COMPLEX REGIONAL PAIN SYNDROME – A MEDICO-LEGAL REVIEW

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A Preliminary Note to Our Readers:

The authors, an attorney, a physician and a soon to be law student, who translated articles from German; hope this Medico-Legal article will be the first of many such carefully researched articles which represent the collaborative efforts of Section Members, neuroscientists, physicians, medical school professors and allied health professionals to provide an educational resource free of bias or "slant". For this inaugural project, the authors specifically selected a medical condition, Complex Regional Pain Syndrome, about which articles in peer-reviewed medical journals abound in numbers far out of proportion to actual incidence of the condition.

While commending the research and scholarship of the medical and scientific community, the authors also recognize that the legal community; particularly in the workers' compensation realm, has allowed the pervasive fear of the diagnosis, the claim cost expected to be incurred (Hendler infra), the present lack of a "cure", to delay treatment at the point in time during the course of the condition when it is the most treatable; most articles in peer-reviewed medical journals having concluded that only a relatively small percentage of patients who are correctly diagnosed with CRPS will ever develop "classic RSD" symptoms and clinical signs, (Harden, Bruehl, Veldman, de Boer, infra). The authors hope that this comprehensive Medico-legal Review Article will "teach" the subject well enough that diagnosis and treatment of the condition will be expedited thereby reducing claim expense and disability.

Whenever possible, the authors have cited articles by national and international academicians, physicians and researchers who support "open access", were published in Journals such as PLOS One, etc., pursuant to "creative commons" (http://creativecommons.org/licenses/by/2.0/) and may also be available on the website of Reflex Sympathetic Dystrophy Association (http://rsds.org/), via Google Scholar, Medline and other similar resources. The authors also invite readers to visit the website, http://apkarianlab.northwestern.edu/ . That website makes available without cost many articles and studies authored by Dr. Vania Apkarian and other neuroscientists who report the strides made in neurodiagnostics across many chronic pain conditions in only the last decade.

This article will be available on the website of the State Bar of Georgia's Workers' Compensation Section:
http://www.gabar.org/committeesprogramssections/sections/workerscompensation/index.cfm

Introduction:

Complex Regional Pain Syndrome, formerly known as Reflex Sympathetic Dystrophy, or, when the result of a known nerve lesion, causalgia, is a fascinating; yet challenging neuropathic condition which is primarily diagnosed by criteria based upon clinical signs and symptoms. There is presently no "gold standard" diagnostic test to confirm or exclude the diagnosis [1]; and, making the diagnostic process more difficult, more frustrating, the "presentation" of the symptoms and even clinical signs may vary over time and even from one office visit to another [2].

The current International Association for the Study of Pain (IASP); Classification of Chronic Pain, Second Edition (Revised) defines Complex Regional Pain Syndrome as

> ". . . characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor edema, and/or trophic findings. The syndrome shows variable progression over time. CRPS type I develops after any type of trauma, especially fracture, soft tissue lesion . . . . CRPS type II occurs after major nerve damage."

IASP describes the "main features" of CRPS as:

> "Pain often, but not always, follows trauma, which may be mild or may be associated with significant nerve injury in the case of CRPS type II. It may follow any type of trauma, especially fracture, soft tissue lesion (e.g. crush injury), laceration, immobilization, or may be related to visceral disease, e.g., angina or central neurological disease such as stroke. The onset of symptoms usually occurs within one month of the inciting event. The pain is frequently described as burning and continuous and is exacerbated by movement, mechanical or thermal stimulation, or stress. The intensity of pain may fluctuate over time, and allodynia, and/or hyperalgesia may be found which are not limited to the territory of a single peripheral nerve. Abnormalities of blood flow occur, including changes in skin temperature and color.
>
> Edema is usually present and may be soft or firm. Increased or decreased sweating may appear. Dystrophic changes of skin, nails, hair, and bone may occur. Impairment of motor function and joint mobility are frequently seen and can include weakness, tremor, and, in rare instances, dystonia. The symptoms and signs may spread proximally or, rarely, spread to involve other extremities." [3,4,5]

The pathophysiology (*the study of how normal physiological processes are altered by disease*) remains unclear; but is [presently] believed to be multi-factorial. Pathogenesis (*the origin and development of a disease*) is also a subject of evolving theory. Impaired Sympathetic Nervous System (autonomic) dysfunction, neurogenic

inflammation, deep tissue microvascular pathology, small-fiber neuropathy, capillary dysfunction/impaired oxygenation [6], central and peripheral sensitization, brain plasticity and even a genetic predisposition are implicated. [7] Adding to the confusion is the changing nosology (*the science of description or classification of diseases*) and terminology.

Reports of the clinical signs and symptoms now associated with CRPS have existed since the 16th century in France when Ambroise Pare is reported to have observed the condition in King Charles IX [8]. Description by Mitchell, Morehouse and Keen in 1864 of the clinical signs and symptoms now associated with CRPS which resulted from nerve damage from gunshot wounds sustained by Union soldiers in the Civil War is the origin of the term, causalgia, "burning pain". [9] In 1900, Sudeck described progressive bone atrophy as well as vasomotor and trophic changes which developed after trauma. [10,11] While numerous different names for the condition are known, the most common are Sudeck's Dystrophy, Algodystrophy or Algoneurodystrophy, Reflex Dystrophy, coined by DeTakats in 1937, [12] and Reflex Sympathetic Dystrophy (RSD), attributed to Evans in 1946 [13].

By 1994, as research and clinical experience continued to advance, it had been observed that dystrophy (atrophy) was reported to be present in percentages which varied between about 15% [14] and 25% of patients diagnosed with CRPS at 0-2 months duration increasing to 49.8% of patients which had been diagnosed after greater than 12 months [15]. Upon that and other emerging discoveries about the condition, diagnostic criteria designed to be more sensitive (i.e., *able to detect the disorder when present*) were developed at the Orlando Conference of IASP. At that conference, the condition was also sub-divided into CRPS Type I (replacing Reflex Sympathetic Dystrophy) and CRPS Type II (replacing causalgia). [16]

The Orlando diagnostic criteria was adopted by the IASP Committee for Classification of Chronic Pain. [17] However, those criteria, while found to be very sensitive, lacked specificity, (*minimizing false positive diagnoses*) resulting in over-diagnosis of CRPS. [18]

A "by invitation only" workshop was held in Budapest, Hungary in August 2003 to review the diagnostic criteria from the 1994 Orlando conference and to propose recommendations for revision to the IASP Taxonomy Committee. [19]

In 2004, at the second of the two meetings held in Budapest, that consensus group endorsed a set of Proposed Research Diagnostic Criteria which were designed to achieve greater specificity. To increase sensitivity, a separate set of Proposed Clinical Diagnostic Criteria were also endorsed. [20] In 2010, the results of a study comparing the diagnostic efficiency of the 1994 Orlando criteria and the "Budapest Criteria" was published demonstrating that the latter "set" of criteria ". . . retained the exceptional sensitivity of the IASP [Orlando Criteria]; but improved upon specificity, corroborating the validity of the Budapest Criteria." [21]

Terminology and Definitions:

Allodynia - Pain due to a stimulus that does not normally provoke pain.
Diagnosis – The determination of the nature of a cause of a disease or the distinguishing of one disease from another.
Diagnosis (Clinical) – Diagnosis based on signs, symptoms, and laboratory findings during life.
Diagnosis (Differential) – The determination of which one of several diseases may be producing the symptoms.
Dysesthesia - An unpleasant abnormal sensation, whether spontaneous or evoked.
Hyperalgesia - Increased pain from a stimulus that normally provokes pain.
Hyperesthesia - Increased sensitivity to stimulation, excluding the special senses.
Hyperpathia - A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
Neuropathic pain - Pain caused by a lesion or disease of the somatosensory nervous system.
Central neuropathic pain - Pain caused by a lesion or disease of the central somatosensory nervous system.
Peripheral neuropathic pain - Pain caused by a lesion or disease of the peripheral somatosensory nervous system.
Neuropathy - A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.
Nociception - The neural process of encoding noxious stimuli.
Nociceptive neuron - A central or peripheral neuron of the somatosensory nervous system that is capable of encoding noxious stimuli.
Nociceptive pain - Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.
Nociceptive stimulus - An actually or potentially tissue-damaging event transduced and encoded by nociceptors.
Nociceptor - A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli.
Noxious stimulus - A stimulus that is damaging or threatens damage to normal tissues.
Paresthesia - An abnormal sensation, whether spontaneous or evoked.
Sensitization - Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.
Central sensitization - Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.
Peripheral sensitization - Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields.
Somatosensory - Relating to or denoting a sensation (such as pressure, pain, or warmth) that can occur anywhere in the body, in contrast to one localized at a sense organ (such as sight, balance or taste).
Sudomotor - Denoting the autonomic (sympathetic) nerves that stimulate the sweat glands to activity.
Vasomotor - Of, relating to, affecting, or being those nerves or the centers (as in the medulla and spinal cord) from which they arise that supply the muscle fibers of the walls of blood vessels, include sympathetic vasoconstrictors and parasympathetic vasodilators, and by their effect on vascular diameter regulate the amount of blood passing to a particular body part or organ.

Pathophysiologic Mechanisms – A Speculative Model:

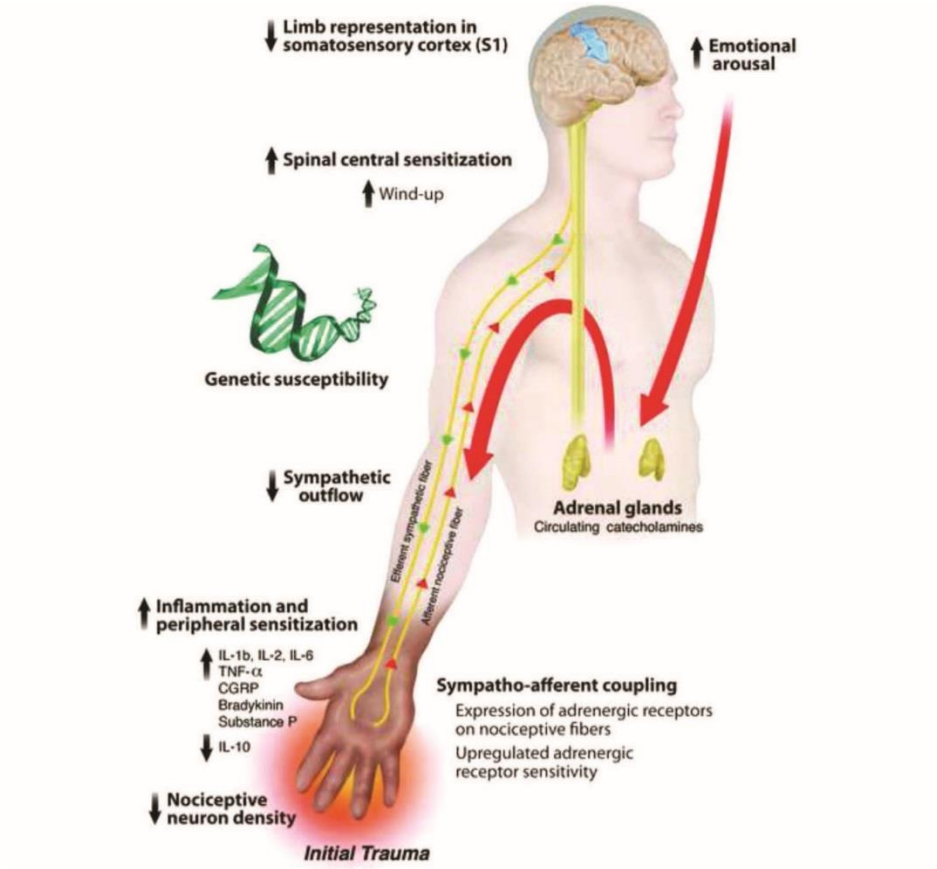

Fig. 1. Speculative model of interacting complex regional pain syndrome mechanisms. CGRP = calcitonin gene-related peptide; IL = interleukin; TNF = tumor necrosis factor.

Used with express written permission by Prof. Stephen Bruehl, Professor Anesthesiology, Vanderbilt University School of Medicine, Nashville, Tenn., and published in Anesthesiology, An Update on the Pathophysiology of Complex Regional Pain Syndrome, Anesthesiology 2010;113 - 713-25

Epidemiology/Incidence/Risk Factors/Inciting Event:

Numerous studies establish that CRPS is diagnosed across a wide demographic spectrum. Age ranges from children to the elderly have been reported by several studies as has a female to male ratio of 4:1; that the condition has been diagnosed more frequently in Caucasians than all other racial groups combined.

Identification of those specific injuries, surgeries, inciting events and demographics which may increase the risk of development of CRPS has been widely studied and reported in the medical literature. Common denominators have been isolated. Distal radial fractures, strains, sprains, carpal tunnel releases, neuromas/resection of neuromas, and immobilization of the affected member are implicated. One study [22] found that the most common injuries were strains/sprains in 39 (29%) of the 134 CRPS patients studied. Thirty-two (32) (24%) developed the

condition after surgery; and 22 (16%) had developed the condition after fractures. Eleven (11) with contusions or crush injuries represented 8%. Only 8 (6%) were found to have "spontaneous" onset; largely because no specific injury could be recalled. Another 11% of the patients developed the condition following lacerations, venipunctures, etc. This study found that 48% of the patients had developed CRPS in lower extremities; 44% in upper extremities. Forty-six percent (46%) had developed the condition on the right and 38% on the left. Sixty-four (64) (47%) of the 134 patients in this study had a history of physician imposed, physical immobilization ["hard" casts/splints] following the injury or surgery for the injury.

These findings are consistent with those made and reported by many other researchers which specifically studied potential risk factors. The most thorough of such articles at the time this article was written (Spring 2015) is the 2015 Review Article, Potential Risk Factors for the Onset of Complex Regional Pain Syndrome Type I: A Systematic Literature Review. [23] This Systematic Review collects and analyzes well-known studies by de Mos, et al. [24], Jellad, et al. [25], Allen et al. [26], Moseley, et al. [27] and others.

Several studies also dispute the contention that the diagnosis is more frequent and that litigation concerning the diagnosis more likely when the condition occurs following a work-related injury. [28]

A population-based study by Sandroni, et al, in Olmsted County, Minnesota (the home of Mayo Clinic), is often cited as having determined an incidence "risk-rate" of only 5.46, per 100,000 person years; a female to male ratio of 4 to 1. However, the Olmsted County study was limited to CRPS Type 1 [29]. The Sandroni study was quickly criticized in a letter to the editor of the medical journal in which the Sandroni study had been published. [30] An incidence rate of 26.2/100,000 person years, which included CRPS Types I and II with a female to male ratio of 3.4 to 1, determined by De Mos, et al., and published in 2007 is generally considered to be more realistic [31].

In one of the studies most frequently cited by CRPS researchers, the landmark study of signs and symptoms of 829 patients diagnosed with Reflex Sympathetic Dystrophy [32], Netherlands researchers Veldman, Raynen, Arntz and Goris found that 628 patients were female (76%), the rest male (24%), essentially a 3:1 ratio. Age range was 9 to 85, the median age, 42. Four hundred eighty-seven (487) (59%) of the patients were diagnosed with the condition in an upper extremity; 342 (41%) in a lower extremity. In 545 (65%), the RSD followed trauma (mostly fractures); in 155 cases (19%), an operation. Other less common inciting events were 15 (2%), reporting an inflammatory process; 34 (4%) precipitants such as injections or intravenous infusions. Neurological symptoms with sensory changes in a "glove" or "stocking" like distribution were regularly reported. Complaints considered to be consistent with a subsequent diagnosis of "RSD" often appeared within 1 day; however, a number of patients did not display symptoms (and/or signs) until at least 1 year after the presumed inciting event.

Thirty-nine (39) patients reported "spread" to one or more limbs; 57 experienced recurrence in the same limb after a period with few or no symptoms. In 30 of the 57 (53%) no cause or explanation for the recurrence could be identified. As it relates to the impact of delayed treatment, the mean elapsed time between the beginning of symptoms and signs later diagnosed as RSD was 405 days; the median 156 days. Consistent with the research performed years later and reported by Harden, Bruehl, et al. (2002) [33] and de Boer (2011) [34], signs characterized as "trophic" were documented when the condition had been present for more than 12 months in less than 40% of the 829 patients. The "Veldman study" also reported generally normal electromyographic (EMG) stimulation; that most cases of RSD did not progress to "classic" RSD clinical signs; and, more than half of the longstanding cases did not show signs of tissue dystrophy or atrophy. The Veldman study also rejected the "staging" theory and suggested that a subdivision into primarily "warm" or "cold" as related to skin temperatures at onset provides ". . . a more realistic description of RSD." [35]

Others studying epidemiology and incidence have reported data similar to the Veldman study. In 2014, researchers in Scotland performed a retrospective cohort study of 390 patients who had undergone elective foot and/or ankle surgery. [36] A total of 17 patients (4.36%) were found to meet the IASP criteria: the mean age was 47.2; 14 (82.35%) were female. Twelve (12) patients (70.59%) had developed "new-onset" CRPS after a primary procedure; 5 (29.41%) after multiple surgeries.

Relevant to the workers' compensation realm, the University of Washington School of Medicine conducted a retrospective chart review of 134 patients published in 1999 [37], reporting a mean age at time of injury/inciting event of 37.7 years; but, the mean age at initial evaluation at the pain center was 41.8 years, many patients not receiving specialized treatment during a mean duration of 30 months. Seventy percent (70%) of the patients were women, 30% male, a ratio similar to other studies.

This study by the University of Washington reported 56% of the patients had sustained and were receiving treatment for work-related injuries, the distribution of the precipitating injuries ranging from most frequent in service occupations (at 14%) to the least, 2.2%, in machine trades.

However, a study performed of patients treated in a Dearborn, Michigan pain clinic between 1995 and 2002, published in 2004, reported only 8% of patients were involved in litigation, 34.4% were being treated for work related lower extremity injuries, a percentage almost equal to the 32.8% being treated under traditional insurance plans [38].

The University of Washington study, consistent with findings from other studies, found Myofascial Pain Syndrome to co-exist in 56% of the cases; also confirming that the longer the duration of CRPS symptoms, the more likely a myofascial pain component was also found; suggesting a Central Nervous System ("CNS") feature common to both conditions.

Other studies focusing specifically on upper extremities have reported incidence of CRPS following distal radius fractures as high as 39% [39] An incidence rate between 5% to 8.3% post carpal tunnel releases, with or without iatrogenic damage (*caused by or arising as a complication of medical or surgical intervention*) is also reported. [40]

There are few studies specifically designed to compare the incidence of CRPS Type I, II and NOS within the same cohort; one epidemiological study [41] performed at two military pain management centers upon male and female soldiers injured in Operation Iraqi Freedom found that of the 162 soldiers studied, 144 were men; 18 were women with an average age of 34.6 years. A total of 10 cases of CRPS were diagnosed; 3 of which were CRPS Type 1; 7, Type II. That ratio may be explained by the nature of the wounds sustained in battle, the CRPS Type II predominance attributable to penetrating wounds from bullets and shrapnel which damaged peripheral nerves. Together, these 10 total cases of CRPS represented 6% of the cohort – well within civilian incidence rates.

However, the recent research article [42] reporting the retrospective Chart Review by Dellon, Andonian and Rosson of Johns Hopkins of 100 patients diagnosed with CRPS Type I ("RSD") is significant for this reason: 40% had undergone upper extremity surgeries, 30% lower extremity surgeries, which did not resolve the patient's pre-surgery symptoms. Seventy (70) of the 100 were discovered to have unresolved neuromas, nerve lesions or continuing nerve compression and then underwent repeat surgery for those unresolved neuromas, nerve injury/lesion/compression. That 40% of the patients reported excellent results following repeat surgery, another 40 "good", suggests that the actual distribution between CRPS Types I and II could be different than historically reported. Dellon, et al., documented that 19 upper extremity and 15 lower extremity neuromas were resected and cite the articles which describe the surgical techniques for resection of neuromas of the radial sensory and lateral antebrachial nerves, the medial antebrachial nerve, the posterior cutaneous nerve (upper extremity) and the deep peroneal nerves, the saphenous nerve and calcaneal nerve of the lower extremity. Of the repeat surgeries performed, resection of neuromas was second (at 34) only to repeat neurolysis (at 52). [43,44] Other studies have also found that excision of neuromas was the most common types of elective foot surgery. [45]

The Reflex Sympathetic Dystrophy Syndrome Association of America (http://rsds.org/), and the Departments of Anesthesiology and Critical Care Medicine of Johns Hopkins collaborated to conduct a web-based Epidemiological survey of Complex Regional Pain Syndrome. Respondents to a questionnaire posted on the website of RSDSA were invited to participate in a 75-question survey between October 2004 and February 2005; 1,359 responded. The average ages of the respondents, the duration of the disease, the ratio of female to male, the inciting events, the symptoms and signs, "spread" of symptoms and signs were all similar to those reported in carefully "controlled" studies reported in the medical literature. [46]

"Spread"/Recurrence:

While still in common usage in the lexicon of CRPS, the term, "spread", is falling into disfavor as the nature and mechanism of this well-documented phenomenon is being revealed through neuroscience and neurodiagnostics. In the exhaustive 2009 article authored by Schwartzman and others entitled, *The Natural History of Complex Regional Pain Syndrome* [47], 844 patients meeting the IASP diagnostic criteria were retrospectively studied. Of those 844 patients, 656 reported a duration of more than one year. Two hundred four (204) (31.1%) reported that their symptoms had "spread" to areas contiguous to the site of the initial injury. Seventy-five (75) (11.5%) reported spread to the contralateral extremity. Other types of "spread" included 71 (10.8%) reporting "spread" to an ipsilateral extremity (e.g., right arm to right leg). Seventy-four (74) (11.3%) reported CRPS symptoms in the other extremity on the opposite side (e.g., right arm to left leg).

Contiguous "spread" occurred the "earliest" (within 1 to 2 years) and remained the most common type during the first 10 years; however, generalized spread to all extremities appeared late in the disease process.

This sequence of the appearance of spread was also reported in a study of 20 patients with longstanding CRPS published in early 2015 and authored by DiPietro and other medical researchers in Australia [48]. The title of that article contains the term increasingly associated with the phenomenon of "spread", i.e., "interhemispheric".

A retrospective study, specifically of the patterns of spread experienced by 27 patients of a pain clinic in Philadelphia, published in Pain in 2000, identified three kinds of spread; but then hypothesized that all of the types of "spread" may be due to aberrant Central Nervous System (CNS) regulation of neurogenic inflammation. [49]

More recently, researchers from the Netherlands, also studying "spread", evaluated 185 CRPS patients retrospectively. [50] These researchers analyzed the type of "spread" and concluded that "spread" frequently occurs spontaneously, that contralateral spread is far more likely to occur than ipsilateral "spread" and that "diagonal" spread is relatively rare. These researchers hypothesized that the patterns of "spread" appear to involve spinal cord and/or supraspinal rather than systemic mechanisms. Significantly, these researchers also speculate that "spread" to the contralateral extremity – the most frequently occurring type of spread – may be contributed to by interhemispheric spread of cortical activation.

Presenting the question whether the mechanism(s) implicated in "spread" may also be involved in "recurrence", is the case of one patient, the subject of a 2011 article authored by clinicians at Duke University Medical Center [51]. A 49-year-old female had developed CRPS in her right upper extremity following an IV Phenergan infiltration which had been performed after bilateral carpal tunnel syndrome surgery in 2004. By 2006, the patient had been diagnosed with CRPS, had undergone treatment, culminating in a Spinal Cord Stimulator implanted in her cervical spine which was controlling her

symptoms. However, on a trip to a North Carolina beach, she was "stung" on her right foot by a jelly fish and developed new CRPS symptoms and clinical signs in the right foot, which were then "mirrored" in the patient's left foot, less than 8 hours after being "stung". The Duke clinicians hypothesized that the neurotoxin released in the jelly fish "sting" caused some form of "trauma" to C fiber and A-delta fibers setting in motion the development of "new" CRPS symptoms in the patient's bilateral lower extremities. The authors theorized that the patient had a poorly regulated sympathetic nervous system with impaired peripheral vasoconstrictor activity for which the patient had undergone implantation of neuromodulation (Spinal Cord Simulator) and was prone to development of CRPS in both lower extremities; the authors concluding that the patient's decreased ability to control vasodilation, coupled with a possible genetic susceptibility, led to development of CRPS in all four extremities. These authors then concluded that patients with a prior history of CRPS who undergo treatment and enter remission should avoid elective surgeries "such as knee and wrist surgeries" which are known to be associated with development of CRPS. Other authors suggest that careful identification and selection of those patients whose previous CRPS had entered remission could undergo successful re-operation; particularly for carpal tunnel syndrome given the high rate of failure of CTS releases and complications [52]; and recurrence of CTS in a reported 19% with 12% requiring re-operation. [53]

Recurrence has been studied; although not nearly as extensively as "spread". The term, "recurrence", denotes a return of CRPS after a period with no or few complaints.

Professors Veldman and Goris performed a study of 1,183 patients with "RSD" between November 1984 and April 1994 [54] and reported their findings in 1996. Eliminating those patients whose symptoms may actually have been "spread" rather than "recurrence" of the condition in the same and/or other body part(s) after a period of "remission", Veldman and Goris reported that 34 (3%) of the 1,183 patients had experienced recurrence in the same limb in which the condition had previously been present after "remission" between 3 months and 20 years. Another 6% (76 of the 1,183 patients) experienced recurrence in a different extremity. Fifty-three percent (53%) of the recurrences appeared spontaneously, the authors estimating that 1.8% of patients with CRPS would experience recurrence.

Diagnosis

As there is not only no "gold standard" diagnostic test; but, as there is also lack of agreement among researchers of the diagnostic value of many of the tests which are performed, [55,56] CRPS is considered by many to be presently a clinical diagnosis of exclusion. Complicating the diagnosis and classification of CRPS has been the IASP redefinition of "neuropathic pain" in 2012. [57] That revision of the former definition, "pain initiated or caused by a primary lesion or *dysfunction* in the nervous system" was considered to be necessary as the former definition was deemed to lack both specificity and anatomic precision. [58] The 2012 redefinition, the recommendation of neurologists, was (and remains), "pain arising as a direct consequence of a lesion *or disease affecting the somatosensory system.*" [59]

Because CRPS Type I was postulated to arise in the absence of a known nerve lesion, the redefinition resulted in continuation of the challenges by some "experts" to the existence of CRPS as a medical condition; [60] and, secondly, an impassioned response signed by many highly regarded CRPS authorities and researchers, reminding the medical community that very recent discoveries had implicated damage to tiny nerve fibers; hence CRPS Type I would qualify as "neuropathic". [61,62,63,64,65,66] Thus, that redefinition may actually hasten the elimination of a distinction between Type I and II (even if diagnosed correctly) [67], a very recent (2014) IASP article stating, "The distinction between CRPS I and CRPS II thus appears to be somewhat artificial." [68]

The distinction between CRPS Type I and Type II has implications beyond the medical/academic community. The ICD-9 Codes 337.20, .21, .22 and .29 did not differentiate between "RSD" and causalgia; however, the ICD-10 does via Codes G90.5 Complex Regional Pain Syndrome Type I (CRPS I); which is then "subdivided" into G90.51 for the upper limbs and G90.52 for the lower limbs, [69] and causalgia, G56.4, G57.7.

ICD-10 Codes G90.5 (RSD) is not a billable code per ICD-10 and excludes causalgia of the upper and lower limbs (G56.4, G57.7, respectively) which are billable codes [70]. In the IASP periodical, *Pain*, published on line ahead of print was the announcement of the formation of an IASP Task Force for development of a new classification for chronic pain for the ICD-11, the revision for which will be subject to approval by vote in 2017 [71]. In an article co-authored by contributors to the chronic pain classification, the IASP Task Force first defined "chronic pain" as that pain which has ". . . endured for 3 months or more, but can be continuous or interrupted by pain-free intervals" recognized that the lack of adequate coding in the ICD ". . . makes the acquisition of accurate epidermiological data related to chronic pain difficult, prevents adequate billing. . . ." The IASP Task Force is responding to the challenge of rational principles of classification adaptable to different types of chronic pain by giving ". . . first priority to pain etiology, followed by underlying pathophysiological mechanisms, and finally body site." [72] With the great strides make in neuroscience/neurodiagnostics in the last 5-10 years, the focus on 'underlying pathomechanisms' may "unify" CRPS Types I and II. (See Neurosciences/Neurodiagnostics, infra.)

The diagnosis of CRPS like many other medical conditions is primarily clinical; requiring accurate patient "history"; i.e., anamnesis (*recollection, a patient's faculty of remembering the origin, emergence, of symptoms, etc. of a medical condition*) and physical examination. [73]

Diagnosticians, classically trained in the process described in the legendary text, *The Elements of Clinical Diagnosis* [74], understand that an accurate diagnosis begins with the patient history, including what can be observed at "bedside". Professor Klemperer's medical text states at p.4, Chapter 1, Anamnesis and General Condition:

> "**Anamnesis –** An exact history of a case is of the greatest importance; for, frequently, the decision of a diagnosis hinges upon it." [75] [76]

In large part, because of the influence Dr. Klemperer had worldwide upon the establishment of a methodical process for "taking a bedside history" to begin the process of formulation of an accurate diagnosis and (only) then to proceed to recommendation for a treatment plan, medical narration became an area of vital interest to medical school professors. [77]

Because the IASP CRPS clinical diagnostic criteria (infra) requires that there be "reports of . . . ." at least one symptom *in three of the four following categories: sensory, vasomotor, sudomotor/edema and motor/trophic,* the physician/co-author believes that proper execution of the anamnestic steps must begin with a thorough, detailed history directly from the patient. A clinician familiar with the variable presentation of CRPS over time, would be likely to discover through skillful probing questions the patient's history of symptoms which might have been misinterpreted or even overlooked by a referring primary care physician or a specialist who rarely sees this condition.

Next, the clinician must perform his/her own physical examination; not rely upon reports of a physical examination performed by a referring physician or prior examining physicians.

After the detailed patient history has been taken and the physical examination performed, the physician/co-author then reviews any diagnostic studies, recognizing that most diagnostic studies add little to the diagnostic process; but, can assist in the differential diagnosis by identifying and implicating other conditions (infra at "Diagnostic Testing").

Similarly, the physician/co-author defers review of the medical records and reports of examinations by previous/other physicians until a history has been taken, his clinical examination performed and he has reviewed diagnostic studies, if any, in order to form his own completely independent diagnostic impression.

Finally, since the diagnosis of CRPS is clinical, few diagnostic studies are likely to add to or alter a diagnostic impression; however, diagnostic "tests" which may confirm, refine – or even exclude – the diagnosis may be ordered/performed.

CLINICAL DIAGNOSTIC CRITERIA

IASP specifies that the differential diagnosis must consider and exclude unrecognized local pathology (e.g., fracture, strain, sprain), traumatic vasospasm, regional vascular disease, cellulitis, other regional infection, Raynaud's disease, thromboangiitis obliterans, thrombosis, specified neuropathy, erythromelalgia, specified regional motor disease, and regional autoimmune process. [78].

The CRPS clinical criteria by the Budapest Consensus are:

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

* A sign is counted only if it is observed at time of diagnosis.

These clinical criteria are used for all subtypes of CRPS i.e., CRPS Type I (formerly "RSD"), CRPS Type II (formerly "Causalgia) and CRPS-NOS (Not Otherwise Specified: Partially meets CRPS criteria; not better explained by any other condition.) [79]

Clinical Evaluation and Testing With Traumatic Nerve Injury and/or Neuropathic Pain:

The Evaluator, History and Examination

The patient who is being seen for evaluation of a possible traumatic nerve injury, or neuropathic pain of unclear origin, possibly related to an injury, has the reasonable expectation that the evaluation will result in a specific diagnosis, recommendations as how to test/prove that diagnosis and what treatments could be instituted to cure or provide relief for the condition. It is imperative to have an accurate diagnosis and testing confirmation when possible to delineate the details of that diagnosis before treatment begins. Diagnostic testing and treatments should be individualized for each patient. This is particularly true for a complex issue like neuropathic pain with its wide spectrum (mild to severe) and many etiologies (*the cause of a disease*), and the signs and symptoms change over time [80].

In the subsections which follow, the crucial steps and features of this clinical evaluation of CRPS/neuropathic pain will be delineated.

Evaluator Skill Set: The medical specialty (e.g. Anesthesiology, Physiatry, Orthopedics, Neurology, Neuropsychiatry, etc.) is less important than the evaluator's knowledge of the peripheral nerve system and secondarily the Central Nervous System (brain, the spinal cord). Most neuropathic pain cases involve trauma to a limb, and in those cases, injury and damage to specific peripheral nerves providing sensation to those limbs (i.e. pain fibers travel from the traumatized area through peripheral nerves to the spinal cord and brain). There are many good texts on peripheral nerve anatomy and injuries [81]. Examiners should choose one highly respected text and refer to it often.

For example, a worker falling off a ladder and impacting the hand/wrist, arm, shoulder and neck may complain of pain and numbness in the little finger (ulnar) side of the hand and forearm. Pain in that distribution could be from damage to the pain fiber of the ulnar nerve anywhere along the nerves course, such as at the wrist or the ulnar nerve at the elbow or the lower part of the brachial plexus or the 8th cervical root. By history and exam the Evaluator will locate the site or sites of damage to the nerve. Not infrequently injuries which result from falls, more than one section of the nerve going from the hand to the spinal cord can be damaged (e.g. a lower brachial plexus injury and ulnar nerve injury at the wrist). If more than one site is injured along the course of that same pain fiber from hand to spinal cord, that is referred to as "double crush." Without knowledge of the peripheral nerve pain conduction system (peripheral nerve neuroanatomy) an accurate diagnosis is difficult to achieve; the clinician must be able to identify the nerve(s) which is/are damaged. Many short focused neurology texts used in medical student training can be useful here [82].

Pain feeding from the injured limb goes into the spinal cord up to the brain (the Central Nervous System). Chronic pain *input* can alter nerve cells in the Central Nervous System and can change the pain pattern, pain distribution and subjective experience of pain. Hence, the examiner must also be knowledgeable in the neuroanatomy of spinal cord and brain pain pathways. It is not uncommon that, following focal nerve damage in a limb, pain sensations spread and enlarge over time, but the main/worst area of a painful nerve injury usually remains the most prominently abnormal on examination. For non-neurologists it is helpful to review a basic pain neuroscience "teaching article" [83]. Having a good working knowledge of neuropathic pain is essential both from a neuroscience stand point [84] and clinically [85].

In a significant percentage of nerve injuries, the Sympathetic Nervous System does feed into the damaged peripheral nerve (Sympathetic Maintained Pain/SMP) [86]. The Evaluator must have an understanding of the Sympathetic Nervous System as it originates in the brain, tracks through to the thoracic spinal cord and out to the limbs by way of the thoracic, cervical (stellate) and lumbar sympathetic ganglion.

All of these neural structures, the peripheral nerves, the Central Nervous System and the Sympathetic Nerve System, can interact and influence one another and can change over time, months and years after the initial injury. Understanding these dynamic modulations over time and the wide spectrum (mild to severe) of neuropathic pain disorders is crucial to evaluating and treating these patients. (See, Treatment, infra).

History and Injury Phenomenology: A thorough history of the etiology and course of the injury is essential for localization and estimation of severity of injuries to the nerves. It is commonly said in medical education that the diagnosis is largely formulated by eliciting the patient's history and then confirmed by exam and testing. The phenomenology of the injury gives much information in localizing which nerves are damaged. A common injury, an inversion sprain of the ankle where the foot rolls on its outside and then oftentimes flexes down can be used as an example. This sprain stretches the nerves of the top and side of the foot; so common nerve injury complaints are the superficial peroneal on top of the foot and sural nerve on the outside of the ankle and foot. A less common injury occurs when the foot is "run over", for example, by a forklift, damaging the nerves on the top (superficial peroneal nerve) and the bottom of the foot (medial and lateral plantar nerves). A side to side compression or clamping of the foot (e.g., a foot trapped between a forklift and a wall) commonly damages the saphenous nerve on the inner ankle/foot, the sural nerve on the outside of the foot and ankle and the compresses interdigital nerves between the toes.

With knowledge of the peripheral nerves, an examiner can identify most of the actual nerves damaged while taking the history and then confirm it with the exam. In addition, patients can relate if the damaged nerve is "touch sensitive" or "cold sensitive", respectively, touch and cold *allodynic*, as well as change of the neuropathic symptoms over time, such as "spread" beyond the original area of injury.

Numerous studies confirm that the more detailed the history, the patient's descriptions of the origin and development of any symptoms experienced, the more likely that terms used by the patient to describe the symptoms will be consistent with the clinical examination in which clinical signs will be documented. [87]

For example, in a/the retrospective study of 64 patients all of whom were diagnosed with CRPS reported subjective "symptoms", describing the nature and quality of their pain in descending order; e.g., 46 of 64 (71.9%) described their pain as "burning". Other descriptions of pain in descending order of report were, sharp, throbbing, aching, shooting, stabbing, numb and tingling with patients reporting these "symptoms" decreasing to 44, 40, 33, 27, 12, 12 and 10, respectively. [88] This retrospective study is also of value as the clinical signs found in the same cohort of 64 also diminished in those otherwise meeting the IASP criteria for CRPS. Findings of clinical signs such as allodynia, edema, erythema, hyperesthesia, decreased skin temperature, peripheral nerve pain, skin atrophy, hyperhydrosis, dysesthesia, hair growth changes, increased skin temperature, decreased toenail growth, hyperpathia and thickened toenails decreased in the 64 patient cohort from 57, 39, 36, 32, 19, 10, 10, 9, 8, 7, 6, 3, 2 and 1, respectively.

Most patients are also able to articulate whether, over time, the areas of pain and touch/cold allodynia "spread" to areas beyond the site of the initial nerve injury (e.g. from a damaged nerve such as superficial peroneal to the whole foot or/and up the leg). This can lead to concern about central sensitization as a focal nerve injury becomes more diffuse and can evolve to a more diffuse CRPS-I from a CRPS-II focal process. Even if pain and other symptoms have spread, the original peripheral nerve injury site may still

remain the most damaged and/or symptomatic. A thorough linear history and timeline are crucial here for both diagnosis and treatment.

Part of a detailed history includes determining what diagnostic testing has already been performed, what therapeutic measures were tried and what improvement (or worsening) occurred. For instance, if any antineuritic pain medications were tried and/or were helpful, improvement with these medications often indicates nerve pain independent of the sympathetic nervous system (Sympathetic Independent Pain/SIP). A 2011 pilot study performed in Germany concluded that if the patient benefited from prior sympathetic nerve blocks, it was a reliable predictor that the pain is maintained by the sympathetic system (Sympathetic Maintained Pain/SMP); and that therapeutic blocks performed after a diagnostic block lasted significantly longer (up to six days) compared to blocks with saline which, even accounting for "placebo effect", lasted less than six hours. [89]

Also, by going over the phenomenology of the injury in detail and the orthopedic history, an examiner can get a good idea of the force applied to the injured limb; the more forceful, the more likely the nerve injury will be more severe or permanent (e.g. a stiletto heel on the top of the foot damaging a branch of the superficial peroneal nerve versus multiple Lisfranc fractures by a forklift driving over the foot causing a severe multi-nerve trauma). An examiner needs to know historically if focal or diffuse nerve pain symptoms were present before or after casting or surgery for an orthopedic fracture or injury. Even with the best techniques, swelling in a cast and/or the necessary dissection for surgery can irritate or damage nerves; immobilization a known, well-documented "risk factor" for development of CRPS.

Hence, with a detailed history alone, the examiner can have a very good idea of which nerves are involved, how severe the nerve injury is likely to be and "guideposts" can be identified to use and focus upon during the exam to further confirm and delineate the specific nerves damaged. It is not uncommon that the focused peripheral nerve history can help reveal multiple orthopedic and nerve injuries that can be contributing to causing pain(s) in the damaged limb or body part; in fact, it is seldom that just one nerve is involved.

Examination and Detailed Neurosensory Exam: Once the history is obtained and recorded in the clinician's notes, a focused orthopedic and general exam of non-neurologic features is helpful in looking for sources of bony, ligamentous, soft tissue and tendon pain (i.e. nociceptive pain producers). Nerves coming from damaged bony or soft tissues will transmit pain (nociceptive pain) from the injury site to the Central Nervous System.

It is important to know the underlying "bony pain picture" upon which the neuropathic pain is superimposed. If the nerves themselves, and the pain fibers within those nerves, are damaged, numbness and/or pain from the damaged nerves (neuropathic pain) can occur. The neuropathic pain will be (at least initially) in the peripheral neuroanatomic distribution of the nerve damaged. During this part of the

exam, the examiner would look for Tinel's signs (*a cutaneous tingling sensation produced by pressing on or tapping the nerve that has been damaged or is regenerating following trauma)* along the course of the peripheral nerves. Contusion, constriction, entrapment by ligaments, swelling, etc., can cause one (or multiple) sites on the peripheral nerve to be damaged. Palpating positive Tinel's signs over the ulnar nerve fibers at the wrist, elbow site, brachial plexus, etc. can help to localize where the nerve is damaged. For example, a Tinel's sign at the wrist may lead to successful decompression at Guyon's canal for ulnar nerve entrapment; but, a blow to the mid-forearm can cause a non-surgically repairable neuroma "in situ" in the ulnar nerve. [90]

A clinician must compare the specific nerve distributions on the injured side to the opposite side and to different nerve distributions on the same side. Patients do not know what the anatomic distributions of each nerve are; but, the clinician does, so it is easy to be precise and objective about which nerves are affected. A patient may complain of "pain in the foot", but the examiner can discern which specific nerves are involved such as sural versus superficial peroneal versus plantar versus calcaneal versus saphenous, etc. This "neuroanatomically" detailed testing exam technique not only helps guide what interventions may be helpful in certain nerves, but it also helps illustrate or rule out any psychological or embellishment on the patient's part. Of course, if the distribution is diffuse as in CRPS-1, the clinician still looks for focal nerve areas that are most affected. If, by history, one or two nerves were most affected and then a general diffuse pattern developed, that would be more compatible with CRPS-2 (focal nerve/causalgia) evolving into diffuse CRPS-1 (or RSD), possibly with a Sympathetic Maintained Pain component. [91]

Each nerve in the injured limb needs to be tested for abnormalities in multiple different sensory modalities. Painful injured nerves can have injury to both small myelinated A-delta pain fibers and very small unmyelinated C-pain fibers. These are tested using light touch (e.g. finger brush, cotton swab or tissue brushing), pinprick and cold evaporant (e.g. acetone drops). Specifically within the peripheral nerve distributions of interest one <u>first</u> looks for mild, moderate or marked diminishment of the normal sensations. <u>Secondly</u>, one is looking for abnormal or pain sensations to these normally non-painful stimulations. To touch and cold stimulation one can get *paresthetic* (odd), *dysesthetic* (uncomfortable), or *allodynic* (painful) sensation to normally non-painful stimuli (See also terminology/definitions, supra). If normal "pin" sensation is substantially more painful than normal, it is "*hyperalgesia*". Other sensations such as pressure, vibration, or position which are transmitted by much larger fibers (and more protected and less vulnerable to trauma), the large myelinated A-beta sensory fibers, can be normal or near normal even in very painful injured nerves. Hence, squeezing or heavy brushing or palpation or monofilament testing or vibration testing can all be fine even with a very painful A-delta and C-fiber mediated traumatic peripheral nerve injury. To be valid and useful diagnostically, an examiner needs a very detailed multi-sensation A-delta and C-fiber exam. Casual, non-peripheral neuroanatomic and non A-delta/C-fiber exams will often yield non-diagnostic "sensory grossly intact", "non-focal sensory exam" or "non-anatomic" descriptions often seen in records. To avoid missing the diagnosis one

has to be very specific and neuroanatomically exact to be accurate and to guide the therapeutic interventions.

One concern about a "sensation based" disorder like painful traumatic nerve injury is that the exam is "subjective"; not "objective". In the "Art of Medicine", a clinician relies on the subjective report of the patient together with the expert examination and intellectual medical formulation to come to the most accurate "physical diagnosis," and then, to guide therapy. With a full and exacting history and neurosensory examination, very good accurate and useful working diagnoses can be obtained. Using neuroanatomic knowledge and performing a complete neurosensory exam technique, the variations of each patient's pain sensitivity and "pain behavior" (or attempts to mislead by a patient) can be minimized. Individual evaluators must, with clinical experience, come to their own "internal" graduaion of pain exam findings; but, research notes various quantifications in "severity scores" that can be helpful [92]. Conversely, not performing a clinical examination in this manner can lead to missing the diagnosis or making a misdiagnosis. The most accurate diagnosis made, as early as possible, usually leads to the best treatment and most expeditious treatment and at the least cost. [93].

Needless to say, a valid, thorough neurosensory exam requires the patient to be in a gown and to have any clothing or coverings (braces, stockings, gloves, anesthetic patches, etc.), any neuromodulatory device (SCS/PNS, etc.) to be off, ideally for 24 hours, [94] and without skin modulating creams or oils (topical antineurotic creams, etc).

Diagnostic Testing

There is no "CRPS Test." A complete and thorough neurosensory/pain history and an exacting neurosensory exam are still collectively the gold standard for traumatic painful nerve injuries and CRPS. While a side-to-side temperature difference of 1°C or greater is considered to be "significant", such temperature differences are also known to fluctuate over time [95]; and even sweating with quantitative sudomotor axon reflex testing (QSART), is variable and nonspecific. The evaluator can also "rule out" other diagnosis(es) including peripheral vascular disease, rheumatologic disease, inflammatory autoimmune peripheral nerve disease, etc. Three-phase bone scans may be of value; but debate exists regarding sensitivity and specificity [96]. With variable presentation and clinical course fluctuations over time and even from patient to patient, in the end, as is reiterated throughout the literature at their core, traumatic painful peripheral nerve traumas and CRPS are "Clinical Diagnoses". There are clinical series and meta-analysis reviews that can give "trends" or probabilities; but these trends and analysis generally are difficult to apply reliably to individual cases and can neither "confirm" nor "rule out" CRPS confidently.

With regard to painful traumatic nerve injuries and CRPS, the core issues of interest are: which nerves are injured, how severely and if the sympathetic system is feeding into the pain. Those are key questions for diagnostic testing and diagnostic maneuvers that are important for case by case therapeutic decision making.

Next, we will focus on electrodiagnostic testing of the nerves and testing for sympathetic impairment.

Electrodiagnostic Testing

The standard NCV/EMG is one testing tool to examine injured peripheral nerves. Nerves have several functional types and sizes of nerve fibers. There are large caliber motor fibers with heavy "insulation" (myelin). There are also large myelinated A-Beta sensory fibers that transmit vibration and position messages. A standard NCV/EMG tests the larger fibers in the major nerves of the body. EMG tests only the intactness of large motor fibers to muscles; *EMG does not test any sensory or pain fibers*. Standard nerve conduction velocities (NCVs) measure the speed an electrical pulse travels down or up the nerve. Electricity follows the "path of least resistance"; therefore, the fastest nerve fiber conductions, the large motor fibers (impulses to make the muscle contract) and the larger myelinated A-beta sensory fibers (e.g. vibration and position fibers), are measured. In standard EMG/NCVs, no A-delta (small myelinated) or C-fiber (very small non-myelinated) pain fibers are measured. Standard EMG/NCV (large fiber) is often reported as "normal" or "negative" when there are actual painful nerve (small fiber) injuries; but with standard EMG/NCV these small-fiber injuries are not detected [97].

It has been known for decades that standard EMG/NCV studies can be negative in clinically confirmed radiculopathy. Also, some small nerves, purely sensory (no motor fibers), can be injured and are difficult or too small to test by standard EMG/NCV. If a painful carpal tunnel is released, the large motor and sensory fibers may work better (becoming normal by NCV) but the smaller A-delta and C-pain fibers (being less hardy) remain impaired and painful. On the other hand, if the standard EMG/NCV is abnormal in a peripheral nerve distribution of interest one can be confident that the nerve is fairly severely damaged or impaired.

One can test the small myelinated A-delta pain fibers, (the voltage based testing is more accurate than the current based testing). [98] It does require more cooperation from the patient, but even small nerves in the body can be tested compared to the non-injured side in a semi-quantitated format. This sensory nerve conduction study testing of the small myelinated A-delta pain fibers can be very helpful in validating and ranking the severity of the impaired or damaged sensory nerves. Small C-fibers can be tested by quantitative sensory testing (cold and heat) techniques as well, but it is less used.

Undoubtedly, the masters of measuring and quantitating damage to traumatized peripheral sensory nerves are the Germans, via the Deutscher Forschungsverbund Neuropatisher Schmerz (DFNS); English translation: German Research Network on Neuropathic Pain: http://www.neuro.med.tu-muenchen.de/dfns/index.html . Much clinical and research data can be gleaned from their 20+ subtypes of neurosensory testing. However, reimbursement in the U.S. is either none or minimal, so these testing modalities are generally not available. However, the German and the European quantitative sensory research and the many testing formats continue to encourage clinical work and research here in the United States.

Diagnostic Nerve Blocks -Sympathetic Maintained Pain/SMP:

During the general exam, the clinician must also check for signs of alterations in autonomic nerve function such as temperature, color, sweating, and skin/hair changes. There is a wide range of changes seen from minimal or none to very severe. These changes (or lack of them) can be seen whether or not the sympathetic system is feeding into the pain; but if they are seen and the more prominent they are, the more likely there is Sympathetic Maintained Pain involved. However, if these signs are not seen one cannot rule out SMP.

The Sympathetic Nervous System, which runs from the brain through the spinal cord and finally out to the sympathetic ganglia (next to the thoracic spine) and eventually to the peripheral nerves of the injured limb, normally controls functions like microcirculation, sweating, etc. But, in a percentage of cases when the peripheral nerve is traumatized and damaged, the sympathetic nerve gets abnormally misconnected to pain fibers, thus worsening the neuropathic pain. This is like "adding gas to the fire". [99].

When sympathetic nerves misconnect and stimulate pain fibers (sympathoafferent misconnection), the sympathetic system then "maintains" or "mediates" the neuropathic pain, so-called "Sympathetic Maintained Pain/SMP" (versus Sympathetic Independent Pain/SIP of the damaged peripheral nerve). [100, 101, 102]. One can have a simple traumatized peripheral nerve injury (SIP only), SMP superimposed upon a peripheral nerve SIP injury (combined SIP/SMP), or a small injury spread via diffuse SMP (SMP only). The SIP only and the SIP/SMP changes can be CRPS-2 and the more diffusely SMP only spread CRPS-1.

The best way to determine the presence of Sympathetic Maintained Pain is to temporarily block the Sympathetic Nervous System and examine the patient while the block is active. In the upper extremity, this is most commonly done by blocking the sympathetic system at the level of the stellate ganglia [103]. As the sympathetic system comes from the brain to the thoracic spinal cord and out of the cord at (T1 through T12) to form the sympathetic chain, it then goes up to the stellate ganglia and out into the arm. The proceduralist (*a physician specialist who performs diagnostic or therapeutic procedures*) uses fluoroscopy and boney landmarks to inject local anesthetic where the stellate ganglia should be, anterolateral near the C6-7 vertebral bodies, thus blocking the sympathetic flow into the arm. Similarly one can block the lumbar sympathetic chain typically near the mid-to-lower lumbar vertebrae. The best diagnostic information to be gained is by examining the patient (with the same neurosensory exam technique as noted above before the block), immediately after the block. If SMP is present, the diagnostic sympathetic blocks will lessen the neuropathic pain on exam: hence Sympathetic Maintained Pain.

The downside of the cervical and lumbar sympathetic chain blocks is that these are very near the regular pain fibers in the brachial plexus and the lumbosacral plexus respectively. Flow of the injected anesthetic (during a sympathetic block) from the

sympathetic chain to the plexus can "numb up" the regular (somatic) pain fibers. When that happens, pain is relieved even if no Sympathetic Maintained Pain is present (false positive for SMP can occur). Even the best proceduralist may not be able to successfully anesthetize the variably anatomically located sympathetic chain (false negatives for SMP can occur). [104] Examining the patient directly after the block helps lessen the diagnostic "misses". Ideally in a successful sympathetic block, warm limbs will result; but producing no somatic pain fiber or motor fiber block, numbness or weakness in the limb. Alternatively, in the upper extremities one can block the sympathetic chain to the arm with a transthoracic T2 vertebral level sympathetic chain block [105]. The advantage at T2 is there is no chance of blocking regular somatic pain fibers; the downside is that the T2 level injection is near the lung so pneumothorax is a possible risk. These stellate, T2 vertebral and lumbar blocks can be therapeutic as well as diagnostic. There is no pure sympathetic lumbar chain block.

Alternatively, another option is to infuse the sympathetic blocking agent, phentolamine, as described by Raja [106] in 1991 and examine the patient while the circulating drug is active. German literature confirmed the usefulness and cost effectiveness of the phentolamine test for diagnosing Sympathetic Maintained Pain [107]. Raja [108] reconfirmed the test's clinical and research validity in his "Classic Papers" review article. The upside is there is no A-delta or C-pain fiber blockade (false positives) and good evidence for sympathetic blockade (reduced false negatives). Phentolamine testing is a diagnostic test; which neither "confirms" nor excludes a CRPS diagnosis; it documents Sympathetic Maintained Pain. Phentolamine also requires a special compounding of the drug and anesthesia monitoring as is done with the injection blocks. Phentolamine does allow testing of multiple limbs, not just one.

Whatever option is chosen for sympathetic blockade, it is crucial to have a good sympathetic blockade and to examine the patient while the sympathetic block is active in order to demonstrate the presence or absence of Sympathetic Maintained Pain. If missed, the diagnosis of SMP would be left untreated and the neuropathic pain would remain or worsen. In the physician/co-author's experience, slightly less than half of those presenting with a complex traumatic neuropathic pain syndrome were positive for Sympathetic Maintained Pain [109]. A patient going on to have multiple blocks or ablative procedures on the other 50%, where only SIP is present, would be unnecessary, ineffective and costly.

Diagnostic Summary: The practical clinical neuroscience for diagnosing traumatically induced neuropathic pain including CRPS includes these three steps:

1. Delineate the force of trauma and the particular orthopedic bony and soft tissue injuries (nociceptive pain generators).
2. By detailed history and exacting peripheral nerve sensory exam determine which nerves were injured and how severely.
3. Determine if Sympathetic Maintained Pain (SMP) is present and superimposed upon the traumatic peripheral nerve injury Sympathetic Independent Pain (SIP).

Then, whether focal or diffuse, a clinician can address therapeutic interventions to the pain producers:

- Nociceptive (bone, ligament, etc.),
- SIP (only) traumatic nerve injury,
- SMP with SIP focal nerve injury or
- diffuse SMP (only).

If SMP has been diffuse but "burns out", leaving a diffuse sympathetic independent central sensitization, that can be treated also as SIP, pharmacologically.

The key to the best individualized treatment for each patient is to make the most accurate diagnosis(es) and then design a treatment program for each component. Doing this early in the clinical course, especially if SMP is present, will give the best clinical outcomes and be the most cost-effective. Undiagnosed or untreated SMP, if worsening over time, is likely to be the poorest outcome and most likely to evolve into a catastrophic status. Accurate diagnosis(es) benefits the patient and other claim participants, enables insurers to estimate costs, set reserves and administratively resolve the case without litigation

.

Treatment:

The IASP considers pain to be chronic when it has persisted beyond the normal tissue healing time. Three (3) months is often the "cut off" point for transition from acute to chronic pain [110]. Prompt diagnosis and commencement of treatment is known to offer the best opportunity for a good outcome with minimal residual pain or symptoms. [111]

Just as the neuroscience and neuroimaging are validating CRPS signs, symptoms and the diagnosis itself, clinicians are now more able to institute successful treatments. There are several credible sources for evidence – based treatment; including, the 2013 4th Edition of "Complex Regional Pain Syndrome: Practical Diagnostic and Treatment Guidelines" 4th Ed (2013). [112] However, treatment guidelines by ODG [113], ACOEM [114], and the Cochrane Collaborative Review [115] should be reviewed and compared carefully to the treatment recommendations found in peer-reviewed medical journals and texts. [116]

Usually in most traumatic limb injuries there is nociceptive pain from bony and soft tissue trauma, pain from injured local small/large sensory nerves and pain fibers, and secondary muscle pain and trigger points proximal in the limb and spine, as well as anxiety and depression. These all need different medications in a complementary co-pharmacy. Early aggressive co-pharmacy is essential to keep the patient "manageable".

Early and accurate diagnosis and treatment of Sympathetic Maintained Pain/SMP (about 50% of these type of complex limb trauma cases) is crucial because SMP does not respond well to medication and is likely a significant pain driver to the brain. Conversely,

CRPS pain to the brain can, as has been seen in imaging studies, drive the autonomic features. Interventions such as blocks, ablations, and neuromodulation (spinal cord stimulation) can substantially reduce an aggressive sympathetically driven CRPS.

With recent brain imaging science suggesting the possibility of brain changes that may not be reversible, it is even more important to work at vigorous early reduction in pain, minimizing administrative/bureaucratic delays, focusing on functional restoration and the emotional/psychological secondary effects of the CRPS pain. Breakthroughs, such as that reported in *Brain*, published November 19, 2014, illustrate advances being made in blocking neuropathic pain receptors.

Particularly with the brain imaging studies validating the emotional and cognitive functional changes in CRPS-affected brains, cooperation among claim parties is necessary to expedite diagnosis, treatment and claim resolution with restoration to suitable employment. It is crucial to remember that, collectively, traumatic nerve injury, CRPS-1 and CRPS-2, is a spectrum of disorders, some mild, some severe, sometimes progressive, sometimes not, and that each patient will require an individualized and adjustable treatment plan. Adherence to rigid "guidelines" can lead to errors in diagnosis, missed diagnosis; and then, ineffective treatment.

Unfortunately, because of the relatively low incidence of CRPS, the condition is often not recognized by primary care physicians, delaying diagnosis and referral to specialists.

Early Diagnosis and Treatment is Critical

Early Diagnosis and Multiple Diagnoses:

Often the orthopedic diagnoses are urgent and focused upon initially and primarily and the neuropathic pain component is not considered until later. This can allow pain from peripheral nerve injury/impairment to feed into and worsen centralized sensitization and/or CRPS/Sympathetic Maintained Pain/SMP. Hence, identifying and treating the sources of the nociceptive neuropathic pain early improves outcomes and usually lessens residual disability. [117]

Simultaneous or Early Treatment of Nerve Entrapment Pain:

There are many bony injuries that need early and rapid, often surgical, repair. Bony fractures, joint disruptions, tendon tears, etc., need to be addressed directly, but screening and examination of the nerve structures early and before and after surgery is necessary to identify and effectively treat nerve injury or CRPS. Swelling and edema in and around orthopaedic injuries can be treated to lessen focal nerve collateral injury. Early steroids can be helpful [118], screening for focal nerve impairments can lead to successful decompressions (e.g. median nerve carpel tunnel impairment near a wrist fracture or impairment of common peroneal nerve at the fibular head with a knee joint injury). Doing a nerve decompression early or at the time of, or soon after, the

orthopaedic surgery can often substantially improve functional outcome [119]. Early diagnosis and treatment of both orthopaedic and neurologic components may prevent development of Sympathetically Maintained Pain or CRPS.

Early Co-Pharmacy Institution:

Identification and early pharmacologic treatment of the multiple sources of pain should include management of nociceptive pain (bone, ligament, soft tissue trauma, etc), myofascial pain (focal spasm and/or trigger points) and SIP neuropathic pain (e.g. focal nerve injury). Sympathetic independent nerve pain can improve with many non-narcotic antineuropathic medications such as seizure medications, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, etc. [120] These are medicines that work on CNS disorders that have secondary positive effect on nerve injury and nerve pain transmission. Topical antineuritic creams can also help focal nerve injuries (local anesthetics, antiepileptic drugs, ketamine, etc.) [121].

In traumatic nerve injuries, co-pharmacy is the rule rather than the exception; lower doses of synergistic medication combinations for the multiple contributing pain sources best manages the overall "pain" picture and improves functional restoration. Nociceptive medications (e.g. opiates) can be helpful for bony pain, but much less effective for nerve injury pain; while medications for nerve pain are less effective for nociceptive bone pain. However, used together to treat bony and nerve pain, they can be quite synergistic and effective. Managing the multiple sources of pain early maximizes the functional restoration and thus lessening the probability of depression.

Nerve Decompression or Ablation:

The earlier an entrapped nerve is decompressed, the less likely permanent or long-term nerve pain will ensue. Nerves have a fair durability, but when chronically or severely compressed they will eventually become painful. If a nerve is decompressed late in the clinical case, even the best surgical technique may be insufficient if the nerve has, by that time, had intrinsic nerve damage that continues to generate neuropathic pain. That is, decompressing a damaged nerve may not be helpful if decompressed too late. Paradoxically, decompressing an entrapped nerve later in the clinical course can lessen numbness but increase pain (i.e. numb compressed pain fibers, now decompressed and functioning better, will become more painful than prior to decompression). Hence when nerve damage is detected and diagnosed, nerve decompressions, even in a setting of CRPS, should be considered as early as possible [122].

Some nerve injuries can be severe enough to leave a traumatic neuroma within the course of a nerve (neuroma in situ) that is unresponsive to anti-neuropathic pain medications and/or in a site where motion constantly irritates the neuroma. Many times these are pure sensory nerves (no motor fibers) and can be considered for selective surgical ablation. For instance, severe foot/ankle trauma can damage the superficial peroneal nerve or sural nerve. These nerves can be surgically cut and the nerve stump can then be "tucked away" in local soft tissue such as muscle [123,124]. Denervation and

numbness then can replace motion induced hyperpathia and touch allodynia. Another example would be section of multiple small branches of nerves in and around the traumatized and postoperative knee (surgical section of the branches of the saphenous, femoral, lateral femoral cutaneous, and peroneal nerve which supply pain fibers in and around the knee joint).

Re-decompression, neurolysis and/or scar revision in a prior operated nerve entrapment/compression can also be successful. A second decompression seldom makes the nerve pain worse and in selected cases can give improvement and/or help the nerve be more amenable to medication treatment. [125]

Regional Nerve Blocks for Neuropathic Pain, CRPS and Sympathetic Maintained Pain:

As noted in the previous diagnoses section, a percentage of traumatic nerve injuries have a component of the pain maintained by the sympathoafferent misconnections (Sympathetic Maintained Pain/SMP). In those cases where SMP can be demonstrated in either CRPS-1 or CPRS-2, blocking the sympathetic nervous system can be helpful in "winding down" the SMP component. (See depiction at Pathophysiologic Mechanisms. A speculative Model, Supra). Local regional blocks (e.g. Guanethadine Bier blocks) generally have not been efficacious and can induce additional sequelae (e.g. tourniquet induced local additional nerve irritation/impairment). [126] And, of course, if patients are shown to have Sympathetic Independent Pain (SIP) only and no Sympathetic Maintained Pain/SMP, blocking the sympathetic system will quickly prove unhelpful. Systemic injections or infusions of potentially peripherally and/or centrally acting anti-neuropathic pain medications; (e.g., ketamine [127]) are of variable benefit at this time.

Empirically, in patients that have a clear component of SMP, repetitive sympathetic blocks (e.g. cervical stellate ganglion and lumbar sympathetic ganglion blocks) can be quite helpful, particularly if done early and in series. Doing single or a couple blocks in isolation usually is partially and temporarily helpful. But, doing a series, (e.g. two blocks per week for 3-4 weeks, total six to eight blocks) can achieve a major improvement. However, it is hard to find large clinical published studies to give statistical support and each case needs individual treatment [128]. In the injuries where there is both focal nerve injury (SIP) and SMP the blocks improve the SMP only, and then the SIP needs to be treated simultaneously with antineuritic pain medication. PT/functional restoration while the blocks are operative increases the extent and enduring benefit of the sympathetic blocks. Blocking the SMP early, vigorously and repeatedly will often get the best outcome. Once SMP is entrenched, or centralized, sympathetic blocks later in the clinical course are less likely to be helpful; there are multiple pathophysiologic contributors to this chronicity [129].

Sympathetic Ablation or Surgical Sympathectomy:

Patient selection here is critical. Many ablations or resections clinically and in published articles have statistically mediocre outcomes with the conjecture being procedures were done on patients or groups of patients who have been less well defined

to make sure a Sympathetic Maintained Pain component is present. That is, if procedures have been performed on patients that have Sympathetic Independent Pain only (and NO SMP) they may have had no improvement. If, with the diagnostic sympathetic block (e.g. diagnostic stellate, T2 level sympathetic chain block, lumbar sympathetic block or diagnostic phentolamine infusion testing) the patient clearly has a component of SMP, the clinical pain improvement with either ablation or surgically resecting the sympathetic system is much higher. Again, this will help with the SMP component but may not change the SIP contributions.

Chemical ablation (e.g. alcohol or phenol, etc.) can be efficacious, but even the best proceduralist can have unexpected spread of the solution (and damage to) to other nearby structures. And likewise, radiofrequency or cryogenic ablation relies on bony landmarks to heat or freeze the local area of tissue where the sympathetic chain "should be" located anatomically. However with individual anatomic variation, even with the most experienced proceduralist, sometimes the ablation misses the sympathetic chain in part or altogether. And radiofrequency also can occasionally affect other nearby structures (e.g. brachial plexus) providing untoward sequelae [130]. These are all known complications of the procedures.

Surgical resection of the sympathetic chain (e.g. transthoracic scope of the T2 vertebral level sympathetic chain or retroperitoneal lumbar sympathetic ganglia section) benefit from the surgeon being able to directly visualize the sympathetic chain and then resect it. [131] Technique is important here to attempt to resect enough of the sympathetic chain and lessen crossing sympathetic reinnervation of contralateral sympathetics. An estimated 25% of individuals have crossing sympathetic fibers that can cause SMP to return and sometimes increasing sympathetic function elsewhere in compensation (e.g. increased sweating contralateral) [132].

Spinal Cord or Peripheral Nerve Stimulation/Neuroaugmentation and Intrathecal Pump Placement:

Placing electrodes over the spinal cord or next to peripheral nerves can allow for small electrical currents to block the pain transmission at sites between the pain generating damaged peripheral nerves and the brain mechanism of SCS. [133] In this fashion, a buzzing or tingling sensation can replace pain sensation. The mechanism by which spinal cord stimulation achieves pain relief is not yet fully known, but electrical and neurochemical are steadily being better understood [134,135]. Biomedical engineering improvements over the years in micro-electronics have allowed better "coverage" of the painful area and multiple "programs" that can be rotated. Many patients, with the newer spinal cord stimulator units for instance, have a 50-70% pain reduction and often commensurate medication reductions.

Spinal cord stimulation also has the advantage of the temporary trialing prior to permanent implantation; which is a "reversible" procedure. In this fashion, those patients with only a little pain reduction need not be permanently implanted.

There is also evidence that implanting spinal cord and peripheral nerve stimulation early rather than late ("last resort") can give better pain control and functional outcomes [136]. This may be particularly true in CRPS I, and makes sense particularly if one recognizes that long-term chronic pain induces changes in the brain that spinal cord stimulation will not affect. That is, in implanting a patient late in the clinical course, the painful input may be blocked by the spinal cord stimulator; but there are already permanent pain induced changes in volume, pain topographic representation, and brain chemical profiles in the corresponding parts of the contralateral brain hemisphere that continue with "centralized" sensitization and abnormal processing of pain and sensation inputs. [137,138,139]

In general, the goal is to lessen SIP, nociceptive and SMP components as much as possible, as early as possible, and if that cannot be accomplished, blocking that pain message from the injured peripheral nerve sites by spinal cord or peripheral nerve stimulation/neuroaugmentation as early as feasible, gives the best outcomes. Multiple studies have demonstrated the cost effectiveness of this spinal cord stimulation with particular attention to long-term medication savings. [140,141]

Likewise, one can trial an intrathecal injection or intrathecal pump. Implanting intrathecal pump permanently can infuse both pain medication (such as opiates), but also other medications with antineuritic qualities (such as Baclofen) that can help neuropathic pain by blocking the pain coming in from the periphery, for instance from the foot in through the cauda equina where the pump delivers low concentration but high strength medication, and then the pain does not go up to the brain. These are refillable pumps (on a monthly basis, sometimes longer), and with a talented pump management team one can often get good relief of pain in, for instance, low back and leg simultaneously.

Cases of SMP with Orthopedic or SIP Surgical Needs:

In cases where the patient has demonstrated SMP present but needs an orthopedic surgery repair (e.g. ACL knee repair) or nerve compression entrapment (e.g. carpal tunnel), special care and sequencing needs to be taken into consideration. One can preemptively block (preop, intraop, postop) sympathetic SMP input to decrease the chances of worsening SMP or flaring or worsening of "spreading" SMP. Ambulatory preoperative epidural catheters can be placed, peripheral nerve anesthetic regional blocks for the actual surgery can be done and continuing epidural sympathetic blockade by catheter after the surgery, can all lessen the probability of SMP worsening with a surgical procedure in a case where SMP is present. Of course, doing a sympathetic ablation or a surgical sympathectomy can also be a great preoperative maneuver to lessen Sympathetic Maintained Pain worsening. However, even with ablation/sympathectomy, using the epidural block pre-, post- and intraoperative regional blocks would still be the best "insurance" to lessen the probability of postop SMP worsening (i.e. some patients can have unusual crossing sympathetic innervation) or recurring.

Treatment Overview:

Basically, each patient's treatment must be individualized according to the contributory pain diagnoses and titrated individually according to the patient's responses. However, simultaneous or closely "sequentialized" treatments of the patient's multiple contributory painful diagnoses as early as possible provides the best outcomes. Delays in diagnoses and/or treatment commonly increases both disability and medical impairment, limiting functionality and reducing the potential for return to suitable work; risks conversion of claims/injuries/condition to catastrophic status. Generally, claim costs are substantially higher with delays or inadequacies in treatment [142].

Determination of Medical Impairment:

Diagnosis and treatment of Complex Regional Pain Syndrome occurs in all medical benefit delivery and disability systems including "group" health; ERISA, Social Security Disability Insurance ("SSDI") [143], Longshore and Harbor Workers' Compensation Act, Defense Base Act [144]. In each of these benefit systems as well as the United States Military and VA-DOD, the IASP/"Budapest" diagnostic criteria is applied.

However, it has been primarily within some state workers' compensation benefit systems which require use of the AMA Guides for determination of permanent medical impairment that controversy has arisen. Perhaps the unsettled pathophysiology, the often "subjective" symptoms, characterized by some as consistent with malingering, etc. [145], a presentation which may vary from one medical office visit to another over time [146], has resulted in making the condition progressively more difficult to rate per the sequential revisions of the *AMA Guides*. However, Christopher Brigham, long associated with AMA Guide development, co-authored an article in 2011, the title of which might suggest another possible explanation: 'Management of Indemnity Costs for Workers' Impairment Ratings, a New Way for Managing Indemnity Costs for Workers' Compensation', which states:

> "To date, many insurance professionals have been given insufficient support to achieve desired claims resolution even though solutions do exist. Data exists demonstrating the efficacy of solutions when properly utilized by these professionals. This paper shares the approaches that can contribute to significant claims savings." [147]

The title to Brigham's 2011 article was prophetic. In 2012, NCCI conducted research concerning the impact upon ratings (and therefore, indemnity for such ratings), comparing "PPD" claims from Georgia and Kentucky which retained the AMA 5th to those from Montana, Tennessee and New Mexico which switched to the AMA 6th. For each of the years 2005-2008, in Kentucky, the number of "PPD" claims was analyzed. The 3,956 in 2005 declined to 3,716 in 2008; and, the average rating declined from 7.7% (whole person) to 7.1%. In Georgia, for the years 2006-2008, (from data submitted to NCCI by the Georgia State Board of Workers' Compensation for a different research project), the number of "whole body" ratings declined from 906 in 2006 to 660 in 2008; and the

average ratings from 9.4% in 2006 to 7.2% in 2008. The ratings for "all others" were averaged 11.1% (for 2,352 claims) in 2006; but declined to an average of 10% for the 2,111 claims in 2008. For both Kentucky and Georgia, NCCI found no connection between which edition of the AMA Guides was used and the decline in ratings; speculating that extrinsic factors such as the economy were involved.

In stark contrast, NCCI found decreases in ratings (and therefore indemnity) in each of Montana, Tennessee and New Mexico, states which had switched from the AMA 5th to the AMA 6th, of 28% in Montana, 25% in Tennessee and 32% in New Mexico; NCCI concluding:

> "The results of this study provide evidence that a decrease in the average impairment rating is realized when a state switches from the fifth edition to the sixth edition of the guides, all else being equal." [148]

In state workers' compensation systems efforts to exclude the diagnosis have been pursued aggressively in some of those states which require the use of the *AMA Guides to the Evaluation of Permanent Impairment,* Fifth Edition, published November 2000. [149] In such states, exclusion of the diagnosis of CRPS is attempted by characterizing as clinical diagnostic criteria permanent medical impairment rating factors listed in Table 16-16, "Objective Diagnostic Criteria (see Terminology and Definitions, supra) for CRPS (RSD and Causalgia)":

Local clinical signs:
Vasomotor changes:
- Skin color: mottled or cyanotic
- Skin temperature: cool
- Edema

Sudomotor changes:
- Skin dry or overly moist

Trophic changes:
- Skin texture: smooth, non-elastic
- Soft tissue atrophy: especially in fingertips
- Joint stiffness and decreased passive motion
- Nail changes: blemished, curved, talon-like
- Hair growth changes: fall out, longer, finer

Radiographic signs:
- Radiographs: trophic bone changes, osteoporosis
- Bone scan: findings consistent with CRPS

Interpretation:
- ≥8 Probable CRPS
- < 8 No CRPS

The AMA Guides 5th Ed. was published in November 2000 and the text quoted below from Table 16-16 was already behind the science, contrary to published data; but also perpetuated the controversy [150], the suspicion directed to patients presenting with "subjective" pain complaints; but lacking some/most of the 11 "objective" clinical signs:

> "Since a subjective complaint of pain is the hallmark of these conditions, and many of the associated physical signs and radiologic findings can be the result of disuse, the differential diagnosis is extensive; it includes somatoform pain disorder, somatoform conversion disorder, factitious disorder, and malingering. Consequently, the approach to the diagnosis of these objective findings. The criteria listed in Table 16-16 predicate a diagnosis of CRPS upon a preponderance of objective findings that can be identified during a standard physical examination and demonstrated by radiologic techniques. ***At least eight of these findings must be present concurrently for a diagnosis of CRPS***. Signs are objective evidence of disease perceptible to the examiner, as opposed to symptoms, which are subjective sensations of the individual." [151] (Emphasis supplied)

In Charter Oak Fire Ins. Co. v. Swanigan, 2012 Tex. App. LEXIS 3312, an "IME" physician testified by deposition that an earlier edition of the AMA Guides required five of eight "criteria" to make the CRPS diagnosis; however, that "IME" physician added that the 5th Edition of The Guides increased the "objective" criteria to eleven, of which eight "signs" must be present. The "IME" physician's opinion was rejected by a Texas jury; but, this decision is indicative of the unfamiliarity of the bench and bar regarding the nature of the condition, the rapidly evolving science as well as the injuries/conditions/factors now regularly associated with CRPS. However, an encouraging appellate trend is seen in Union County and P.Comp v. Workers' Compensation Appeal Court (Feaster) Commonwealth Court of Pa. 2013 Pa. Commw. Unpub. LEXIS 803. While noting that Pennsylvania law ". . . directs that the AMA's guides to the Evaluation of Permanent Impairment shall be used in determining a claimant's degree of Impairment due to a compensable injury, we are aware of no authority which declares the AMA the final, controlling authority in the diagnosis of medical conditions and the practice of medicine." That trend is seen in decisions which properly limit the AMA Guides 5th Ed. to determination of permanent medical impairment; not clinical diagnostic criteria of the condition, itself. See, e.g., Tokico (USA) Inc. v. Kelly, Ky, 2009) 281 S.W. 3d 771. 2009 Ky LEXIS 47; Brown v. W. W. Martin Plumbing & Heating, Inc., 72 A. 3d 346; 2013 Vt. LEXIS 39.

Courts have recognized the same deficiencies regarding earlier editions of the AMA Guides. Hill v. Jackson County Bd. Of Educ., Supreme Court of Appeals of West Virginia, 2014 W. Va. LEXIS 1018 (AMA Guides 4th ed. 1993). Effective July 1, 2001, Georgia amended O.C.G.A. §34-9-263(d) requiring the use of the 5th Ed. of the AMA Guides for determination of permanent medical impairment which had been published the year before (2000). There was no change to the existing text of O.C.G.A. §34-9-263(a) which uses the word "disability"; not "impairment". Subsection (d) states, "In all cases arising under this chapter, any percentage of *disability* or bodily loss ratings. . . ." The retention of the word, "disability", given the definition of "disability" found in Table 1-1 of the AMA Guides 5th Edition's Definitions and Interpretations of Impairment and Disability [152] suggests that both disability and medical impairment could be combined in Georgia to

achieve a rating which recognizes the effect upon bodily systems, central nervous, brain, vascular, etc., which are now known to be affected by CRPS.

Almost as soon as the AMA Guides 5th Ed. was published, those Guides quickly became the target of considerable criticism nationally and internationally; and, not necessarily for reasons limited to the obsolete and/or rejected "science" relating to CRPS upon which Table 16-16 had been constructed. Among those criticizing the AMA Guides 5th Ed. methodology, specifically with regard to CRPS, were Professor John Burton who participated in performing an evaluation of California's Permanent Disability Rating System for the Rand Institute for Civil Justice at the request of the California Commission on Health and Safety and Workers' Compensation. The report thereof, published in 2005, specifically addressed Reflex Sympathetic Dystrophy, noting that "the area does not offer any empirical validation for its rating scales or its classification scheme" [153]. In 2002, the American Academy of Disability Evaluating Physicians (AADEP) issued a Position Paper: "Complex Regional Pain Syndrome I (RSD): Impairment and Disability Issues", which proposed methodology specific to CRPS for the evaluation of impairment and functional residual capacity in CRPS I. [154]

That the contributors to the AMA 5th actually increased the required "objective" "signs" to 8 out of 11 [155] from the previous edition is difficult to understand; much less reconcile with the science which already existed when the AMA Guides 5th Ed. were published. Seven (7) years earlier (1993), Prof. Veldman's landmark retrospective study of 829 patients had been published in *The Lancet* [156] an internationally respected peer reviewed medical journal. A search of Scopus [157] revealed 699 published documents which cite the Veldman article. The AMA Guides is not one of those documents. Prof. Veldman's study found that many of the AMA Guide 5th Edition's "objective" criteria were present in less than half of the patients who had been diagnosed with CRPS for more than 12 months – the opposite of the "staging" theory which had long existed; and upon which the 8 of 11 "objective signs" was premised.

Reliance upon obsolete science with regard to the use of Table 16-16 as clinical diagnostic criteria was also challenged by empirical research reported two years after the AMA Guides 5th Ed. was published. That research by internationally recognized CRPS authorities; which included Dr. Norman Harden of Northwestern University, Dr. Stephen Bruehl of Vanderbilt University and Dr. Michael Stanton-Hicks of The Cleveland Clinic, confirmed Prof. Veldman's 1993 conclusions that the clinical signs upon which Table 16-16 is based do not emerge progressively, sequentially over time in "stages" as the condition "worsens". The research found, instead, that the clinical signs required by the AMA Guides 5th Ed., Table 16-16 at p. 496, might appear in one of the three CRPS subtypes identified, but those clinical signs occurred ". . . in the group with the briefest pain duration." [158]

A medical study authored by de Boer, et al., published in 2011 [159] considered by many to be definitive, described the ". . .signs and symptoms in CRPS1 in 692 patients between July 2004 and October 2007", which met the IASP (Orlando) criteria. This

study, designed to assess the occurrence of signs and symptoms in relation to disease duration and to compare those to historical data based on a different diagnostic criteria set (Veldman) [160] found that signs that were least prominent in the total sample were hypoalgesia, sweating abnormalities, trophic changes, dystonia and tremor; (5 of the 11 clinical signs "required" by Table 16-16 of the AMA Guides 5th) which focus prominently on trophic changes:

- Skin texture smooth, nonelastic
- Soft tissue atrophy, especially in fingertips
- Joint stiffness and decreased passive motion
- Nail changes: blemished, curved, talon like
- Hair growth changes: fall out, longer, finer.

Because the table below documents the variable presentation of CRPS over specific periods of duration from "inciting event" to in excess of one year; at which point in time the condition would be "chronic" for those patients which remained symptomatic, displayed clinical signs, the authors requested and were give express written permission to reproduce and include in this article Table 3 from the original published article by de Boer, et al.:

Table 3.

Distribution of the signs and symptoms categorized according to the duration of complaints for IASP patients.

	0–2 Months		2–6 Months		6–12 Months		>12 Months		Total sample									
	n = 48		n = 211		n = 70		n = 352		n = 681									
	n	Positive	%	n	Positive	%	n	Positive	%	n	Positive	%	n	Positive	%			
Symptoms																		
Spontaneous pain	48	41	85.4	211	184	87.2	70	65	92.9	352	334	94.9	681	624	91.6			
Increasing pain after exercise	47	44	93.6	209	198	94.7	70	67	95.7	349	334	95.7	675	643	95.3			
Unexplained diffuse pain	47	42	89.4	204	193	94.6	69	66	95.7	345	335	97.1	665	636	95.6			
Area larger than original trauma	48	43	89.6	208	189	90.9	70	67	95.7	352	292	83	678	591	87.2			
Signs																		
Sensory																		
Allodynia deep pressure pain	46	15	32.6	194	80	41.2	67	36	53.7	301	207	68.8	608	338	55.6			
Allodynia pain after movement	46	21	45.7	196	89	45.4	66	39	59.1	307	206	67.1	615	355	57.7			
Allodynia after light touch	48	15	31.3	209	58	27.8	70	29	41.4	349	158	45.3	676	260	38.5			
Hyperesthesia	47	10	21.3	209	58	27.8	69	27	39.1	351	143	40.7	676	238	35.2			
Hypoesthesia	45	13	28.9	197	56	28.4	68	22	32.4	314	126	40.1	624	217	34.8			
Hyperalgesia	48	24	50	207	80	38.6	70	39	55.7	350	207	59.1	675	350	51.9			
Hypoalgesia	46	7	15.2	194	42	21.6	67	13	19.4	312	91	29.2	619	153	24.7			
Vasomotor																		
Color change/difference	47	29	61.7	209	136	65.1	70	43	61.4	352	170	48.3	678	378	55.8			
Temperature difference	47	32	68.1	207	119	57.5	69	39	56.5	350	177	50.6	673	367	54.5			
Sudomotor/edema																		
Transpiration disturbance	48	15	31.3	210	37	17.6	69	14	20.3	349	70	20.1	676	136	20.1			
Edema	48	29	60.4	211	136	64.5	70	34	48.6	350	132	37.7	679	331	48.7			
Trophic																		
Hairgrowth change	47	10	21.3	207	75	36.2	69	18	26.1	319	56	17.6	642	159	24.8			
Nail growth change	47	3	6.4	205	33	16.1	69	14	20.3	321	100	31.2	642	150	23.3			
Trophic skin disturbance	47	11	23.4	205	55	26.8	67	13	19.4	324	101	31.2	643	180	28			
Motor																		
Limitation of movement	48	37	77.1	208	142	68.3	68	50	73.5	348	268	77	672	497	74			
Limitation of strength	45	15	33.3	200	86	43	65	34	52.3	314	209	66.6	624	344	55.1			
Dystonia	47	3	6.4	203	13	6.4	69	5	7.2	318	103	32.4	637	124	19.5			
Tremor	47	3	6.4	204	11	5.4	69	3	4.3	317	58	18.3	637	75	11.8			
Bradykinesia	46	25	54.3	189	92	48.7	67	34	50.7	297	214	72.1	599	365	60.9			

Contrary to the "staging" upon which Table 16-16 of the AMA Guides 5th Ed is premised, the conclusions by de Boer, et al., are consistent with those of Veldman (1993), Harden and Bruehl (2002); but are also pertinent to an intriguing article by Huge, et al., from 2008 [161] which may explain the subtypes found by Harden and Bruehl based upon

pathomechanisms involved in CRPS; that is, an ongoing aseptic peripheral inflammation process in "acute" CRPS, a degeneration of A-delta and C-fibers in both "acute" and "chronic" diagnoses; then Central Nervous System involvement (which would explain contralateral changes) (see "spread/recurrence" supra).

In his article in the 2008 IAIABC Journal, entitled "AMA Guides Sixth Edition" New Concepts, Challenges and Opportunities" [162], Brigham neither denies nor disputes the criticism of the AMA 5th, [163,164].

While appearing to adopt in the 6th Ed. of the Guides the IASP Budapest diagnostic criteria [165], the AMA 6th Ed. continues to require for "rating" purposes "signs" based upon many of the same now discarded notions regarding CRPS:

> "Complex regional pain syndrome (CRPS) is a challenging and controversial concept that is dealt with in Section 15.5 (pp. 450-454). CRPS is difficult to diagnose accurately, and epidemiological studies indicate that most such diagnoses are made within a workers' compensation context; therefore, this is a particularly challenging diagnosis to rate. CRPS is only rated when the diagnosis is confirmed by defined objective parameters (present at the time of the rating), the diagnosis has been present for at least one year and verified by more than one physician, and other etiologies (physical and psychological) have been excluded. If these criteria are met, then adjustment factors (functional history, physical examination findings, and clinical studies are defined) and the number of "objective diagnostic criteria points" (Table 15-25, p. 453) are used in Table 15-26 (p.454) to define the class and magnitude of impairment. This same approach is used in the lower extremity chapter." [166] at p. 42]

And, from p. 538 of Guides to the Evaluation of Permanent Impairment, Sixth Ed:

> "The pain is associated with specific clinical findings, including signs of vasomotor and sudomotor dysfunction and later, trophic changes of all tissues from skin to bone." (Emphasis supplied) [167]

Not only are an increasing number of States expressing reservations regarding the use of the AMA Guides as "clinical" diagnostic criteria; but, Korea which generally adopted The AMA Guides 5th Ed., but then specifically rejected the pain-related impairment process, chose CRPS as the first object of its national impairment evaluation for pain. [168,169]

The authors recognize that effort to construct a means to assess "impairment" for "pain" is difficult for most chronic pain conditions. However, for a medical condition such as CRPS, as more is being learned about its true nature and mechanisms, the authors suggest that a more reliable, more accurate means of assessment of disability and medical impairment should be used such as the AADEP Position Paper, [170], or the Severity

Score developed in 2010 by Harden, Bruehl, Perez and other international CRPS experts 171].

In the past decade, it has become increasingly evident that CRPS I and II should not be "rated" based upon the injury to a specific member; which resulted in development of CRPS since the condition does involve the Central Nervous System 172]. The first known decision to that effect was issued recently in California in accordance with the AMA Guides 5th Ed. [173] A Power Point by UCLA Medical School Professor, Dr. Mark H. Hyman provides guidance in calculating impairment coordinating the CNS damage within the AMA 5th. [174]

Neurodiagnostics: The Future is Here

In the last two decades remarkable advances have been made in the use of neurodiagnostics to study the effect of pain upon the brain [175].

To begin to understand the complexity of induction of pain "signals" and transmission, that pain does not obey somatopic borders led to the realization that neural substrates that mediate pain are plastic; which, in turn, required that neuroscientists and medical researchers study and understand that chronic pain has a cellular and neural basis. [176]

The advent of neurodiagnostic imaging has quickly furthered understanding of pain mechanisms. [177] Imaging techniques such as fMRI enable researchers to study functional reorganization across a number of different chronic pain conditions. [178] For example, Diffusion Tensor Imaging ("DTI") detects the relationship between gray matter decreased density and white matter connectivity. [179]

Within the past five years, the trickle of discoveries made by neurodiagnostics has become a torrent. By 2011, researchers at Northwestern University and The University of Toledo (Ohio) had reported that the brain has distinct morphological "signatures" across different chronic pain conditions; including CRPS. [180]

In 2009, researchers in Germany reported their findings from functional (fMRI) imaging confirming Central Nervous System involvement in CRPS. [181]

Brain imaging studies show activity in the cortex, other grey matter and white matter: "pain neuromatrix" structures in CRPS patients. [182] Changes in both volume of brain matter and function of brain matter can be seen by *f*MRI. [183,184] Changes in the brain grey-white matter interactions help explain CRPS clinical symptoms and signs in the autonomic nervous system (Sympathetic temp/sweat/swelling, etc.), as well as emotional and cognitive symptoms frequently dismissed by some as manifestations of psychological or personality disorders. Proven brain structure and functional imaging changes seen in CRPS patients illustrate neurocognitive and neuropsychiatric symptoms which were previously difficult to explain. The neuroimaging by Apkarian and others,

specifically of the brains of CRPS patients, the discovery of abnormal gray-white matter interactions in emotional and autonomic regions of the brain is "objective" corroboration of recent conclusions by other researchers which have found that CRPS patients do not have predisposing psychological conditions, states or disorders. [185,186,187] These studies also illustrate how these brain findings in CRPS are different than, for example, low back pain. [188] Motor (e.g. dystonia) changes are also seen. [189,190]

In short, we are seeing science confirm physical and psychological brain changes from CRPS, and even some showing reversal of some of the brain CRPS changes with successful treatment. [191] It is realistic to expect the routine use of functional brain imaging to assist in diagnosing CRPS and other Chronic Pain Conditions in the near future. [192]

Conclusion:

Since 1864, when Mitchell, Morehouse and Keen co-authored the first known description of the neuropathic condition now known as Complex Regional Pain Syndrome and correlated the condition with injuries to nerves, theories about the pathogenesis, pathophysiology and even the course of the condition have changed as frequently as the "name" of the condition. As this Medico-legal article establishes, in the absence of any "gold standard" diagnostic test, the condition must be diagnosed by a detailed anamnestic patient history and a thorough clinical examination; the process, steps and components of which have been discussed herein. The development of "The Budapest Criteria" in 2004, as modified by Harden/Bruehl in 2007, increasing the sensitivity and specificity of those criteria, has resulted in diagnosing the rarely occurring condition correctly in most instances despite the very vicissitudinous nature and variable presentation of the condition over time. When diagnosed early, with appropriate treatment, patients have the best chance of recovery and a return to a productive life. Until use of the neurodiagnostics and the clinical protocols for such use, as described by Dr. David Borsook of Harvard Medical School in his 2011 article, "How Close Are We in Utilizing Functional Neuroimaging in Routine Clinical Diagnosis of Neuropathic Pain?", becomes commonplace, the diagnosis must be made by clinical examinations performed by physicians with the integrity and the experience necessary to diagnose the condition correctly and to institute effective treatment promptly.

[1] Carroll, I, Curtin, C. Management of Chronic Pain Following Nerve Injuries/CRPS Type II. Hand Clin 29 (2013) 401-408

[2] Groeneweg, G, Huygen, F, Coderre, T, Zijlstra. Regulation of peripheral blood-flow in Complex Regional Pain Syndrome: clinical implication for symptomatic relief and pain management. BMC Muscoloskeletal Disorders 2009, 10:116

[3] http://www.iasp-pain.org/PublicationsNews/Content.aspx?ItemNumber=1673&navItemNumber=677 (See Part II A, Group I, Complex Regional Pain Syndrome)

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