limb after injection of noradrenaline in the unaffected limb [9]. The sensory nerves in the sympathectomized limb preserve their supersensitivity to the circulating norepinephrine [9,311] with persistence of pain after surgery.

6. The patient's age plays a major role in the success or failure of sympathectomy. Most studies done on postsympathectomy patients have been on the soldiers in major wars. The soldiers are usually teenagers (ages 17 to 20). It is a well-known fact that CRPS in children and teenagers has a better prognosis than in adults [22,23]. The partial success of sympathectomy in teenagers does not prove that adults can attain the same beneficial outcome. Even among teenage soldiers, proper long-term studies of sympathectomies have not been done.

7. It would not be logical to expect sympathectomy to relieve CRPS. By the time the sympathectomy is undertaken, the disease is usually too advanced and in late stages. The pain is mainly sympathetically independent pain and is expected to be nonresponsive to ablation of the sympathetic ganglia. Sympathectomy aggravates the already existing sympathetic dysfunction [302].

8. Chemical and radiofrequency sympathectomy cause chemical damage and scarring of adjacent tissues. This is especially true in the case of alcohol or phenol chemical sympathectomy [312]. The scar of such chemicals becomes a new source of neuropathic pain. Chemical or radiofrequency ablation surgical procedures are justifiable as an act of mercy for advanced cancer patients, but CRPS patients usually have a few decades of life expectancy and cannot be expected to live for several years with the pain due to the scar of such destructive procedures.

9. Regarding civil versus war experience with sympathectomy; review of the literature reveals that the sympathectomies done in wartime were for treatment of causalgia in acute early stages and were done in young soldiers [312]. In contrast, in civil cases, the surgery is done in late stages and the patients are older. Obviously, in acute early stages of the disease, the pain is more likely to be sympathetically maintained pain and would be expected to respond positively to sympathetic block or sympathectomy. This is not true with chronic civil cases.

10. According to Bonica [87], "About a dozen patients with reflex sympathetic dystrophy in whom I have carried out preoperative diagnostic sympathetic block with complete pain relief, sympathectomy produced either partial or no relief. Postoperative examination with a sweat test and psychogalvanic reflex revealed residual sympathetic function, and this was confirmed with subsequent sympathetic blocks which produced both sympathetic denervation and pain relief [87]." On the same page, Bonica wrote, "There are other possible explanations for failure of sympathectomy to relieve pain and causalgia. One is that, although sympathectomy relieves burning pain, it may not affect the deep, tearing, stabbing, and bursting pain [87]."

11. At times after lumbar sympathectomy, the patient may develop Horner's syndrome on the same side and marked vasoconstriction of the hand on the same side, reflecting the complex connections of the sympathetic nervous system [29]. Cooper and colleagues [313] have shown vasoconstriction in the hand during electrical stimulation of the lumbar sympathetic chain. De novo reflex sympathetic dystrophy has also been noted in the ipsilateral hand in two patients after lumbar sympathetic block [29].

12. The beneficial effects of sympathectomy are reported in a surgical series of patients followed for a few months, as short as 1 to 4 months. The follow-up of up to 5 yrs reveals a high incidence of recurrence of symptoms and signs after sympathectomy [29].

13. Repeated sympathectomies are no guarantee to success [87,88]. If anything, the repetitive surgical damages cause further deterioration of the condition.

14. Unlike somatic nerves, sympathetic nerves can regenerate after sympathectomy. Matassi and colleagues [314], have reported practically complete regeneration of T1, T2, and T3 sympathetic nerves. This regeneration was histologically confirmed after two sympathectomies [314]. Koltzeburg and coworkers [315] have shown that the sympathetic vasoconstrictor neurons have a high capacity to functionally regenerate in the autonomic effector organs. Moreover, they [315] noted that the target blood vessels showed an exaggerated response to alpha agonists. This explains the fact that the sympathectomized extremity in humans is as cold or colder than the contralateral extremity.

After a few months to a few years, the sympathectomized extremity becomes progressively hypothermic. Laser Doppler flowmetry [205] showed that, in the months following sympathectomy, denervation hypersensitivity of the blood vessels [186] and intense vasomotor dysfunction may be associated with recurrence of pain and hypothermia in the extremity [205]. Palliative sympathectomy makes sense in a patient with a life expectancy of no more than 1 to 4 yrs, such

as advanced Buerger's disease or severe diabetic neurovascular disease with risk of impending amputation.

*Surgery and Amputation*

Elective surgery for presumptive conditions such as carpal tunnel, tarsal tunnel, and thoracic outlet syndrome—in spite of normal nerve conduction studies—only adds a new source of neuropathic pain at the surgical scar. According to Cherington and coworkers [316], there is a tendency for unnecessary thoracic outlet syndrome surgery. As noted in Table 4, elective surgery is the strongest predictor ($p <0.001$) of poor treatment outcome (please see "Treatment Outcome").

According to Rowbotham [317], "Amputation is not to be recommended as pain therapy." All 11 patients in our series (Table 4) who underwent amputation showed marked deterioration postoperatively. The surgical stump was the source of multiple neuromas with severe CRPS II type intractable pain. Amputation should be avoided by all means due to its side effects of aggravation of pain and tendency for spread of CRPS. Dielissen and colleagues [318] reported the results of amputation in 28 reflex sympathetic dystrophy patients who had undergone 34 amputations in 31 limbs. Only two of 28 patients reported partial pain relief. In 26 of 28 patients, stump involvement with reflex sympathetic dystrophy made it impossible to wear a prosthesis [318].

*Surgery and Immune System*

Surgical procedures in neuropathic pain patients, in general, are sources of stress and produce characteristic neuro-endocrine and metabolic responses and local inflammation and can cause disturbance of immune system function [45,48,49,187].

The body responds in the opposite direction to surgery for somatic vs. neuropathic pain. An acute appendicitis or cholecystitis responds quite nicely to surgery. On the other hand, surgery in the area of the extremity involved with neuropathic pain has the potential of aggravating the condition [45]. Tissue damage from the surgical procedures results in the local release of inflammatory neurokines [45]. This biochemical and cellular chain of events leads to upregulation of the immune system and nervous system activation by releasing substance P, histamine, serotonin, CGRP, bradykinin, prostaglandins, and other agents [45]. This leads to a local vasodilation response in the area of the surgical scar, increased capillary permeability, and sensitization of the peripheral afferent nerve fibers, resulting in allodynia and hyperpathia [46,47]. Surgery can cause suppression of immune function aggravating the manifestations of neuropathic pain [48,49,307]. Postoperatively, there is a tendency for dysfunction of the lymphocytic role in immune regulation. This is manifested by a decrease in number of T-cell lymphocytes [319,320] and the function of the T-cell lymphocytes [49, 319,320]. The disturbance and suppression of the immune system due to surgery enhances malignant tumor growth and metastasis [321–323]. Surgery ". . . results in a perturbation of nervous, endocrine and immune systems as well as their interregulatory mechanisms leading to compromised immunity" [169]. This disturbance of immunity may manifest in skin ulcerations, noted in two of 11 amputees referred to our clinic during the 1990 to 1995 period. A similar case of an amputee with skin ulcers has been recently reported [209].

There are times that surgery is unavoidable. For examples, tear of ligament or cartilage in the knee joint that would preclude weight bearing. In such patients, epidural nerve block with a combination of bupivacaine and 20 to 30 mg prednisolone before, during, and after surgery (with the help of an epidural catheter) helps reduce the side effects of surgical trauma. Another example is extensor deformity of a finger causing useless hand, which, in turn aggravates CRPS.

*Side Effects of Surgery and Blocks*

Unnecessary surgery, immobilization of the extremity with application of a cast, and insertion of a needle for nerve block into the injured area of the extremity such as foot, ankle, knee, wrist, or hand, aggravates the disease. These areas are already undergoing sympathetic dysfunction. The traumatic needle insertion causes further sensitization of dermal and subdermal $\alpha$-1 adrenoreceptors [186]. In these patients, severe irreversible flexion deformity of the traumatized joint may develop in a few days.

## Treatment Outcome

Four potential variants influencing treatment outcome were studied: (1) modes of therapy; (2) the nature of pathology; (3) patient's age; (4) delay in diagnosis and treatment (Table 4; see page 5).

1. The type of treatment was the critical predictor of outcome. For example, in patients younger than 21 yrs, the surgical treatment reversed the beneficial prognostic value of youth ($p <0.001$). Moreover, application of ice over 2 mos ($p <0.001$), application of ice less than 2 mos ($p <0.001$), amputation ($p = 0.025$), and sympathectomy, were the strong predictors of poor prognosis (Table 4).

   Emergency surgical treatments unrelated to CRPS, such as appendectomy and cholecystectomy in CRPS patients, were excluded from this study. Only surgical procedures electively aimed at treatment of CRPS were included to avoid contamination by unrelated diseases. Eleven amputee CRPS patients were referred to us (Table 4). Except for one patient with foot gangrene, the other 10 amputations had not been done on an emergency-last resort basis. Amputation had been preformed to provide better analgesia. However, the surgical stump neuromas became additional sources of intractable pain.

2. The nature of pathology was an accurate predictor of outcome. For examples, chemical sympathectomy with neurolytic agents (alcohol, phenol, or other agents) was performed in 13 patients. Chemical sympathectomy was the third group of poor prognosis after venipuncture and amputation, regardless of other risk factors (Table 4). One probable reason explaining such a poor prognosis may be the fact that the lytic agent infiltrates beyond the target area of injection.

   The venipuncture CRPS group of 17 patients showed the worst prognosis and the most rapidly deteriorating course (Fig. 5), regardless of age at onset, any delay in diagnosis or mode of therapy. Venipuncture CRPS is the purest form of selective sensory nerve injury in the wall of skin and subcutaneous microvasculature. The poor

prognosis may be due to lack of simultaneous somatic sensory nerve stimulation, which would overshadow the neuropathic microvascular sensory nerve irritation.

3. In regard to age at onset, prognosis was good among the 138 patients with onset at 2 to 22 yrs. The exception to this rule was 32 patients in this group who had undergone surgical procedures with poor results, and five other patients ages 3 to 21 yrs who had been accused of having Münchausen syndrome (Table 2), followed by years of no treatment (Fig. 7).

4. As Poplawski and coworkers [218] have emphasized, early diagnosis is important in the management of CRPS. However, if the disease is not diagnosed early, it is of no value if the patient is treated with stressors such as ice, surgery, or cast application. Additionally, if the original pathology is severe and irreversible in nature, early diagnosis is of little value.

The group with the best prognosis was typified by CRPS patients with mainly cold extremity treated with no surgery or ice. The patients with a permanently warm extremity, due to sympathetic nerve damage, fared poorly.

## Conclusion

Complex regional pain syndrome/reflex sympathetic dystrophy is a complex chronic pain syndrome with four main features: hyperpathic/allodynic pain; vasomotor dysfunction and flexor spasms, inflammation, and limbic system dysfunction. Elective surgery and amputation are at the top of the list of aggravating factors. Complex regional pain syndrome is usually caused by a minor injury and requires proper evaluation and multidisciplinary treatment addressing the multifaceted pathological processes that evolve during its chronic course. The patient's age, the nature of pathology, and the mode of therapy influence the outcome of treatment. If at all possible, surgery, ice and cast applications should be avoided. There is a desperate need for research in the proper management of CRPS.

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