WONDER WHY?

The Theoretical Basis for and Treatment of Complex Regional Pain Syndrome with Prolotherapy

Ross A. Hauser, MD & Debra K. Brinker, RN

ABSTRACT

Complex regional pain syndrome (CRPS) typically refers to post-traumatic pain that spreads from the site of injury, exceeds in magnitude and duration the expected clinical course of the inciting event, and progresses variably over time. Burning pain is the primary symptom, but patients frequently report allodynia, changes in the color or temperature of the skin, and if the condition progresses, trophic changes of the skin, nails, and bone occur. The condition produces a high degree of suffering, lost productivity and cost of treatment. While there are many theories as to why CRPS occurs, success in treatment of CRPS with traditional medical therapies is dismal.

CRPS generally appears following a physical trauma, involving the bone and soft tissues which are treated with long periods of immobility. While this immobility itself may be needed to heal a bone injury such as a fracture, it encourages ligament injuries to not heal. Stress deprivation or immobility causes a protracted state of progressive atrophy and lack of mechanical strength in the injured ligaments. The high density of both myelinated and unmyelinated nociceptors in the non-healed ligaments then become sensitized to the point that even normal or less than normal activities activate them to fire causing severe burning pain. These activated nociceptors through local and feedback loops in the central nervous system, cause autonomic phenomenon in the extremity including referral pain, edema and temperature disturbances. Research by George S. Hackett, M.D., who coined the term Prolotherapy, found that ligament relaxation (his term for non-healed ligament injuries) caused bone dystrophy (osteopenia/osteoporosis), which is a common feature of CRPS. He also noted that ligament relaxation often activated the sympathetic nervous system and that when Prolotherapy was performed to the injured ligament(s), not only did the local pain remit, but so did the autonomic phenomenon. Since traditional treatments do not address non-healed ligament injuries, this entity could be the reason that so many cases of CRPS are never resolved. Since Prolotherapy causes ligament regeneration, it should be in the arsenal of any clinician treating patients with unresolved CRPS symptoms.

Journal of Prolotherapy. 2010;2(2):356-370.
KEYWORDS: allodynia, CRPS, chronic regional pain syndrome, ligament injury, nociceptors, Prolotherapy, RSD, reflex sympathetic dystrophy, sympathetic nervous system.

INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic pain and potentially disabling syndrome which typically affects the extremities. It is characterized by a variety of autonomic and vasomotor disturbances, of which diffuse pain, spreading edema, temperature disturbances, and functional impairment are most prominent.[1] CRPS generally appears following a physical injury, is disproportionate to the precipitating event or level of tissue damage, progresses inconsistently over time, and is associated with nonspecific signs and symptoms.[2] It is a disease with an unpredictable and uncontrollable nature, and is a syndrome covered in controversy and confusion.[3, 4] CRPS may appear at any age, indiscriminately affecting young and old, male and female. It spreads like wild fire, perhaps starting in the foot, moving its way up to the knee and back, then down the other leg, and up into the arms.

SIGNS AND SYMPTOMS OF CRPS

Complex regional pain syndrome typically refers to post-traumatic pain that spreads from the site of injury, exceeds in magnitude and duration the expected clinical course of the inciting event, and progresses variably over time. It is characterized by a variety of nonspecific symptoms and signs. (*See Figure 1.*) In a large sample of patients, 81% noted burning or stinging pain as the number one symptom.[5] Patients frequently report allodynia, where the skin becomes so exquisitively sensitive to touch or temperature that normal light contact, such as clothing touching the skin or a draft blowing on the affected area, produces severe pain.[6] Other common symptoms of CRPS include changes in the color or temperature of the skin, asymmetric sweating, trophic changes of the skin, nails and hair.[7] Galer et al. noted that the most common symptoms included severe pain (100%), abnormal swelling (96.7%), and weakness (96.7%). Other initial symptoms were abnormal coldness or heat, color changes, inability to move an extremity, muscle spasms, abnormal sweating, tremors, skin dryness, and feelings as though the

Signs and Symptoms of CRPS

- Abnormal swelling/edema
- Allodynia
- Change in skin color
- Change in skin temperature
- Changes in skin, hair, and nail growth
- Decreased ability to exercise
- Feeling of limb disconnect
- Hyperalgesia
- Hyperesthesia
- Hyperpathy
- Inability to move extremity
- Incoordination
- Involuntary movements
- Limited range of motion/movement
- Muscle and skin atrophy
- Muscle spasms
- Osteoporosis
- Paraesthesias
- Paresis
- Pseudoparalysis
- Severe pain
- Sweating asymmetry
- Tremor

Figure 1. The signs and symptoms of complex regional pain syndrome (CRPS).

limb were disconnected.[8, 9] The swelling may spread with accompanied muscle and joint stiffness. CRPS patients may then experience limited movement in the affected area, with atrophied muscles, limited range of motion, and possible contractures.[10]

HISTORY AND NOMENCLATURE

CRPS has gone through a progression of names. The first description of CRPS may have dated back to 1634 when King Charles IX suffered persistent pain following a bloodletting procedure.[11] In 1872 an American Civil War physician, Weir Mitchell described cases of a burning pain syndrome following gunshot wounds as causalgia.[12]

"*We have some doubt as to whether this form of pain ever originates at the moment of wounding…Of the special cause, which provokes it, we know nothing, except that it has sometimes followed the transfer of pathological changes from a wounded nerve to unwounded nerves, and has then been felt in their distribution, so that we do not need a direct wound to bring it about. The seat of the burning pain is very various; but it never attacks the trunk, rarely the arm or thigh, and not often the forearm or leg. Its favorite site is the foot or hand…Its intensity varies from the most trivial burning to a state of torture, which can hardly be credited, but reacts on the whole economy, until the general health is seriously affected…The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyperanesthetic, so that a touch or tap of the finger increases the pain.*" –Silas Weir Michell, 1872

In 1900, Paul Sudeck described an extremity pain syndrome which developed after bone fractures, which was referred to as Sudeck's syndrome and in European countries as Sudeck's Atrophy.[13] Other names have included minor causalgia, post-traumatic pain syndrome, post-traumatic painful arthrosis, Sudeck's dystrophy, post-traumatic edema, shoulder-hand syndrome, chronic traumatic edema, algodystrophy, peripheral trophoneurosis and sympathalgia.[14] Based on the experience that some patients were obtaining relief from sympathetic blocks, the term Reflex Sympathetic Dystrophy (RSD) was introduced in 1946 by J.A. Evans to accommodate the role of the sympathetic nervous system.[15] The term Sympathetically Maintained Pain was introduced in 1986 as a synonym of RSD.[16] Then due to lack of pain relief in some patients after sympathetic block, the term sympathetically independent pain was used to describe pain states similar to RSD.[17] In an effort to clarify the nomenclature, the International Association for the Study of Pain met in 1993 and came up with the term Complex Regional Pain Syndrome.[18] (*See Figure 2.*)

Names for CRPS

- Algodystrophy
- Causalgia
- Chronic traumatic edema
- Complex regional pain syndrome
- Minor causalgia
- Peripheral trophoneurosis
- Post-traumatic edema
- Post-traumatic pain syndrome
- Post-traumatic painful arthrosis
- Reflex sympathetic dystrophy
- Shoulder-hand syndrome
- Sudeck's atrophy
- Sudeck's dystrophy
- Sudeck's syndrome
- Sympathalgia
- Sympathetically independent pain
- Sympathetically maintained pain

Figure 2. Nomenclature has changed through history regarding this disease. In 1993, the International Association of the Study of Pain (IASP) coined the term complex regional pain syndrome (CRPS) to embody all of the above names.

DIAGNOSIS AND DIAGNOSTIC CRITERIA

The nature of, diagnostic criteria for, and even the naming of CRPS have been controversial.[19] *See Figure 3* for the IASP Diagnostic Criteria.[20] Taking into consideration the controversy in nomenclature, the Special Interest Group "Pain and the Sympathetic Nervous System" of the International Association for the Study of Pain (IASP) at a workshop in Orlando in 1993 came up with the new name after "extensive grappling."[21] Robert A. Boas describes the terminology, "The umbrella term for all disorders falling within the domain of causalgia and reflex sympathetic dystrophy was now designated as a complex regional pain syndrome (CRPS). *Complex* describes the

Diagnostic Criteria for CRPS

1. The presence of an initiating noxious event, or a cause of immobilization.
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Figure 3. International Association for the Study of Pain (IASP) criteria for someone to meet the diagnosis of complex regional pain syndrome (CRPS).

varied and dynamic nature of the clinical presentation within a single person over time, and among persons with seemingly similar disorders. It also included the features of inflammation, autonomic, cutaneous, motor, and dystrophic changes, which distinguish this from other forms of neuropathic pain. *Regional* – as in the wider distribution of symptoms and findings beyond the area of the original lesion—is a hallmark of these disorders. Such symptoms and signs usually affect the distal part of a limb but occasionally can involve discrete regions or spread to other body areas. *Pain* is the *sine qua non* for the CRPS syndrome—pain that is disproportionate to the inciting event. This is not just burning pain, but includes spontaneous pain and thermal or mechanically induced allodynia. *Syndrome* – the constellation of symptoms and signs of CRPS represents a series of correlated events that are sufficient to be designated as a distinctive entity, even though we are not sure what constitutes each of these events, or which are essential, nor the nature of the pathological changes that ensue."[22]

There are three classifications of this syndrome. CRPS type I usually occurs after an illness or injury that did not directly damage the nerves in an affected limb or region of the body. It was previously termed reflex sympathetic dystrophy (RSD), but the current research suggests multiple causes rather than the sympathetic nervous system as the culprit. Complex regional pain syndrome type II, formerly known as causalgia, has been commonly distinguished by evidence of neuronal damage. However, recent studies suggest that there may not be a clear distinction between the syndromes.[23] CRPS III was created for the difficult cases that contained pain and sensory changes, with either motor or tissue changes, but did not comply fully with the more classical forms.[24, 25]

The diagnostic criteria are not yet optimized or even standardized in the literature, and there is reportedly no noticeable difference since the introduction of the criteria.[26-28] Although the criteria are an important step in the right direction, they lack specificity, which makes it difficult to determine new treatment approaches targeted at particular pain mechanisms.[29, 30] There are several other clinical criteria, including Bruehl's or Veldman's clinical criteria, however the IASP criteria are cited more widely in the literature and treatment trials.[31] Stages of progression of CRPS have also been set forth, however an eight year study of 829 subjects failed to identify these stages.[32] A second IASP conference in 2000 also rejected the concept of staging.[33]

HOW COMMON IS CRPS?

There are only a few published epidemiological studies regarding the incidence of CRPS in the general population. The most recent studies by M. de Mos began in 1992 with ongoing data collection utilizing electronic patient records.[34] The first of two de Mos studies included 600,000 patients throughout the Netherlands from1996-2005.[35] The conclusion of the study was an incidence rate of CRPS at 26.2 new cases per 100,000 annually.[36] Applying the results from the de Mos study to the U.S. census bureau population estimates of 299,665,000; one would expect over 50,000 new cases of CRPS-I annually.[37] Most of these patients are at an economically productive age, but CRPS seriously limits their ability to work. The Reflex Sympathetic Dystrophy Foundation conducted a study of 1,348 CRPS patients and found that work was seen to increase pain in 79% of the cases, 38% were unemployed, 17.4% worked full time, 8% part time, and 21% worked at one time but had to stop because of CRPS.[38]

In another study from 2006 of 168 patients, 28% were officially disabled because of CRPS, and the cost of physical therapy for a year per patient was estimated at $6,000.[39] The costs for physical therapy alone for the officially disabled percentage (28-38%) of 50,000 new cases annually calculates to 84-114 million dollars per year. This does not take into account the cost of therapy for those who are not considered officially disabled, or the surgery, or the pain medications, etc. It is clear that CRPS is a disabling disease and has a severe impact physically, vocationally, and economically. Michael Rowbotham, MD comments, "Overall, the present situation is most

unfortunate, considering the very high burden of suffering, lost productivity, and a cost of treatment that may exceed $100,000 (per patient)."[40]

THE CAUSE OF CRPS

Clearly, a substantial number of patients are at risk for and will develop CRPS each year. What then is the precipitating factor of this disabling syndrome? CRPS may develop after a traumatic injury or without any obvious trigger event. A chart review by Birklein et al. of 145 patients in 2000, suggested 41.3% of cases were due to fractures, 32% from soft tissue injuries, 9% due to surgeries, and 17.7% from minor traumas and lesions.[41-43] In the Duman study from 2006, which included 168 patients from two hospitals, the percentage of CRPS from fractures was 55.3%, from soft tissue trauma was 28%, and 16.7% from incisive injuries.[44] A review of 140 cases at the Mayo Clinic over a two year period also noted 65% from external trauma including 28.6% after soft tissue trauma, 20% after fractures, and 16.4% of those cases were a result of surgery.[45] In the majority of pediatric cases, CRPS follows a soft tissue or joint injury.[46] It is perceivable that the aforementioned 55-65% of trauma cases including sprains, fractures and surgery also involved damage to the soft tissues including ligaments. If we were to imagine the force required to break a bone, we could also appreciate that the ligaments supporting the joints would also be injured. Connelly et al. comments, "It should be emphasized that the energy of injury is transferred to the soft tissue as well as to the bone. It is easy to forget this when we mistakenly emphasize the radiograph in our acute evaluation of injuries. Soft tissue injury occurs directly when an object impacts it and occurs indirectly when it is stretched, twisted, or torn at the instant of injury. The soft tissue envelope is the key to understanding most problems in fracture care."[47] The injured soft tissue includes the ligaments and tendons. Ligaments are bands of flexible, tough, dense white fibrous connective tissue which attach one bone to another bone. Tendons are bands of dense fibrous tissue forming the termination of a muscle and attaching the muscle to the bone.[48] Ligaments stabilize and support the joints through their full range of motion, therefore an injury to the ligament negatively affects the joint mechanics.[49] *Is it possible that this ligament injury is involved in the subsequent development of some forms of CRPS?*

It has been noted that the majority of CRPS cases occur after orthopedic procedures.[50] To further delineate the frequency of CRPS as far as fractures, a study of 109 patients indicated an incidence of CRPS at 25-37% after wrist fractures.[51, 52] In the group of 145 patients with CRPS, 42% had previous fractures.[53, 54] In the second de Mos study of 186 CRPS patients, a fracture was the most common precipitating injury in 49% of the cases.[55] As far as surgery, the estimates include 2.3-4% after arthroscopic knee surgery, 2.1-5% after carpal tunnel surgery, 13.6% after ankle surgery, 0.8-13% after total knee arthroplasty, and 7-37% after wrist fractures.[56] Reuben noted that the development of CRPS is a common complication after fasciectomy for Dupuytreen contracture giving an estimate of 4.5-40%.[57, 58] (*See Figure 4.*)

Figure 4. CRPS precipitating events. Fracture and soft tissue injury are the most common precipitating events leading to CRPS.

Study name	Duman [44]	Mayo Clinic [45]	Birklein [41-43]	de Mos 2006 [35]	de Mos 2008 [55]
Patient #'s in study	**168**	**140**	**145**	**238**	**186**
Fracture	55.3%	20.0%	41.3%	43.5%	49.0%
Soft tissue injury	28.0%	28.6%	32.0%	22.6%	26.0%
Surgery	16.7%	16.4%	9.0%	13.6%	11.0%
Spontaneous		15.0%		10.6%	8.0%
Other events, lesions, minor trauma, injections		19.0%	17.7%	9.6%	6.0%

As stated earlier, these fractures and surgeries cause soft tissue damage involving the ligaments. (The reverse is also true; weakness of the ligaments could have caused the bony structure to be susceptible to fracture.) Blood supply to bone is excellent, whereas blood supply to ligament tissue is poor. If the blood vessels supplying blood to the ligaments are sheered by fracture or surgery, this further impedes the ability of the ligaments to heal. (*See Figure 5.*) The ligaments (and other soft tissues) not healed, sets up a perpetual cascade leading to CRPS. We will continue to explore the role of ligament injury and the development of CRPS later in this article.

ALTERED PHYSICAL FUNCTION, QUALITY OF LIFE, AND DISABILITY

Patients with CRPS will face significant quality of life consequences as this pain syndrome dramatically alters their lives as well as the lives of their families and

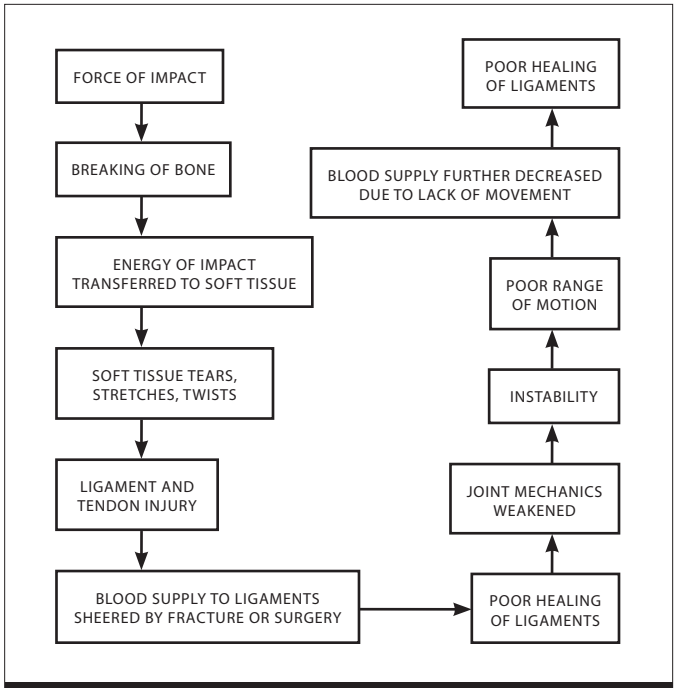


Figure 5. How trauma leads to poor healing of ligaments.

friends. As noted previously, the effects of CRPS can potentially lead to permanent disability. Galer et al. noted that a majority of patients felt that symptoms caused "substantial interference" with general activities (74%), mood (74.2%), mobility (67.7%), normal work (74.2%), relations (64.5%), sleep (67.7%), and social activities (74.2%). Interference in self-care was identified in 45.2%. This study also noted the mean duration of CRPS in the 31 patients surveyed to be 3.3 years. The need to use a device, such as a cane, walker, or wheelchair, was reported by 35% of the participants. The participants in the Galer study reported moderate to severe pain intensity with substantial disability.[59] A survey of CRPS patients by the RSD Foundation found that 23% of the respondents had to stop daily activities occasionally due to pain, 74% had to stop them frequently due to pain, and 87% suffered from constant or nearly constant pain.[60] These reports confirm that CRPS can have a very constricting effect on functional capacity. Caregivers of 51 CRPS patients were reported to suffer significant strain, low mood and poor adjustment.[61] A study of 65 patients noted 30% of RSD patients had to stop work for more than a year. (*See Figure 6.*) They also noted high rates of unemployment and financial compensation, establishing RSD as a disabling disease.[62, 63] In the retrospective chart review of 134 patients, 54% had a workers' compensation claim related to the CRPS, and another 17% had a lawsuit. This is consistent with another study noting that 64% of those surveyed had a work related injury resulting in their symptoms.[64, 65] CRPS is a syndrome that causes millions of Americans to suffer from chronic, unremitting pain.

WHAT ARE THE MECHANISMS BEHIND CRPS?

The mechanisms triggering the pain as well as the associated changes that occur in patients with CRPS remain largely obscure. As with other factors surrounding CRPS, the pathophysiology is also unclear. Divergent theories abound since the spectrum of presentations of this syndrome is so diverse.[67] Multiple components have generally been proposed as the pathophysiological mechanisms, and hypothesis include a neuropathic mechanism which is sympathetically maintained, an immunological mechanism including inflammation, and an altered expression of human leukocyte antigens. The hypotheses exist for both peripheral and central mechanisms. None of this data however is conclusive.[68] They may include the somatic and visceral sensory systems, the central control systems, the sympathetic nervous systems, the somatomotor system, and the neuroendocrine systems.[69] These systems are further differentiated to include the following symptoms noted in CRPS: (1) The nociceptive system: spontaneous pain, hyperalgesia, allodynia. (2) The sympathetic nervous system: abnormal regulation of blood flow and sweating. (3) Sympathetic nervous system, afferent system: edema of the skin and subcutaneous tissues. (4) Sympathetic system,

Figure 6. The percentage of participants in the Galer Study who felt that CRPS affected these activities of daily living, and the percentage of participants in the RSD Foundation Study who changed their daily lives due to the pain from CRPS.

Galer Study	
General activities	74.0%
Mood	74.2%
Mobility	67.7%
Normal work	74.2%
Relations	64.5%
Sleep	67.7%
Social activities	74.2%
Self-care	45.2%
RSD Foundation Study	
Frequently stop activities	74.0%
Occasionally stop activities	23.0%
Constant/nearly constant pain	87.0%

afferent system, somatomotor system: trophic changes of skin, appendages of skin, and subcutaneous tissues. (5) Somatomotor system: active and passive movement disorders, including physiological tremor.[70] A more recent mechanism set forth in explaining the pathophysiology of CRPS is an inflammatory response. An unknown stimulus induces an excessive production of inflammatory mediators, leading to an imbalance in production and clearance of toxic radicals. This excessive production of oxygen radicals results in destruction of healthy tissue.[71] (*See Figure 7.*)

Possible CRPS Mechanisms

- Afferent system involvement
- Altered expression of leukocyte antigens
- Central control mechanisms
- Central mechanisms
- Deactivation pain theory
- Genetic predisposition
- Immunonologic mechanism
- Inflammatory mechanism
- Neglect theory
- Neuroendocrine system involvement
- Nociceptive system involvement
- Peripheral mechanisms
- Somatic and visceral mechanisms
- Somatomotor system involvement
- Sympathetic nervous system involvement
- Sympathetically maintained neuropathic mechanism

Figure 7. Proposed mechanisms and theories behind CRPS.

Animal studies involving ligation of the L5 spinal nerve in rats demonstrate that these animals develop similar symptoms (allodynia) as CRPS patients. Subsequent surgical sympathectomy reportedly showed significant reversal of these symptoms, demonstrating a sympathetic component.[72] There are studies, however, involving L5 nerve ligation of rats noting that neuropathic pain behavior does not depend on the sympathetic nervous system.[73] Other studies show neuropathic pain behavior possibly resulting from a mechanical injury to a peripheral nerve.[74] CRPS may also be triggered by the arrival in the central nervous system of a transmission like injury discharge, produced by traumatized tissues (ligaments/tendons) with or without nerve injury.[75] CRPS may involve damage to small diameter nociceptive fibers.[76] A nociceptor is a sensory receptor that sends signals that cause the perception of pain in response to a potentially damaging stimulus. Nociceptors are silent receptors and do not sense normal stimuli. Only when activated by a threatening stimulus do they invoke a reflex, as would occur when a ligament or soft tissue is injured.[77] (*See Figure 8.*)

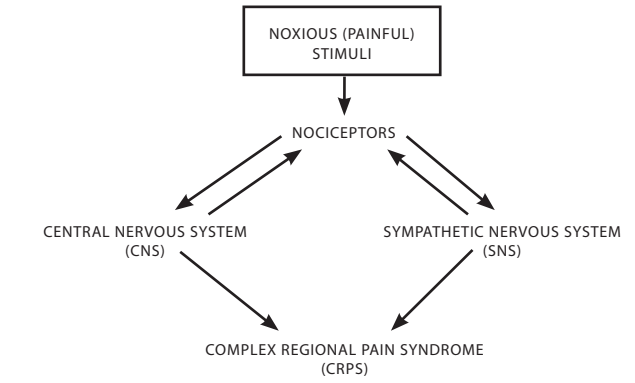


Figure 8. Nociceptors and CRPS. Any noxious or painful stimuli can activate nociceptors which sets up a cascade involving the central nervous system (CNS) and sympathetic nervous system (SNS) resulting in CRPS.

It is also proposed that there is a genetic predisposition to CRPS.[78] The conclusion set forth after years of patient observation and research on humans and animals, is that CRPS is a complex neurological disease, involving the brain at several integrative levels.[79]

TESTING FOR CRPS

There are no specific diagnostic tests for CRPS which can reliably confirm or exclude the diagnosis.[80, 81] Diagnostic criteria is purely clinical.[82-84] It is based on history and physical examination and is not determined by test results, since the utility of diagnostic tests has not been demonstrated.[85-87] Although there is no definitive test for CRPS, physicians try to use such tools as volumetry to measure edema, thermometry to measure skin temperature differences, and resting sweat output (RSO) to measure sweating, however it is not clear that objective measurement is precise. This instrumentation is used to measure clinically apparent signs like those included in the diagnostic criteria, however due to the confounding nature of CRPS, ie. changing body temperature, time of day, and exact placement of the device, it is unclear if objective measurement is even practical.[88] Testing may be invasive or noninvasive, but data is not available for sensitivity or specificity of the tests.[89] In a study comparing testing to clinical diagnosis, instrumentation added little to the overall accuracy of diagnosing CRPS type I, while no single test identifies all persons with CRPS.[90, 91]

A myriad of diagnostic tests have been studied for CRPS. Bone scans may be normal or show increased or decreased uptake in CRPS.[92] (*See Figure 9.*) The bone scan also suffers from the subjective interpretation of the radiologist. Furthermore, researchers disagree on its adequacy, specificity, and sensitivity.[93, 94] Tourniquet ischemia test appears to produce a progressive blockade of nerve transmission, but the interpretation of this test is under intense scrutiny. Plain radiographs help rule out issues such as fractures, which may be responsible for the symptoms, but for CRPS there are no radiographic changes or evidence of osteoporosis in the acute phase.[95] Radiographic demineralization may be noted in the later phase of CRPS using X-rays when comparing the affected area with a normal area, however this is also noted with disuse or immobilization of the limb. Other tests like EMG's, laser Doppler, and microneuronographic measurement of peripheral sympathetic function also have not yet proven their utility.[96] MRI may show nonspecific soft tissue changes.[97] Sympathetic nerve blocks were once considered diagnostic for CRPS type I, however they are not entirely reliable, reproducible, easy to interpret, and they lack specificity.[98] There is also a problem of placebo effect and false-positive results. The diagnosis therefore of CRPS is one of exclusion, with these tests being used as an aid to the total clinical picture.[99] Clinical assessment remains the gold standard of diagnosis of CRPS.[100]

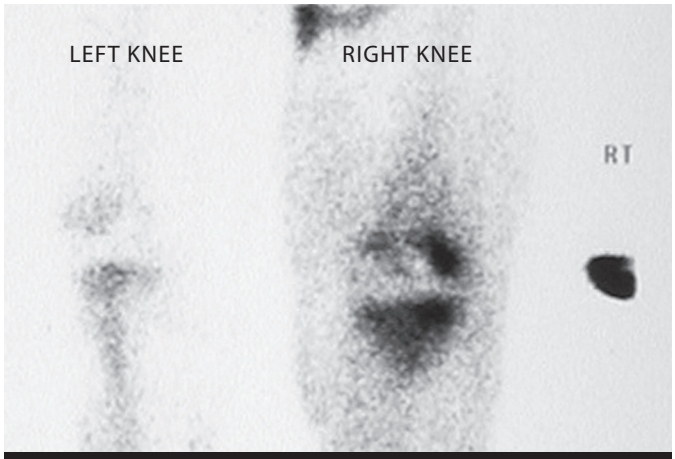


Figure 9. Bone scan of knees. In this bone scan, increased uptake can easily be seen in the right knee. This patient was diagnosed with CRPS.

The physician should take a detailed medical history considering an initial trauma and any history of sensory, autonomic and motor disturbances. The clinician should ask for the development, time course, distribution and characteristics of pain. A general neurological examination is needed. Detection of any swelling, sweating, trophic, temperature and motor abnormality in the disturbed area is important. Muscle strength of the affected limb, as well as characteristics and distribution of somatosensory abnormalities should be investigated in detail. The physician should also test whether the pain can be elicited by movements and pressure at the joints.[101] If the ligaments or soft tissues are still traumatized, stressing them by motion or pressure will elicit sharp pain. This can be documented with a dolorimeter. (*See Figure 10.*)

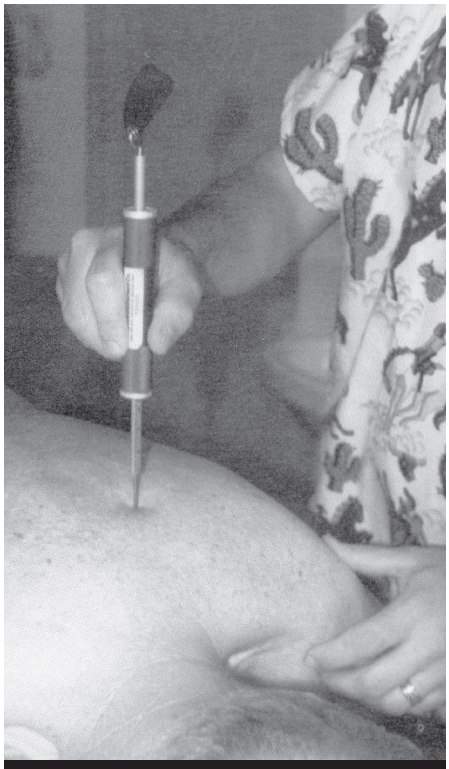


Figure 10. Dolorimeter pressure assessment. A dolorimeter measures the amount of pressure required to elicit pain at a specific location. Less pressure is needed to elicit pain at the ligaments in the CRPS patient.

Essential to the diagnosis is the presence of some initiating event and/or cause of immobilization.[102] The clinical picture includes continuing pain that is out of proportion to the event which caused it; sensory changes such as hyperesthesia; autonomic abnormalities such as changes in skin blood flow, or abnormal sweating at the site of pain, and swelling or edema which is typically peripheral, and may come and go; trophic changes of the skin and appendages; and motor dysfunction such as weakness of the muscles.[103-106] It is also necessary to exclude other conditions that may account for the pain or symptoms.

THE ROLE OF IMMOBILIZATION IN CRPS

There is strong clinical research supporting the disuse model as a basis for most of the signs and symptoms of CRPS. Most people diagnosed with CRPS have experienced an inciting injury, such as a fracture

or an identifiable soft tissue trauma with a period of immobilization or an invasive procedure requiring immobilization. The explanation that most of the signs and symptoms of CRPS may be due to immobilization has been mostly ignored.[107] The IASP diagnostic criteria itself requires the presence of an initiating noxious event, or a cause of immobilization for diagnosing CRPS. Bonica's 1953 Staging of RSD describes limitation of movement and limitation of motion as indicators of RSD.[108] Immobilization leads to both motor and sensory changes that have been the hallmark of CRPS.[109] A typical history involving a twisting injury or fracture involves casting, with the added complaint of burning pain, several more casts or walking boots may be applied for months.[110] Signs and symptoms associated with CRPS are much like those seen shortly after cast immobilization. Symptoms of prolonged casting include muscle atrophy, stiffness, skin discoloration, and often coarseness of the skin, hair, and nails.

The person with CRPS typically has intense burning pain. This pain is excruciating, whereby touching just a sheet of paper or a bed sheet to the affected limb can feel like fire. The person with CRPS learns to guard that extremity. Since movement increases the pain, those with CRPS stop moving and using their affected limbs in efforts to minimize their suffering. Many of the CRPS signs and symptoms can be produced with disuse alone, and longstanding pain from the disuse encourages further immobilization. Research has shown that this causes a sensitization of the central nervous system.[111, 112] The pain and other symptoms continue even after the original injury is healed because of the tissue changes which occurred from prolonged disuse of the limb. Most CRPS patients have reduced range of motion, however at times, passive range of motion is possible even when active range of motion is not. If the reduced range of motion was a motor function alteration then both passive and active range of motion should be affected. These deficits are thought to be due to specific alterations of central regulation of the motor functions caused by the disease. A proposed mechanism for this dysfunction is a change in the central representation induced by increased nociceptive input and by decreased sensory cutaneous and proprioceptive input due to immobilization.[113] In essence, the prolonged immobilization causes the person to be more sensitive to movement because of increased sensitivity of the small autonomic nerves.[114, 115]

Clinicians at the University of Washington Pain Center conducted a prospective study in collaboration with colleagues from Uppsala University and the Academic Hospital at Uppsala.[116] Twenty-three volunteers were casted in the non-dominant forearm for four weeks. No painful stimulus was added, since the purpose of the study was to look at immobility alone. All volunteers had temperature differences between the limbs after the casts were removed. PET (positron emission tomography) scanning showed that the immobility of the limb caused increased cerebral blood flow in areas associated with sensory processing, motor function, and emotions. Other changes caused by the immobility involved abnormal sweating, skin, hair or nail changes, hyperpathia and hypersensitivity. All of these signs and symptoms resolved following an active course of physical therapy. The researchers noted that in animal studies involving immobilization of the wrist and hind paw of rats, there was a clear demonstration of sensory changes from non-noxious to noxious findings such as thermal hyperalgesia to warmth, mechanical allodynia, and cold allodynia.[117, 118] In one study, just seven days of hind paw immobilization produced several weeks of both tactile and thermal allodynia in rats.[118] In conclusion they wrote, "It seems evident from the available data that many of the signs and symptoms of CRPS can be produced by immobilization alone…These data suggest we consider these signs and symptoms as the normal response to disuse."[119]

If disuse is primarily responsible for the signs and symptoms of CRPS, then increasing sensory input through activity and other sensory stimulation should improve the situation or at least prevent further changes.[120-122] While range of motion and physiotherapy remains one of the top priorities to prevent CRPS and to curb its symptoms, what about the person who received all of these therapies but is left with significant disabilities and pain? The question remains, if immobility is largely responsible for the chronic symptoms of CRPS/RSD is there something else that can be done to resolve the condition, once it becomes established?

LIGAMENT DAMAGE AND HEALING

As already discussed, most cases of CRPS/RSD occur after some type of trauma to bones, joints and soft tissues. One of the tissues injured in these traumas are ligaments. A ligament connects two bones and is involved in the stability of the joint. A sprain is a stretched or

injured ligament. Because ligaments generally have a poor blood supply, incomplete healing is common after injury.[123] Motion loss of the joint, connected by the ligament, is also common after injury.[124, 125] This is increased when multiple ligaments are injured, the joint is dislocated or if surgery or prolonged immobility occurs after the ligament injury.[126, 127] Prolonged immobilization has detrimental effects on periarticular cartilage, bone, and soft tissues and can lead to more motion loss.[128-130] During immobilization, connective tissues shorten, thereby further decreasing range of motion of the joint.[131] This connective tissue shortening, increases compressive forces between the articular surfaces to three times normal in just four weeks of immobilization.[132] Degenerative or osteoarthritic changes including atrophy of articular cartilage, increased fibrosis of periarticular tissues, regional bony eburnation, sclerosis and resorption can be found after only two weeks of immobilization.[133] The negative effects of periodic short-term immobilization on joints and soft tissues is cumulative.[134] In one animal study, changes in the joint and soft tissues around the joint can be seen within one week of immobilization, with marked degenerative changes appearing by four weeks. Within 80 days of immobilization, joint mobility was lost and severe destruction of the joint often followed.[135] Another study showed that even an immobilization period of four days has a cumulative effect in producing joint degeneration, and an interval of four weeks between immobilization periods does not prevent osteoarthritis from developing. In addition, this study showed that immobilization, periodic or continuous, over more than 30 days will lead to progressive joint destruction. The authors concluded that "it can be assumed that all situations which lead to the immobilization of a joint can cause osteoarthritis changes. Of interest, is that all radiology, photography, and histology showed some degree of degenerative changes also in the contralateral nonimmobilized limb."[136] Another study found that irreversible changes can occur in the joints after eight weeks of immobilization.[137]

It is easy to assume that when a person is subjected to a force significant enough to fracture a bone, that ligaments close to the fracture site would also be injured. The immobilization that follows, induces destructive changes in the joint, that itself could be painful. Once the cast is removed, for instance, the patient has numerous causes for pain including joint or muscle contractures, as well as failed ligament healing, though the fracture itself healed. Perhaps it is the failed ligament healing that is responsible for the chronic signs and symptoms of CRPS?

Ligaments are extremely sensitive to immobilization, also known as stress deprivation. Gross inspection of the ligaments after stress deprivation shows them to be less glistening and more "woody" on palpation.[138] Under a microscope the collagen of the ligament is very random and has more degradation. Chemically, the ligaments lose water and glycosaminoglycans (which help maintain structure) so there is a net loss of mass in the ligaments.[139] On close examination, it is clear that non-healed ligaments (also known as ligament scars) differ in some critical ways from normal ligament tissue. (*See Figure 11.*)

Figure 11. Differences between normal ligaments and scars.[138]

Normal Ligaments	Ligament Scars
Collagen aligned	Collagen disorganized
Collagen densely packed	Flaws between fibers
Bimodal (large) collagen fibrils	Smaller collagen fibrils
Mature collagen cross-links	Immature collagen cross-links
Primary collagen Type I	More collagen III (and others?)
Primary small proteoglycans	Large proteoglycans
Cell and matrix turnover low	Cell and matrix turnover high
Rare cell division	More cell division
Low cell density	Higher cell density
High matrix-cell ratio	Lower matrix-cell ratio

Ligament healing is a complex process similar to wound healing, but due to the poor vascularity of ligaments, the initial inflammatory phase takes longer than in wound healing.[140] Immobilization influences the appearance and biomechanical properties of ligaments, and early motion has a beneficial effect on ligament function.[141] The mechanical stress applied by the functional load with movement improves the reorientation of the collagen fiber bundles, and increases the fibril size and density. In contrast, immobilization is followed by a protracted state of catabolism within the ligament, and the degradation of the structural matrix leads to progressive atrophy and lack of mechanical strength.[142] Negative effects histologically (under a microscope) can be seen in ligaments as early as six days after immobility and proceeded destructive joint changes.[143] Other research confirms that negative structural changes in the ligaments precedes articular cartilage degeneration.[144, 145] Knee ligaments immobilized for even a few weeks showed that the ultimate load, linear stiffness, and energy-absorbing capacity of a bone-ligament-bone preparation is reduced to about one

third of normal.[146, 147] Other studies noted a decreased resistance to stretch when ligaments were subjected to immobility.[148-150] Ligaments, with their low resting blood supply, are dependent on substantial increases in blood flow and vascular volume during the initial stages of repair.[151] This healing response, however, is greatly compromised with lack of movement. Also, if the small feeder vessels are sheared during an initial injury the ligaments are unable to receive the nutritional support for healing. Effective healing responses are dependent on an adequate blood supply to provide the mediators necessary for tissue repair and to maintain joint homoeostasis during injurious episodes.[152]

Ligament injuries are very common, and they typically afflict the younger population. Ligaments in the knee and foot for instance, withstand forces of up to five times body weight which occur in each of the 1.2 million steps a person takes each year.[153, 154] While ligaments are notoriously slow healers, the repair and regeneration of the ligaments starts at 48 to 72 hours. Most ligament growth occurs between the third and sixth week after injury. One study found the maximum level of collagen in the ligament itself at six weeks.[155] Even though ligaments heal for a full year after injury, often the strength of the ligament after injury is only 50 to 70% of the original.[156] Other studies found ligaments regained only 30% of normal strength after severe injuries.[157-159]

LIGAMENT INJURY AND THE SYMPATHETIC NERVOUS SYSTEM

Ligaments have long been thought of as inert structures whose primary function is to provide stability to a joint. What has not been so appreciated is the sequelae when ligaments are injured, not just on the joint, but on the sympathetic nervous system. Non-healed ligament injuries sensitize their own nociceptors to motion. Recall that nociceptors are specialized sensory neurons (nerve cells) that respond to tissue damage. The detection of noxious chemical, thermal, and mechanical stimuli are mediated by receptors on these cells.[160] There is a high density of both myelinated and unmyelinated nociceptors in the ligaments throughout the body.[161-164] These nociceptor sympathetic nerve fibers in injured ligaments elicit pain when the ligament is under too much tension. The density and distribution of these nociceptors, also known as substance-P nerve fibers, within the ligaments is significantly affected by injury, as well as the time since injury.[165, 166] Damage done to ligaments may not initially result in a lot of pain, but the damage done to them, along with the degree of irritation on the surrounding nerve endings, may alter the firing pattern from these nerve endings in such a manner so as to cause increased activation of the sympathetic nervous system causing referral pains up and down the extremity.[167] (*See Figure 12.*) Referral pain patterns from injured ligaments is a well established phenomenon.[168-171] Ligament and other soft tissue injuries have been shown to cause regional and segmental variations in sympathetic activity including cutaneous sudomotor and vasomotor manifestations.

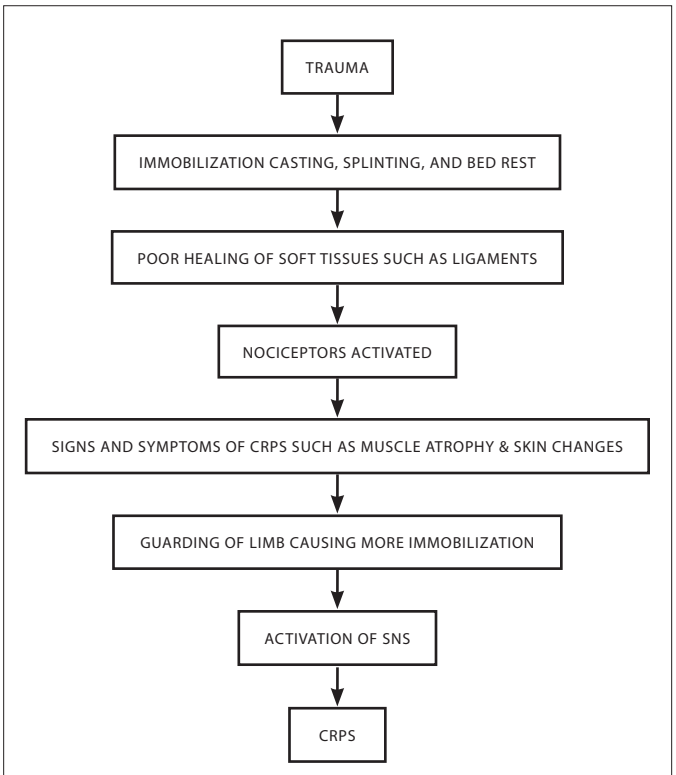


Figure 12. The non-healed ligament injury/CRPS connection. The poor healing of soft tissues, such as ligaments from immobilization, can sensitize nociceptors which ultimately can lead to CRPS.

These can include coldness and clamminess of the skin.[172, 173] For instance, when hypertonic saline (6% NaCl) is injected into the interspinous ligaments or the periosteum of the spinous processes, the local transient pain was soon followed by a crescendo of deep pain in areas often remote from the site of injection, followed by autonomic nervous system changes in the referral pain sites. The condition whereby a hyperirritable spot (myofascial trigger point) causes referral pain from that location and autonomic

phenomena is known as myofascial syndrome. The authors noted that "visceral, circulatory and thermoregulatory functions, controlled by the autonomic nervous system are continually coupled, in highly organized patterns, to musculoskeletal activity and changes in posture." They go on to say, "In these stressful and, in some cases, painful experimental situations affecting small parts of the musculoskeletal system, the afferent volleys of impulses entering through individual dorsal roots appear to have become so prepotent as to dominate that part (i.e., corresponding and neighboring segments) of the sympathetic nervous system, and to take precedence over vertically organized patterns they ordinarily serve, and even to disrupt them. They do not, therefore, meet any particular functional demand, they are not adaptive and, in many cases, they persist after the provoking insult has ended. The autonomic concomitants of local myofascial irritation, injury, stress or pathology have not received widespread recognition in clinical practice…Whether reflexly or directly provoked, the hyperactivity of isolated portions of the sympathetic outflow serves no obvious adaptive function."[174, 175] In summary, these authors found that even a small irritation of the musculoskeletal system can cause such an enormous stimulation of the sympathetic nervous system (SNS) that the pain and overstimulation of the SNS overtakes everything and it serves no useful function.

It is important to realize that the majority of cases (56% to 61%) of CRPS have a myofascial component. Myofascial dysfunction is more prevalent in the affected upper extremity (69-70%) than the lower extremity (42-47%).[176, 177] Likewise, it is known that patients with known musculoskeletal problems, including myofascial pain syndromes, have exaggerated regional sympathetic responses. When the normal limb is compared in regard to the sudomotor and vasomotor activity including edema, changes in skin floor, decreased electrical skin resistance are profoundly altered in the painful limb.[178] These heightened sympathetic responses are not anomalous reflexes, but modifications of normally operating patterns of somato-autonomic coordination that represent changes in sensory input arising in nociceptors in the injured musculoskeletal tissues.[179] Nociceptors in injured soft tissues such as joint capsules and ligaments have a lowered stimulus threshold to induce pain.[180] These nociceptors can activate the sympathetic nervous system to produce symptoms and also change blood flow to the affected joint which can affect healing.[181] In addition, joint instability caused by ligament injury, can affect the firing of nociceptors which then in turn affects proprioception (position sense) and muscle coordination.[182, 183]

According to an interdisciplinary expert panel for CRPS, the goal of treatment in patients with CRPS is to improve function, relieve pain, and achieve remission. They go on to state, "increasing evidence suggests that some cases are refractory to conservative measures and require flexible application of the various treatments…There is widespread agreement among experts that patients who do not respond to an acceptable level of treatment by 12 to 16 weeks should be given a trial of more interventional therapies…"[184] Again, to go back to the International Association for the Study of Pain Diagnostic Criteria for CRPS *one must have the presence of an initiating noxious event, or a cause of immobilization*. Surely ligaments can and probably are injured in most of the initiating noxious events that start the CRPS including the traumas that fracture bones and injure the soft tissues. As discussed, immobilization of a joint itself can cause articular cartilage and joint degeneration as well as set up a scenario whereby the soft tissue injuries including the ligaments, don't heal. Most patients with CRPS will describe weeks and even months of partial and total immobilization of the painful extremity. If underlying non-healed ligament injury is the primary causative factor for ongoing sympathetic activity, then the only treatment that would have curative effects long-term must address this issue. Most therapies offered to CRPS patients do not address ligament weakness and injury.

TREATMENT

Success in traditional treatment of CRPS is dismal. "No other chronic pain syndrome is as shrouded in confusion and controversy—to the detriment of efforts to rigorously define an evidence-based treatment strategy."[185] A study of 146 patients found that only 29% were pain free.[186] In another series, 64% of CRPS patients with severe pain lasting more than one year rated their pain as a 7 on a 1-10 scale, with 10 being the highest level of pain.[187, 188] CRPS was also noted to be present 10 years after a fracture of the distal radius in 9% of patients studied in a review of 100 patients with Colles' fracture.[189] In a Korean study involving 150 patients, one third had intractable chronic pain even after treatment, and some required a limb amputation. The Korean study noted that the patients had suffered for over two years before being referred to a specialist, and that the intractable chronic pain increases

as the time between the onset of symptoms and diagnosis increases. It is not unusual, however, that years go by before the CRPS patient even receives a correct diagnosis, thereby prolonging treatment.[190] This is possibly due to a misconception that the pain is a psychiatric disorder, or unbelief that the patient could possibly have this much pain, or even that such a small injury could lead to total body pain.[191]

Treatment is often based on the possible mechanisms that cause CRPS, however as previously noted, these causes are elusive.[192] The primary goal of treatment is to facilitate functional restoration, however, the natural history of CRPS treatment suggests that reported outcomes of pain relief, functional capacity, and disease remission are far from optimal.[193-195] Due to the historic disagreements over diagnosis of the syndrome, there are no scientifically well-established treatment guidelines. Although there are obvious difficulties in treating this disorder, there are few randomized controlled trials of the most widely accepted treatment approaches.[196-199] Clinical trials that have been performed had either small numbers of patients or limited clinical follow-up.[200] "The consensus of treatment should be to convince the patient and family that CRPS is the diagnosis and that movement of the involved extremity is key for rapid return to function."[201]

WHAT ARE THE TRADITIONAL TREATMENT OPTIONS?

Options available for CRPS include interventional, pharmacologic, physical/occupational therapy, and psychologic techniques. Staton-Hicks et al. note in their treatment guidelines that failure to achieve a favorable response with any treatment modality should not persist beyond two weeks.[202] Quisel et al. suggest these same treatment guidelines are summarized without a systematic or evidence-based approach, and also raise the question whether any treatment makes a difference, or that possibly CRPS type I resolves on its own.[203]

Interventional approaches include various sympathetic ganglion blocks (i.e., stellate, thoracic, lumbar), intravenous regional sympathetic blocks (Bier blocks), somatic blocks (i.e., peripheral nerve blocks, brachial plexus), and epidural blocks.[204]

If CRPS is a pathologic reflex of the sympathetic nerves causing blood flow irregularities, constant pain, muscle atrophy, and fibrosis, then those who support this hypothesis cite pain relief from a sympathetic block as supportive evidence. Sympathetic blocks, however, did not prove to be a reliable predictor of treatment response.[205]

The following is a note taken from a proponent of the success of the stellate ganglion block: "If the pain returns, and it does in many instances, the patient should receive a series of blocks. In the cases where the pain returns in a few hours, the first four to five blocks should be given once a day and the next three to five blocks, once every three to four days. Persistent, intensive therapy is important. If the disease is well established, the results of stellate ganglion therapy are not as promising."[206] Invasive therapies such as the sympathetic ganglion block are minimally, if at all, effective.[207]

The use of the regional sympathetic block is based on the theory that chronic pain results from either a central hyperactivity of the sympathetic nervous system or a peripheral hypersensitivity to circulating catecholamines.[208] Efficacy of these blocks in treating CRPS is unclear because separate studies dealing with similar patient populations report contradictory levels of response to treatment. Some studies show no difference between the use of the drugs and the saline control, while others report an improvement in 75% of the patients.[209, 210] In a study of the effectiveness of sympathetic blocks, one series showed only 12% of patients were pain free at a three-year follow-up.[211, 212] Only the subset of CRPS patients with sympathetically maintained pain (SMP) exhibit pain responsiveness to the blockade.[213] Many practitioners believe that some patients obtain real benefit from the sympathetic block, and other practitioners do not. Unfortunately, one cannot tell beforehand whether the patient will be one that would respond.[214]

Pharmacological approaches, including narcotic pain medications, are of little restorative value and frequently result in drug dependence without improving limb function.[215, 216] Given these limitations, treatment approaches are based heavily on clinical experience. The best treatments appear to be non-invasive and completely within the realm of family medicine.[217] (*See Figure 13.*) Guidelines help, but creativity, compassion and flexibility are essential.[218]

Early intervention is paramount. A multifaceted treatment approach is thought to be most effective. Pain management techniques to restore function are based on a steady progression from very gentle movements on an

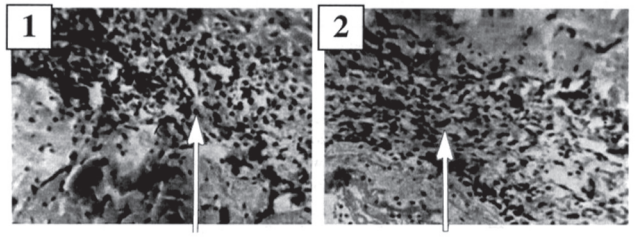
Figure 13. Traditional treatments given to 134 patients, diagnosed with CRPS, in the Allen Study.[42]	
Immobilization	47%
Tricyclic antidepressants	78%
SSRI's	38%
Anticonvulsants	60%
Opiates	70%
Physical therapy	88%
Occupational therapy	45%
Nerve blocks	82%
Spinal cord stimulation	6%
Psychological treatment	50%

active basis to gentle weight bearing. This progresses to more active load bearing techniques. These strategies also include progressive stimulation using different textures and different temperatures of bath water. It is thought that this gradual normalization of sensation occurs due to a resetting of the altered central processing in the nervous system. Moving and using the limb is paramount to healing.[219-221]

PROLOTHERAPY FOR NON-HEALED LIGMENT INJURIES AND ITS ASSOCIATED AUTONOMIC PHENOMENON

George S. Hackett, M.D., a trauma surgeon at Mercy Hospital in Canton, Ohio, coined the term Prolotherapy. As he describes it, "The treatment consists of the injection of a solution within the relaxed ligament and tendon which will stimulate the production of new fibrous tissue and bone cells that will strengthen the "weld" of fibrous tissue and bone to stabilize the articulation and permanently eliminate the disability."[222] Dr. Hackett showed that Prolotherapy stimulated the normal inflammatory reaction by studying the effects of Prolotherapy on animal tissues. For instance, rabbit tendons injected with Prolotherapy solution examined at various intervals histologically showed an infiltration of normal inflammatory cells without any evidence of necrosis (damage) to nerves, blood vessels or tendon tissue. (*See Figure 14.*) The rabbit tendons were also noted to increase in diameter by 40% and the tendon-bone interface diameter (fibro-osseous junction) increased by 30%.[223] Dr. Hackett turned animal research into clinical application as he published numerous scientific papers advocating Prolotherapy. The main emphasis in his papers was his findings that most chronic pain was due to non-healed ligament injuries causing joint instability. Prolotherapy stimulated ligament growth and repair causing joint stabilization.[224-226] For instance, in 1955, Dr. Hackett analyzed 146 consecutive cases of undiagnosed low back disability during a two-month period. He found that 94% of the patients experienced joint ligament injury, or what he called relaxation.[227] In other words, they had non-healed ligament injuries. In 1956, a similar survey of 124 consecutive undiagnosed low back disability patients revealed that 97% of patients possessed joint instability from ligament weakness. Even though 50% had already undergone back surgery for a presumed disc problem, Prolotherapy produced cures of their low back in 80% of the cases.[228] In his largest case series involving 1,857 patients, Dr. Hackett found non-healed ligament injuries as the cause of pain in 1,583 of the cases. Follow-up on the patients 12 years after treatment found that Prolotherapy cured 82% of the patients.[229] Similar results were found when Prolotherapy was done to ligaments in the neck that caused neck pain and headaches.[230, 231] Dr. Hackett's conclusion that ligaments are a primary cause of chronic joint pain and instability that is successfully treated by Prolotherapy, has been confirmed by numerous authors for low back pain,[232-235] knee pain,[236, 237] TMJ pain,[238, 239] and many other joints.[240-245]

Dr. Hackett coined the term "ligament relaxation" to explain the weakness associated with non-healed ligament injuries. He noted, "Ligament relaxation is a condition in which the strength of the ligament fibers has become impaired so that a stretching of the fibrous strands occurs when the ligament is submitted to normal or less than normal tension."[246] When the weakened ligament is stretched, Dr. Hackett noted that it caused not only local



1. Arrow points to moderate infiltration of lymphocytes 48 hours after injection of proliferating solution. Note absence of cell-death in surrounding tissues.
2. Beginning fibroblastic organization present in adjacent tissues. Arrow points to capillary proliferation with moderate infiltration of lymphocytes. *Two weeks after injection, this microphotograph shows new tissue growth.*

Figure 14. Micrographs of sections from rabbit Achilles tendons following the injection of the proliferant, Sylnasol. The same technique was done as that which is used clinically.

Used with permission of Beulah Land Press © 2007 Oak Park, IL. *Prolo Your Pain Away! Curing Chronic Pain with Prolotherapy.*

pain but also referral pains throughout the body. Those referred pain patterns of ligaments were outlined in Dr. Hackett's observations after he performed more than 18,000 intraligamentous injections to 1,656 patients over a period of 19 years.[247] For instance, he found the most common cause of sciatic pain down the leg was from sacroiliac ligament relaxation.[248] He also observed that non-healed ligament injuries commonly caused bone dystrophy,[249] another term for the decalcification of bone commonly known as osteopenia or osteoporosis.

He explained in detail the pathophysiology involved, "When the ligament fibers do not regain their normal tensile strength following strain, the fibers stretch under normal tension and permit excessive tension-stimulation of the non-stretchable sensory nerve fibrils, which are abundant within the fibro-osseous attachments. This is the original of noxious barrages of sensory afferent and antidromic impulses which cause pain and bone dystrophy (decalcification). Tension stimulation on afferent sensory nerves within the weak fibro-osseous attachments of ligament to bone is the origin of barrages of afferent impulses transmitted to the spinal cord and to the brain where they are interpreted as pain and referred pain. While from the same origin, barrages of antidromic impulses pass directly and by axon reflex to bone blood vessels and cause a neurovascular disturbance of bone metabolism that results in direct decalcification, which further weakens the ligamentous attachment to bone. From the afferent stimulation in the spinal cord, there are noxious barrages of efferent impulses that cause muscle spasm, while other efferent and sympathetic impulses pass from the same and adjacent cord segments and cause a reflex neurovascular decalcification of large areas of bone. This weakens the attachment of all ligaments and tendons in the decalcified areas and completes a vicious circle of ligament relaxation and decalcification."[250] (*See Figure 15.*)

The decalcification or weakening of bone is one of the hallmark features of chronic CRPS.[251-253] Dr. Hackett showed that Prolotherapy not only could resolve the localized ligament pain, but also the autonomic nervous system phenomenon of referral pain, vasomotor changes, and bone dystrophy.[254-257] The resolution of disorders involving the autonomic nervous system including reflex sympathetic with Prolotherapy has subsequently been reported.[258-260]

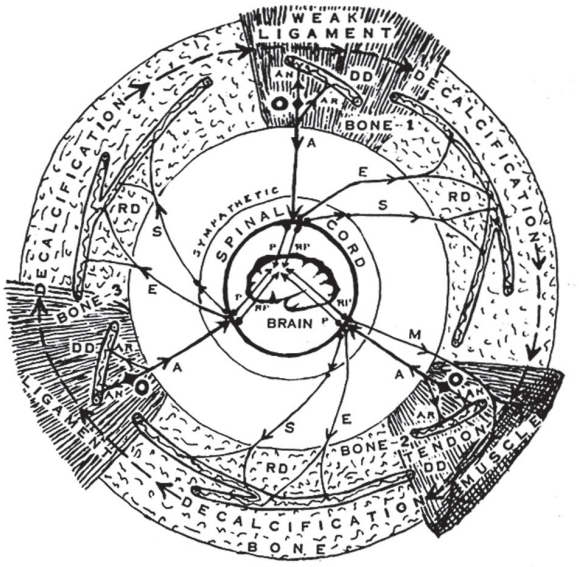


FIGURE 1

O—Origin of neural impulse by traction-stimulation of nerve fibrils within weakened fibro-osseous attachment of ligament to bone
A—Afferent sensory somatic noxious impulse to spinal cord
AR—Axon reflex neurovascular impulse in antidromic direction through afferent fibril
AN—Antidromic neurovascular impulse
DD—Direct decalcification (metabolic)
E—Efferent neurovascular impulse
S—Sympathetic neurovascular impulse
RD—Reflex decalcification (metabolic)
M—Reflex motor impulse to muscle
P—Pain impulse to brain
RP—Referred pain impulse to brain

Note: The etiology may be trauma or disease. All ligament-tendon attachments become weakened when invaded by decalcification and are the origin of most pain in all types of osteoporosis.

Figure 15. Pathophysiologic schemata connecting ligament weakness to bone decalcification.[250]

COMPLEX REGIONAL PAIN SYNDROME CASE REPORT

R.A., a 27 year-old female college student sustained a severe injury to her left foot after twisting her left ankle while out walking in the fall of 2002. X-rays revealed a metatarsal fracture in November, 2002. Initial treatment involved primarily rest and several prolonged sessions of immobilization involving the patient wearing a walking boot. She was also prescribed NSAIDs, narcotics, and received several spinal blocks because of the intense pain. She remained on these treatments for two years after the initial injury but only saw her pain increase to the point where she could not put pressure on the left foot, and was unable to walk without a crutch. She said she could not wear a sock, slept with her foot outside the covers, and even the water from a shower caused intense pain. Her studies suffered, and she needed higher and higher doses of narcotics and anti-depressant medications just to get through the day. She saw around 20 specialists during a two year span including orthopedists, podiatrists, psychiatrist

pain specialist and various therapists. In December 2004, an MRI revealed a torn tendon in the foot which was surgically repaired. Unfortunately, surgery did not help her symptoms. The severe pain and swelling in the foot and ankle increased and persisted. Treatment at this time included several rounds of steroid and trigger point injections, immobilization, more NSAIDs, immobility and physical therapy without success. In 2005, she was diagnosed with reflex sympathetic dystrophy (CRPS).

In April, 2005 she presented to Caring Medical in Oak Park, Illinois with the hopes that Prolotherapy would offer her some relief. By this time, she was on Norco® 10/325, needing 10-14 tablets per day for pain. She was seeing a psychiatrist for depression, and was taking Cymbalta® for her anxiety and depression. Aside from intense pain she had the following concerns: severe insomnia, night sweats, weight gain of over 60 pounds since her injury, fatigue, and constipation. Her initial physical exam noted a cold, swollen and discolored left foot and ankle. She had significant tenderness (evidenced by dolorimeter measurements) in the ligaments supporting primarily the lateral and medial ankle. Because of her myriad of symptoms, a comprehensive natural medicine laboratory analysis was done which revealed low testosterone and DHEA levels. Natural hormone replacement for testosterone and DHEA were then prescribed. She was also asked to change her diet as she had significant food sensitivities for dairy and moderate sensitivities to gluten and eggs. Her venous blood pH being elevated, she was started on a hypoallergenic vegetarian diet.**

Prolotherapy was started in the April 2005. Because of the severe pain in her left foot, she received conscious sedation to get through the Prolotherapy treatments. When she was seen for her third treatment in June, 2005 she was happier and reported that her standing tolerance had remarkably increased, and her pain level was down 15%. She continued to improve and was able to start wearing an electromesh sock on her left foot to help her foot tolerate more and more stimulation. The CRPS symptoms gradually improved. By the sixth visit no temperature or color asymmetry was present and the skin sensitivity significantly diminished in the left foot and ankle. By the seventh visit she was off all narcotics and antidepressant medications. Prolotherapy allowed her to finish graduate school, get married and she is now working full time as a social worker. It has been four years since her last Prolotherapy visit and she continues to live a normal, active life.

SUMMARY

To diagnose CRPS, according to the International Association for the Study of Pain Diagnostic Criteria, an initiating noxious event or a cause of immobilization must be present. Complex regional pain syndromes present as amplified somatic, motor, and sympathetic responses to injury or immobilization. CRPS is often precipitated by a deep tissue injury such as a ligament sprain or fracture. Typically, the injury is treated by casting, splinting or orthopedic surgery, which itself requires a period of immobilization. Immobilization itself has been shown to reproduce many of the symptoms of CRPS and itself can contribute to the non-healing of soft tissue injuries such as ligaments. Following trauma, ligaments show poor healing responses which themselves can contribute to a loss of motion of the joint. There is a high density of nociceptors in the ligaments of the body. These nociceptors have heightened activity to injury which can cause an exaggerated vasomotor and sudomotor response in the involved extremity, including edema, changes in skin blood flow, or decreased electrical skin resistance. Since CRPS is an extremely painful condition, patients do not move the involved extremity much. Since ligaments are very sensitive to immobilization, also called stress deprivation, they never heal, though other injuries, like bony fractures, resolve. This non-healed ligament injury continues to activate the sympathetic nervous system and the patient continues with the chronic symptoms, including the severe burning pain of CRPS. While traditional therapies such as physiotherapy, range of motion exercises, and pain medications offer temporary relief, they often do not cure the condition because they do not address the underlying ligament weakness/injury. Prolotherapy, an injection technique designed to stimulate tendon and ligament repair, has shown promise from some anecdotal reports. Prolotherapy, by stimulating ligament regeneration, not only resolves the pain, but also the sympathetic hyperactivity and the related symptoms of CRPS. Prolotherapy is a treatment that patients with CRPS and the doctors who treat them should consider. ■

** Giraffe Diet Type according to the book *The Hauser Diet*. Beulah Land Press, Oak Park, IL, 2007.

BIBLIOGRAPHY

1. Perez R, et al. Treatment of patients with complex regional pain syndrome type 1 with mannitol: A prospective, randomized, placebo-controlled, double blind study. *The Journal of Pain.* 2008;9(8):678-686.
2. Reuben S. Preventing the development of complex regional pain syndrome after surgery. *Anesthesiology.* 2004;101:1215-1224.
3. Rowbotham M. Pharmacologic management of complex regional pain syndrome. *Clin J Pain.* 2006;22:425-429.
4. Blake H. Strain and psychological distress among informal supporters of reflex sympathetic dystrophy patients. *Disabil Rehabil.* 2000;22(18):827-832.
5. Harden NR, et al. Diagnosis of complex regional pain syndrome: Signs, symptoms, and new empirically derived diagnostic criteria. *Clin J Pain.* 2006;22:415-419.
6. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.
7. Harden NR, et al. Diagnosis of complex regional pain syndrome: Signs, symptoms, and new empirically derived diagnostic criteria. *Clin J Pain.* 2006;22:415-419.
8. Aronoff GM, et al. American Academy of Disability Evaluating Physicians(AADEP) position paper: Complex regional pain syndrome (RSD): Impairment and disability issues. *American Academy of Pain Medicine.* 2002;2(3):274-288.
9. Galer BS, et al. Course of symptoms and quality of life measurement in complex regional pain syndrome: A pilot study. *J Pain Symptom Manage.* 2000;20:286-292.
10. Hodnett C, et al. Complex regional pain syndrome. 2008; winter. www.painpathways.org.
11. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.
12. Wasner G, et al. Complex regional pain syndrome-diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord.* 2003;41:61-75.
13. Ibid.
14. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.
15. Wasner G, et al. Complex regional pain syndrome-diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord.* 2003;41:61-75.
16. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.
17. Ibid.
18. Wasner G, et al. Complex regional pain syndrome-diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord.* 2003;41:61-75.
19. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.
20. Stanton-Hicks MD, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Practice.* 2002;2(1):1-16.
21. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.
22. Boas RA. Complex regional pain syndromes: Symptoms, signs, and differential diagnosis. In: W. Janig and M. Stanton-Hicks MD, eds, R*eflex Sympathetic Dystrophy: A Reappraisal, Progress in Pain Research and Management.* Seattle: IASP Press; 1996. p. 80-81.
23. Inchiosa MA, et al. Treatment of complex regional pain syndrome type I with oral phenoxybenzmine: rationale and case reports. *Pain Practice.* 2008;8:-7085.
24. Boas RA. Complex regional pain syndromes: Symptoms, signs, and differential diagnosis. In: W. Janig and M. Stanton-Hicks MD, eds, *Reflex Sympathetic Dystrophy: A Reappraisal, Progress in Pain Research and Management*. Seattle: IASP Press; 1996. p. 80-81.
25. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.
26. Ibid.
27. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.
28. Van de Beek WJ, et al. Diagnostic criteria used in studies of reflex sympathetic dystrophy. *Neurology.* 2002;58:522-526.
29. Harden RN, et al. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain.* 1999;83:211-219.
30. Galer BS, et al. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. International Association for the Study of Pain. *Clinical Journal of Pain.* 1998;14:48-54.
31. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.
32. Veldman PH, et al. Signs and symptoms of reflex sympathetic dystrophy; prospective study of 829 patients. *Lancet.* 1993;343:1012-1016.
33. Harden RN, et al. *Complex regional pain syndrome.* Seattle: IASP Press; 2001.
34. de Mos M, et al. Medical history and the onset of complex regional pain. *Pain* (2008), doi:10.1016/j.pain.2008.07.002
35. de Mos M, et al. The incidence of complex regional pain syndrome: A population based study, *Pain* (2006), doi:10.1016/j.pain.2006.09.008
36. Bruel S, et al. How common is complex regional pain syndrome-Type I? *Pain.* 2007;129:1-2.
37. Ibid.
38. Aronoff GM, et al. American Academy of Disability Evaluating Physicians(AADEP) position paper: Complex regional pain syndrome (RSD): Impairment and disability issues. *American Academy of Pain Medicine.* 2002;2(3):274-288.
39. Duman I, et al. Reflex sympathetic dystrophy: a retrospective epidemiological study of 168 patients. *Clin Rheumatol.* 2008;26:1433-1437.

40. Rowbotham M. Pharmacologic management of complex regional pain syndrome. *Clin J Pain.* 2006;22:425-429.
41. Birklein F, et al. Neurological findings in complex regional pain syndromes-analysis of 145 cases. *Acta Neurologica Scandinavica.* 2000;101:262-269.
42. Allen G, et al. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. *Pain.* 1999;80:539-544.
43. Stanton-Hicks MD, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Practice.* 2002;2(1):1-16.
44. Duman I, et al. Reflex sympathetic dystrophy: a retrospective epidemiological study of 168 patients. *Clin Rheumatol.* 2008;26:1433-1437.
45. Pak TJ, et al. Reflex sympathetic dystrophy: Review of 140 cases. *Minn Med.* 1970;53:507-512.
46. Small E. Reflex sympathetic dystrophy: Reflections from a clinician. *Adolesc Med.* 2007;18:221-225.
47. Connolly JF, et al. Principles of closed management of common fractures. In: Browner B, et al. *Skeletal Trauma: Fractures, Dislocations, Ligamentous Injuries*. Vol 1. Philadelphia: W.B. Sauders Company; 1992. p. 211-229.
48. Kayfetz DO. Occipital-cervical (whiplash) injuries treated by Prolotherapy. *Medical Trial Technique Quarterly.* 1963;June:9-29.
49. Nerlich ML, et al. Biology of soft tissue injuries. In: Browner B, Jupiter J, Levine A, Trafton P. *Skeletal Trauma: Fractures, Dislocations, Ligamentous Injuries.* Vol 1. Philadelphia: W.B. Sauders Company; 1992. p. 77-94.
50. Reuben S. Preventing the development of complex regional pain syndrome after surgery. *Anesthesiology.* 2004;101:1215-1224.
51. Perez R, et al. Treatment of patients with complex regional pain syndrome type 1 with mannitol: A prospective, randomized, placebo-controlled, double blind study. *The Journal of Pain.* 2008;9(8):678-686.
52. Atkins RM, et al. Algodystrophy following Colles' fracture. *J Hand Surg.* 1989;14:161-164.
53. Birklein F, et al. Neurological findings in complex regional pain syndrome-analysis of 145 cases. *Acta Neurologica Scandinavica.* 2000;101:262-269.
54. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.
55. de Mos M, et al. Medical history and the onset of complex regional pain. *Pain* (2008), doi:10.1016/j.pain.2008.07.002
56. Reuben S. Preventing the development of complex regional pain syndrome after surgery. *Anesthesiology.* 2004;101:1215-1224.
57. Ibid.
58. Reuben S, et al. The incidence of complex regional pain syndrome after fasciectomy for Dupuytren's contracture: A prospective observational study of four anesthetic techniques. *Anesth Analg.* 2006;102; 499-503.
59. Galer BS, et al. Course of symptoms and quality of life measurement in complex regional pain syndrome: a pilot study. *J Pain Symptom Manage.* 2000;20:286-292.
60. Aronoff GM, et al. American Academy of Disability Evaluating Physicians(AADEP) position paper: Complex regional pain syndrome (RSD): Impairment and disability issues. *American Academy of Pain Medicine.* 2002;2(3):274-288.
61. Blake H. Strain and psychological distress among informal supporters of reflex sympathetic dystrophy patients. *Disabil Rehabil.* 2000;22(18):827-832.
62. Geerzten JH, et al. Reflex sympathetic dystrophy of the upper extremity-a 5.5 year follow-up. Part II. Social events, general health and changes in occupation. *Acta Orthopedic Scand Suppl.* 1998;279:19-23.
63. Duman I, et al. Reflex sympathetic dystrophy: a retrospective epidemiological study of 168 patients. *Clin Rheumatol.* 2008;26:1433-1437.
64. Allen G, et al. Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. *Pain.* 1999;80:539-544.
65. Ochoa JL, et al. Pathophysiological spectrum of organic and psychogenic disorders in neuropathic pain patients fitting the description of causalgia or reflex sympathetic dystrophy. In: Gebhart GF, Hammond DL, Jensen TS (Eds.). *Progress in Pain Research and Management.* Vol. 2. Proceedings of the 7th World Congress on Pain. Seattle, WA: IASP Press; 1994. p. 483-494.
66. Chung OY, et al. Complex regional pain syndrome. *Current Treatment Options in Neurology.* 2003;5:499-511.
67. Hogan CJ, et al. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.
68. Stanton-Hicks MD, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Practice.* 2002;2(1):1-16.
69. Janig W. CRPS-I and SRPS-II: A strategic view. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 3-15.
70. Janig W, et al. The value of animal models in research on CRPS. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 75-85.
71. Perez R, et al. Treatment of patients with complex regional pain syndrome type 1 with mannitol: a prospective, randomized, placebo-controlled, double blind study. *The Journal of Pain.* 2008;9(8):678-686.
72. Chung K, et al. Sympathetic involvement in the spinal nerve ligation model of neuropathic pain. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 19-26.
73. Habler H-J, et al. Neuropathy after spinal nerve injury in rats: A model for sympathetically maintained pain? In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 39-52.
74. Ringkamp M, et al. The role of injured and uninjured afferents in neuropathic pain. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 27-38.
75. Vatine J-J, et al. A model of CRPS-I produced by titanic electrical stimulation of an intact sciatic nerve in the rat: Genetic and dietary effects. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001, p. 53-74.
76. Inchiosa MA, et al. Treatment of complex regional pain syndrome type I with oral phenoxybenzmine: rationale and case reports. *Pain Practice.* 2008;8:-7085.

77. Wikipedia.com. Nociceptor. Available at: http://en.wikipedia.org/wiki/Nociceptor. Accessed on January 30, 2010.

78. Vatine JJ, et al. A model of CRPS-I produced by titanic electrical stimulation of an intact sciatic nerve in the rat: Genetic and dietary effects. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001, p. 53-74.

79. Janig W. CRPS-I and SRPS-II: A strategic view. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p.3-15.

80. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.

81. Hogan CJ, Hurwitz SR. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.

82. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.

83. Allen RJ, et al. Excessive limb guarding may increase complex regional pain syndrome risk. *Sympathetic Dystrophy Syndrome Association.* Available at: http://www.rsds.org/2/library/article_archive/pop/allen_koshi.pdf. Accessed on January 30, 2010.

84. Chung OY, et al. Complex regional pain syndrome. *Current Treatment Options in Neurology.* 2003;5:499-511.

85. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.

86. Chung OY, et al. Complex regional pain syndrome. *Current Treatment Options in Neurology.* 2003;5:499-511.

87. Allen RJ, et al. Excessive limb guarding may increase complex regional pain syndrome risk. *Sympathetic Dystrophy Syndrome Association.* Available at: http://www.rsds.org/2/library/article_archive/pop/allen_koshi.pdf. Accessed on January 30, 2010.

88. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.

89. Wilson PR, et al. Diagnostic algorithm for complex regional pain syndromes. In: Wilfred J, Stanton-Hicks MD, eds, *Regional Sympathetic Dystrophy: A Reappraisal: Progress in Pain Research and Management.* Seattle: IASP Press; 1996. p. 93-105.

90. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.

91. Wilson PR, et al. Diagnostic algorithm for complex regional pain syndromes. In: Wilfred J, Stanton-Hicks MD, eds, *Regional Sympathetic Dystrophy: A Reappraisal: Progress in Pain Research and Management.* Seattle WA: IASP Press; 1996:93-105.

92. Small E. Reflex sympathetic dystrophy: Reflections from a clinician. *Adolesc Med.* 2007;18:221-225.

93. Zyluk A. The usefulness of quantitative evaluation of three-phase scintigraphy in the diagnosis of post-traumatic reflex sympathetic dystrophy. *J Hand Surg.* 1999;24:16-21.

94. Hogan CJ, et al. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.

95. Wilson PR, et al. Diagnostic algorithm for complex regional pain syndromes. In: Wilfred J, Stanton-Hicks MD, eds, *Regional Sympathetic Dystrophy: A Reappraisal: Progress in Pain Research and Management.* Seattle: IASP Press; 1996. p. 93-105.

96. Stanton-Hicks M, et al. Use of regional anesthetics for diagnosis of reflex sympathetic dystrophy and sympathetically maintained pain: A critical evaluation. In: Wilfred J, Stanton-Hicks MD, eds, *Regional Sympathetic Dystrophy: A Reappraisal: Progress in Pain Research and Management*. Seattle: IASP Press; 1996. p. 217-237.

97. Small E. Reflex sympathetic dystrophy: Reflections from a clinician. *Adolesc Med.* 2007;18:221-225.

98. Wilson PR, et al. Diagnostic algorithm for complex regional pain syndromes. In: Wilfred J, Stanton-Hicks MD, eds, *Regional Sympathetic Dystrophy: A Reappraisal: Progress in Pain Research and Management.* Seattle: IASP Press; 1996. p. 93-105.

99. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.

100. Oerlemans HM, et al. Signs and symptoms in complex regional pain syndrome type I/reflex sympathetic dystrophy: judgment of the physician versus objective measurement. *Clin J Pain.* 1999;15:224-232.

101. Wasner G, et al. Complex regional pain syndrome-diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord.* 2003;41:61-75.

102. Allen RJ, et al. Excessive limb guarding may increase complex regional pain syndrome risk. *Sympathetic Dystrophy Syndrome Association.* Available at: http://www.rsds.org/2/library/article_archive/pop/allen_koshi.pdf. Accessed on January 30, 2010.

103. Dommerholt J. Complex regional pain syndrome TI: history, diagnostic criteria and etiology. *Journal of Bodywork and Movement Therapies.* 2004;8:167-177.

104. Allen RJ, et al. Excessive limb guarding may increase complex regional pain syndrome risk. *Sympathetic Dystrophy Syndrome Association.* Available at: http://www.rsds.org/2/library/article_archive/pop/allen_koshi.pdf. Accessed on January 30, 2010.

105. Wilson PR, et al. Diagnostic algorithm for complex regional pain syndromes. In: Wilfred J, Stanton-Hicks MD, eds, *Regional Sympathetic Dystrophy: A Reappraisal: Progress in Pain Research and Management.* Seattle: IASP Press; 1996. p. 93-105.

106. Wasner G, et al. Complex regional pain syndrome-diagnostic, mechanisms, CNS involvement and therapy. *Spinal Cord.* 2003;41:61-75.

107. Bonica JJ. Causalgia and other reflex sympathetic dystrophies. In: Bonica JJ (ED). *The Management of Pain.* Philadelphia: Lea & Febiger; 1990. p 220-243.

108. Butler S, et al. Immobility in volunteers transiently produces signs and symptoms of complex regional pain syndrome. In: *Proceeding of the 9th World Congress on Pain.* Seattle: IASP Press; 2000. p.657-660.

109. Butler S. Disuse and CRPS. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 141-151.

110. Small E. Reflex sympathetic dystrophy: Reflections from a clinician. *Adolesc Med.* 2007;18:221-225.

111. Butler S. Disuse and CRPS. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001; p. 141-151.

112. Allen RJ. Deactivation pain: developmental sequelae of secondary pain generation sites resulting from reduced mobility. Presented at: *Physical Therapy 2001: Annual Conference & Exposition of the American Physical Therapy Association.* Anaheim, Ca, 2001.

113. Schattschneider J, et al. Kinematic analysis of the upper extremity in CRPS. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p.119-128.

114. Ringkamp M, Wu G. The role of injured and uninjured afferents in neuropathic pain. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press, 2001, pp.27-38.

115. Vatine J-J, et al. A model of CRPS-I produced by titanic electrical stimulation of an intact sciatic nerve in the rat: Genetic and dietary effects. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 53-74.

116. Butler S. Disuse and CRPS. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press, 2001; p. 141-151.

117. Ushida T, et al. Effect of contracture-induced pain in rat: electrophysiological and behavioral study. Abstracts: *8th World Congress on Pain.* Seattle: IASP Press; 1996. p. 6.

118. Maves TJ, et al. Pain behaviors and sensory alterations following immobilization of the rat hindpaw. Abstracts: *8th World Congress on Pain.* Seattle: IASP Press, 1996. p. 118.

119. Butler S, et al. Immobility in volunteers transiently produces signs and symptoms of complex regional pain syndrome. In: *Proceeding of the 9th World Congress on Pain.* Seattle: IASP Press; 2000. p.657-660.

120. Allen RJ, et al. Excessive limb guarding may increase complex regional pain syndrome risk. *Sympathetic Dystrophy Syndrome Association.* Available at: http://www.rsds.org/2/library/article_archive/pop/allen_koshi.pdf. Accessed on January 30, 2010.

121. Galer BS, et al. Motor abnormalities in CRPS: A neglected but key component. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 135-140.

122. Schattschneider J, et al. Kinematic analysis of the upper extremity in CRPS. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p.119-128.

123. Browner, B. *Skeletal Trauma.* Philadelphia, PA: W.B. Saunders Company; 1992. p. 87-88.

124. Cole BJ, et al. The multiple ligament injured knee. *Clinical Sports Medicine.* 1999;11:81-88.

125. Millett PJ, et al. Motion loss after ligament injuries to the knee. *The American Journal of Sports Medicine.* 2001;29:664-675.

126. Marks PH, et al. The anterior cruciate ligament in the multiple ligament-injured knee. *Clinical Sports Medicine.* 1993;12:825-833.

127. Irrgang JJ, et al. Loss of motion following knee ligament reconstruction. *Sports Medicine.* 1995;19:150-159.

128. Sisto DJ, et al. Complete knee dislocation. A follow-up study of operative treatment. *Clinical Orthopedics.* 1985;198:94-101.

129. Paulos LE, et al. Infrapatellar contracture syndrome: an unrecognized cause of knee stiffness with patella entrapment and patella infera. *American Journal of Sports Medicine.* 1987;15:331-341.

130. Enneking WF, et al. The intra-articular effects of immobilization on the human knee. *Journal of Bone and Joint Surgery.* 1972;54A:973-985.

131. Videman T. Connective tissue and immobilization. *Clinical orthopaedics and related research.* 1987;221:26-32.

132. Enneking WF, et al. The intra-articular effects of immobilization on the human knee. *Journal of Bone and Joint Surgery America.* 1972;54:973-985.

133. Videman T. Changes of compression and distances between tibial and femoral condyles during immobilization of rabbit knee. *Archives of Orthopedic Trauma Surgery.* 1981;98:289-295.

134. Eronen I, et al. 3H-Proline incorporation in vivo in capsular tissues and menisci during the development of osteoarthritis. An experimental study with rabbits. *Scandanavian Journal of Rheumatology.* 1984;13:121-130.

135. Langenskiold A, et al. Osteoarthritis of the knee in the rabbit produced by immobilization. Attemps to achieve a reproducible model for studies on pathogenesis and therapy. *Acta Orthop. Scand.* 1979;50:1-8.

136. Videman T. Experimental osteoarthritis in the rabbit. Comparison of different periods of repeated immobilization. *Acta Orthop Scand.* 1982;53:339-347.

137. Liebenson C. Pathogenesis of chronic back pain. *Journal of Manipulative Physiol. Ther.* 1992;15:299-308.

138. Ford H. Physiology of Soft Tissue Healing. Chapter 4 in *Rehabilitation of the Knee: A Problem Solving Approach.* Greenfield. Philadelphia: F.A: Davis Company; 1993. p. 85-109.

139. Shrive CF, et al. Optimisation of the Biology of Soft Tissue Repair. *Journal of Science and Medicine in Sport.* 1999;2(3):190-210.

140. Nerlich ML, et al. Biology of soft tissue injuries. In: Browner B, et al. *Skeletal Trauma: Fractures, Dislocations, Ligamentous Injuries.* Vol 1. Philadelphia: W.B. Sauders Company; 1992. p. 77-94.

141. Nerlich ML, et al. Biology of soft tissue injuries. In: Browner B, Jupiter J, Levine A, Trafton P. *Skeletal Trauma: Fractures, Dislocations, Ligamentous Injuries.* Vol 1. Philadelphia: W.B. Sauders Company; 1992. p. 77-94.

142. Langenskiold A. Osteoarthritis of the knee in the rabbit produced by immobilization: attempts to achieve a reproducible model for studies on pathogenesis and therapy. *Acta. Orthop. Scand.* 1979;50:1.

143. Ibid.

144. Brandt KD, et al. Osteoarthritis is not a cartilage disease. *Annals of Rheumatic Diseases.* 2006;66:1261-1264.

145. Tan AL, et al. Combined high-resolution magnetic resonance imaging and histological examination to explore the expression of early hand osteoarthritis. *Annals of Rheumatic Diseases.* 2006; 65:1265-1272.

146. Noyes F. Biomechanics of anterior cruciate ligament failure: an analysis of strain rate sensitivity and mechanisms of failure in primates. *Journal of Bone and Joint Surgery.* 1974;56A:236-242.

147. Ford, H. Physiology of Soft Tissue Healing. Chapter 4 in *Rehabilitation of the Knee: A Problem Solving Approach* by Bruce H. Greenfield. Philadelphia: F.A: Davis Company; 1993. p. 85-109.

148. Noyes F. Biomechanics of ligament failure. Part 2: An analysis of immobilization, exercise and reconditioning effects in primates. *Journal of Bone and Joint Surgery.* 1974;56A:1406-1415.

149. Laros G. Influences of physical activity on ligaments insertions in the knees of dogs. *Journal of Bone and Joint Surgery.* 1971;53:275-283.

150. Arnoczky, S. Meniscal degeneration due to knee instability: an experimental study in the dog. *Trans. Orthop. Res. Soc.* 1979;4:79-91.

151. Nerlich ML, et al. Biology of soft tissue injuries. In: Browner B, Jupiter J, Levine A, Trafton P. *Skeletal Trauma: Fractures, Dislocations, Ligamentous Injuries.* Vol 1. I Philadelphia: W.B. Sauders Company; 1992. p. 77-94.

152. Ivie TJ, et al. Denervation impairs healing of the rabbit medial collateral ligament. *Journal of Orthopaedic Research.* 2002;20:990-995.

153. Frank C, et al. Optimisation of the biology of soft tissue repair. *Journal of Science and Medicine in Sport.* 1999;2:190-210.

154. Fleming BC, et al. Ligament injury, reconstruction and osteoarthritis. *Curr Opin Orthop.* 2005;16:354-362.

155. Frank C. Healing of the medial collateral ligament of the knee. *Acta Orthop Scand.* 1983;54:917-923.

156. Andriacchi, T. *Injury and Repair of the Musculoskeletal Soft Tissues.* Park Ridge, IL: AAOS; 1987. p. 103-128.

157. Frank CB. Ligament healing: current knowledge and clinical applications. *Journal of the American Academy of Orthopedic Research.* 1996;4:74-83.

158. Frank CB, et al. Molecular biology and biomechanics of normal and healing ligaments-a review. *Osteoarthritis and Cartilage.* 1999;7:130-140.

159. Bishop PB, et al. Abnormal joint mechanics and the proteoglycan composition of normal and healing rabbit medial collateral ligament. *Journal of Manipulation and Physiol Therapy.* 1993;16:300-305.

160. Wood JN, et al. The primary nociceptor: special functions, special receptors. Chapter 6 from *Proceedings of the 9th World Congress on Pain.* Progress in Pain Research and Management Vol 16 edited by Devor M, Rowbotham MC. Seattle, WA: IASP Press; 2000. p. 47-62.

161. Szadek K, et al. Nociceptive nerve fibers in the sacroiliac joint in humans. *Regional Anesthesia and Pain Medicine.* 2008;33:36-43.

162. Mashoof AA, et al. Neural anatomy of the transverse carpal ligament. *Clincal Orthopedics and Related Research.* 2001;386:218-221.

163. Tamai M, et al. Quantitative analysis of neural distribution in human coracoacromial ligaments. *Clinical Orthopedics and Related Research.* 2000;373:125-134.

164. Fortin JD, et al. Sacroiliac joint innervation and pain. *American Journal of Orthopedics.* 1999;28:687-690.

165. Witonski D, et al. Distribution of substand-P nerve fibers in intact and ruptured human anterior cruciate ligament: a semi-quantitative immunohistochemical assessment. *Knee Surg Sports Traumatol Arthrose.* 2004;12:497-502.

166. Denti M, et al. Anterior cruciate ligament mechanoreceptors. Histologic studies on lesions and reconstruction. *Clinical Orthopaedics.* 1994;308:29-32.

167. Holm S, et al. Sensorimotor control of the spine. *Journal of Electromyography and Kinesiology.* 2002;12:219-234.

168. Hackett G. *Ligament and Tendon Relaxation Treated By Prolotherapy.* Third Edition. Springfield, IL: Charles C. Thomas, 1958.

169. Hackett G. Prolotherapy in whiplash and low back pain. *Postgraduate Medicine.* 1960;Feb:214-219.

170. Phillips D, et al. Ligamento-muscular protective reflex in the elbow. *Journal of Hand Surgery.* 1997;22:473-478.

171. Yahia H, et al. Neurohistology of lumbar spine ligaments. *Acta Orthop Scand.* 1988;59:508-512.

172. Korr IM.Experimental alterations in segmental sympathetic (sweat gland) activity through myofascial and postural disturbances. *Federal Proceedings.* 1949;88:8-15.

173. Kellgren JH. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci.* 1938;4:35-46.

174. Korr IM, et al. Effects of experimental myofascial insults on cutaneous patterns of sympathetic activity in man. *Acta Neurovegetativa.* 1962;23:329-355.

175. Travell J, et al. Effects of referred somatic pain structures in the reference zone. *Fed Proc.* 1944;3:49-60.

176. Allen G, et al. Epidemiology of complext regional pain syndrome: a retrospective chart review of 134 patients. *Pain.* 1999;80:539-544.

177. Rasiq S, et al. Proximal myofascial dysfunction in complex regional pain syndrome: a retrospective prevalence study. *Clinical Journal of Pain.* 1999;15:151-153.

178. Korr IM, et al. Cutaneous patterns of sympathetic activity in clinical abnormalities of the musculoskeletal system. *Acta neurovegetativa.* 1964;25:589-606.

179. Thomas PE, et al. The automatic recording of electrical skin resistance patterns on the human trunk. *Electroencephalography.* 1951;3:361-368.

180. Felson DT. The source of pain in knee osteoarthritis. *Current Opinions in Rheumatology.* 2005;17:624-628.

181. McDougall JJ, et al. Spatial variation in sympathetic influences on the vasculature of the synovium and medial collateral ligament of the rabbit knee joint. *Journal of Physiology.* 1997;503:435-443.

182. Takebayashi T, et al. Mechanosensitive afferent units in the lateral ligament of the ankle. *Journal of Bone and Joint Surgery* (British). 1997;79B:490-493.

183. Holm S, et al. Sensorimotor control of the spine. *Journal of Electromyography and Kinesiology.* 2002;12:219-234.

184. Stanton-Hicks MD, et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Practice.* 2002;2:1-16.

185. Rowbotham M. Pharmacologic management of complex regional pain syndrome. *Clin J Pain.* 2006;22:425-429.

186. Zyluk A. The sequelae of reflex sympathetic dystrophy. *J Hand Surg.* 2001;26:151-154.

187. Low P, et al. Clinical characteristics of patients with reflex sympathetic dystrophy(sympathetically maintained pain)in the USA. In: Wilfred J, Stanton-Hicks MD, eds, *Regional Sympathetic Dystrophy: A Reappraisal: Progress in Pain Research and Management.* Seattle WA: IASP Press; 1996:49-66.

188. Stanton-Hicks MD, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Practice.* 2002;2(1):1-16.

189. Warwick D, et al. Function 10 years after Colles' fracture. *Clin Orthop.* 1993;295:270-274.

190. Choi YS, et al. Epidemiology of complex regional pain syndrome: A retrospective chart review of 150 Korean patients. *J Korean Med Sci.* 2008;23:772-775.

191. Hodnett C, et al. Complex regional pain syndrome. *Pain Pathways.* 2008; winter.

192. Baron R, et al. National Institutes of Health workshop: reflex sympathetic dystrophy/complex regional pain syndromes-state-of-the-science. *Anesth Analg.* 2002;95:1812-1816.

193. Stanton-Hicks M, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Practice.* 2002;2(1):1-16.

194. Stanton-Hicks M, et al. Complex regional pain syndrome: guidelines for therapy. *The Clinical Journal of Pain.* 1998;14:155-166.

195. Harden RN. Complex regional pain syndrome. *Br J Anaest.* 2001;87:99-106.

196. Chung OY, et al. Complex regional pain syndrome. *Current Treatment Options in Neurology.* 2003;5:499-511.

197. Baron R, et al. National Institutes of Health workshop: reflex sympathetic dystrophy/complex regional pain syndromes-state-of-the-science. *Anesth Analg.* 2002;95:1812-1816.

198. Hogan CJ, et al. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.

199. Small, E. Reflex sympathetic dystrophy: Reflections from a clinician. *Adolesc Med.* 2007;18:221-225.

200. Stanton-Hicks M, et al. An updated interdisciplinary clinical pathway for CRPS: Report of an expert panel. *Pain Practice.* 2002;2(1):1-16.

201. Quisel A, et al. Complex regional pain syndrome: which treatments show promise? *The Journal of Family Practice.* 2005;54:599-603.

202. Chung OY, et al. Complex regional pain syndrome. *Current Treatment Options in Neurology.* 2003;5:499-511.

203. Hogan CJ, et al. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.

204. Moore DC. Reflex sympathetic dystrophy. In: *Stellate Ganglion Block.* Springfield, IL: Charles Thomas Publisher; 1954. p. 220-226.

205. Quisel A, et al. Complex regional pain syndrome: which treatments show promise? *The Journal of Family Practice.* 2005;54:599-603.

206. Hogan CJ, et al. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.

207. Blanchard J, et al. Intravenous regional sympatholysis: a double-blind comparison of guanethidine, reserpine, and normal saline. *J Pain Symptom Management.* 1990;5:357-361.

208. Eulry F, et al. Regional intravenous guanethidine blocks in algodystrophy. *Clin Rheumatol.* 1991;10:377-383.

209. Wang JK, et al. Sympathetic blocks for reflex sympathetic dystrophy. *Pain.* 1985;23:13-17.

210. Hogan CJ, et al. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.

211. Chung OY, et al. Complex regional pain syndrome. *Current Treatment Options in Neurology.* 2003;5:499-511.

212. Bennett G. Epilogue. In: *Complex Regional Pain Syndrome.* Seattle: IASP Press; 2001. p. 323-325.

213. Hogan CJ, et al. Treatment of complex regional pain syndrome of the lower extremity. *J Am Acad Orthop Surg.* 2002;10:281-289.

214. Perez R, et al Treatment of patients with complex regional pain syndrome type 1 with mannitol: a prospective, randomized, placebo-controlled, double blind study. *The Journal of Pain.* 2008;9(8):678-686.

215. Quisel A, et al. Complex regional pain syndrome underdiagnosed. *The Journal of Family Practice.* 2005;54:524-532.

216. Harden RN. Complex regional pain syndrome. *Br J Anaest.* 2001;87:99-106.

217. Ibid.

218. Allen RJ, et al. Excessive limb guarding may increase complex regional pain syndrome risk. *Sympathetic Dystrophy Syndrome Association.* Available at: http://www.rsds.org/2/library/article_archive/pop/allen_koshi.pdf. Accessed on January 30, 2010.

219. Butler SH, et al. Immobility in volunteers transiently produces signs and symptoms of complex regional pain syndrome. In: Devor M, Rowbotham MC, Wiesenfield-HallinZ (eds). *Progress in Pain Research and Management*, vol 16, Proceeings of the 9th World Congress on Pain. Seattle: IASP Press; 2000. p. 657-660.

220. Allen RJ. Deactivation pain: developmental sequelae of secondary pain generation sites resulting from reduced mobility. Presented at: Physical Therapy 2001: Annual Conference & Exposition of the American Physical Therapy Association, Anaheim, CA, 2001.

221. Chung OY, et al. Complex regional pain syndrome. *Current Treatment Options in Neurology.* 2003;5:499-511.

222. Hackett G. *Ligament and Tendon Relaxation Treated by Prolotherapy.* Third Edition. Springfield IL: Charles C. Thomas; 1958.

223. Hackett G. *Ligament and Tendon Relaxation Treated by Prolotherapy.* Fifth Ed. Oak Park IL: Gustav A. Hemwall; 1993. p. 94-96.

224. Hackett G. Joint stabilization: An experimental, histologic study with comments on the clinical application in ligament proliferation. *American Journal of Surgery.* 1955;89:968-973.

225. Hackett G. Referred pain from low back disability. *AMA Archives of Surgery.* 1956;73:878-883.

226. Hackett G. Referred pain and sciatica in low back diagnosis. *Journal of the American Medical Association.* 1957;16:183-190.

227. Hackett G. Prolotherapy for sciatica from weak pelvic ligaments and bone dystrophy. *Clinical Medicine.* 1961;68: 1-10.

228. Hackett G. Low back pain. *The British Journal of Physical Medicine.* 1956;19:25-35.

229. Hackett, G. Back pain following trauma and disease-*Prolotherapy. Military Medicine.* 1961;126: 517-525.

230. Hackett G. Prolotherapy for headache. *Headache.* 1962 Apr:3-11.

231. Kayfetz D, et al. Whiplash injury and other ligamentous headache-its management with Prolotherapy. *Headache.* 1963;3:1-8.

232. Klein, RC, Dorman, TA, and Johnson CE. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measurements of lumbar spine mobility before and after treatment. *Journal of Neurology and Orthopaedic Medicine and Surgery.* 1989; 10:123-126.

233. Klein R, et al. Prolotherapy: an alternative way of manageing low back pain. *Journal of Musculoskeletal Medicine.* 1997; 45-49.

234. Klein R. A randomized double-blind trial of dextrose-glycerine-phenol injections for chornic, low back pain. *Journal of Spinal Disorders.* 1993; 6:23-33.

235. Hooper RA, et al. Retrospective case series on patients with chronic spinal pain treated with dextrose Prolotherapy. *Journal of Alternative and Complementary Medicine.* 2004;10:670-674.

236. Reeves KD, et al. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *Alternative Therapies.* 2000;6:68-79.

237. Reeves KD, et al. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. *Alternative Therapies and Complementary Medicine.* 2003; 9:58-62.

238. Hakala RV. Prolotherapy (proliferative therapy) in the treatment of TMD. *The Journal of Craniomandibular Practice.* 2005;23: 1-6.

239. Schultz LW. Twenty years-experience in treating hypermobility of the temporomandibular joints. *American Journal of Surgery.* 1956;92:925-928.

240. Schwartz R. Prolotherapy: A literature review and retrospective study. *J Neurology, Orthopic Medicine and Surgery.* 1991;12-:220-223.

241. Tsatsos G, et al. Prolotherapy in the treatment of foot problems. *Journal of the American Podiatric Medical Association.* 2002;92:366-368.

242. Hooper RA, et al P. Case series on chronic whiplash related neck pain treated with intraarticular zygapophysial joint regeneration injection therapy. *Pain Physician.* 2007; 10:313-318.

243. Centeno CJ, et al. Fluoroscopically guided cervical prolotherapy for instability with blinded pre and post radiograph reading. *Pain Physician.* 2005; 8:312-326.

244. Reeves KD, et al. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger joints: evidence of clinical efficacy. *The Journal of Alternative and Complementary Medicine.* 2000; 6:311-320.

245. Reeves K. Prolotherapy: Basic science, clinical studies, and technique. *Pain Procedures in Clinical Practice.* Second Ed. Edited by Lennard, T. Philadelphia: Hanley and Belfus, Inc; 2000. p. 172-189.

246. Hackett G. *Ligament and Tendon Relaxation Treated by Prolotherapy.* Third Edition. Springfield, IL: Charles C. Thomas; 1958. p. 5.

247. Hackett G, et al. *Ligament and Tendon Relaxation Treated by Prolotherapy.* Fifth Edition. Oak Park, IL: Gustav A. Hemwall; 1993. p. 20.

248. Hackett G. Shearing injury to the sacroiliac joint. *Journal of the International College of Surgeons.* 1954;22:631-642.

249. Hackett G. Prolotherapy in whiplash and low back pain. *Postgraduate Medicine.* 1960 Feb:214-219.

250. Hackett G, et al. Prolotherapy for sciatica and weak pelvic ligaments and bone dystrophy. *Clinical Medicine.* 1961;68:2301-2316.

251. McBride A, et al. Complext regional pain syndrome. *Current Orthopaedics.* 2008;19:155-165.

252. Maillefert JF. Treatment of refractory reflex sympathetic dystrophy with pamidronate. *Annals of Rheumatic Diseases.* 1995;54:187.

253. Chard MD. Diagnosis and management of algodystrophy. *Annals of Rheumatic Diseases.* 1991; 50:727-730.

254. Hackett, G. Ligament relaxation and osteoarthritis, loose jointed vs. close jointed. *Rheumatism.* 1959;15:28-33.

255. Hackett G. Uninhibited reversible antidromic vasodilation in brochiogenic pathophysiologic disease. *Lancet.* 1966;86:398-404.

256. Hackett G. Uninhibited reversible antidromic vasocilation in pathophysiologic diseases: arteriosclerosis, carcinogenesis, neuritis and osteoporosis. *Angiology.* 1966; 17, #2.

257. Hackett G. Prolotherapy in low back pain from ligament relaxation and bone dystrophy. *Clinical Medicine.* 1961;68:2301-2316.

258. Hauser R, et al. *Prolo Your Pain Away!* Third Edition. Oak Park; Beulah Land Press. 2007.

259. Kayfetz DO. Occipito-cervical injuries treated by prolotherapy. *Medical Trial Technique Quarterly.* 1963;3:1-8.

260. Hemwall G. Barre-Lieou Syndrome. *Journal of Orthopedic Medicine.* 1989;11:79-82.