

An Overview of CRPS

A brief overview of some of the principles and components of the evaluation and management of CRPS.

By Peter Moskovitz, MD



The name CRPS is not important; it will probably change, not any time soon, but eventually. CRPS is still commonly known as reflex sympathetic dystrophy. People who suffer from the disease often refer to themselves as RSD'ers.¹ Clinicians and scientists who study CRPS are persuaded to think that it is a neuro-immune disease whose pathophysiology we will eventually understand. Until such a time, CRPS remains a collec-

tion of symptoms and signs that most clinicians will encounter during the course of their practice. Be not deceived, most of us will probably have missed, and will miss again, the diagnosis on first encounter with a patient suffering with CRPS.

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The Irony of CRPS

The peculiar nature of CRPS makes it the object of intense study and also, for some, the object of skepticism and derision. CRPS obtains an intensity of pain and disability that is shared by few neuropathic pain disorders. The hallmark symptom of CRPS is pain that is out of proportion to its apparent inciting cause. Colles' fractures and ankle sprains are

common antecedent events. They usually heal within a predictable and reasonably short period of time. Surgical wounds that heal without infection shouldn't cause prolonged, severe pain. It doesn't make sense that they should be followed by pain of such severity that the experience of it represents not only a medical crisis, but also an existential and, often, a spiritual crisis. The “reality” of CRPS is counter-intuitive.

It has been said of an unrelated disease, myositis ossificans progressiva—as it has of other conditions—that “more people study the disease than have it.” In that particular case it is because the disease illuminates the normal mechanism and the genetic variation of the ossification of skeletal tissues. It therefore attracts great scientific interest even though it is exceedingly rare. Similarly, the study of CRPS has much to say about the normal regulation of nociception and the experience of pain. Tragically, many more people have CRPS than study it. In the Netherlands, the TREND (Trauma RELATED Neural Dysfunction) Consortium has registered 8,000 people with the confirmed diagnosis of CRPS² and there is an estimated

incidence of 26.2 per 100,000 patient years.³ The population of the Netherlands is 16 million, making the incidence of new “cases” of CRPS greater than 4,000 per year. The prevalence of registered patients may underestimate the true prevalence of CRPS by 50%. With a population of 300 million, the United States may have between 150,000 and 250,000 people suffering with CRPS.

Comparison between the United States and the Netherlands is instructive in another sense. With a landmass of 33,900 square kilometers, Holland has a population density of 485 people per square kilometer, one of the highest in the world. The population density of the United States is 31 persons per square kilometer over a land mass of more than 9 ½ million square kilometers. My point is that the Netherlands is able to provide a series of dedicated CRPS treatment centers from Maastricht in the south, through Rotterdam, Leiden and Amsterdam, to Groningen in the north. For most Netherlanders, a CRPS treatment center is within a reasonable distance by a reasonably-priced train ride. That is not to say there are not excellent CRPS centers in the United States. There are many, but they are too few and too far between.

Pain practitioners across North America, at one time or another during their careers, consult with their orthopaedic, neurosurgical, physiatry, neurology, anesthesiology and medical colleagues in the care of people with CRPS. They will assume responsibility for care that might ideally take place in a center that is capable of implementing

diagnostic and treatment protocols in a controlled environment and using controlled methodology with well-validated outcome measures. What is ideal is not always practical.

The characterization of CRPS is incomplete. Although there are a number of excellent reports on the natural history and patterns of symptoms and signs in people with CRPS, a taxonomy of the types and sorts of the condition based on the predominant mechanisms of disease is not yet possible. RSD'ers intuitively know that their CRPS has widespread and long-lasting effects on their long term health and wellness. There may be chronic organ system impairments, perceptual impairments and even cognitive impairments that are as yet unstudied. Recently, the not-for-profit Reflex Sympathetic Dystrophy Syndrome Association,⁴ with the funding support of the Brodsky Family Foundation, has launched a 20-year, Internet-based, longitudinal study of the natural history and collateral health effects of CRPS.⁵ The first 2-year interim report should be ready for public disclosure in 2012.

Diagnostic Criteria for CRPS

The International Association for the Study of Pain (IASP) developed diagnostic criteria for CRPS in 1994^{6,7} and modified them at its Budapest conference in 2004.⁸ The diagnostic criteria are under continuous review to improve their specificity while maintaining adequate sensitivity.⁹ The clinician is inclined to make the diagnosis more easily and begin treatment early for some patients who may not have CRPS (using diagnostic criteria that are sensitive but not very specific), rather than miss the diagnosis and permit CRPS to progress in intensity as well as duration (using criteria that are specific but not sensitive enough). Table 1 presents the current IASP diagnostic criteria for CRPS. The “clinical criteria” are more sensitive while the “research criteria” are more specific.

Treatment Opportunities for CRPS

Table 2 presents a summary of some of the treatments used for CRPS. There have been two Cochrane reviews of such treatment. The science is incomplete. This particular Table contains, in part, recommendations of the treatment guidelines that were published by the Netherlands Society of Rehabilitation Specialists and

TABLE 1. Diagnostic Criteria proposed by the Committee for Classification of Chronic Pain of the IASP ¹⁰		
	Clinical Criteria	Research Criteria
Pain	Continuing pain which is disproportionate to any inciting event	Continuing pain which is disproportionate to any inciting event
Symptoms 4 Categories. By report : Sensory : hyperaesthesia and/or allodynia Vasomotor : temperature, and/or color asymmetry, and/or change Sudomotor : edema, and/or sweating asymmetry, and/or change Motor/Trophic : <ROM, and/or motor dysfunction, and/or skin/hair/nail changes	One in 3 or more of 4 categories	One in 2 of 4 categories
Signs 4 Categories. By observation at the time of diagnosis: As above.	One in 2 or more of 4 categories	One in 4 of 4 categories
There is no other diagnosis that better explains the signs and symptoms above.		

the Netherlands Society of Anaesthesiologists in 2006.¹¹ Most practitioners who do not treat CRPS on a regular basis should create for themselves something like this table to which they can refer from time to time. Each practitioner's table will contain those treatments with which he or she is knowledgeable and comfortable. That requires a bit of study and experience. Experience with the variety of treatments for CRPS is troublesome when the average clinician might make the diagnosis of CRPS for only a handful of patients over a lifetime. Even a specialty pain practitioner consults with only a handful of patients with CRPS during each year of practice, even where quaternary care CRPS treatment centers are few and far between.

Table 2 is organized in three rows of treatment goals: functional restoration, symptom control, and disease control. Because the mechanism of disease for CRPS is uncertain, disease control is problematic in the proper sense of the word—in other words, of questionable outcome. If disease control is uncertain, then symptom control is the next best thing. Even when symptom control is incomplete, and particularly if symptom control is incomplete, functional restoration is first and foremost among the treatment goals.

There are other treatment guidelines by which a practitioner might construct a list or table such as Table 2. Norman Harden and colleagues present a set of papers, copiously referenced, that are quite complete though not in the form of a Cochrane review¹⁰ as are the Guidelines from the Netherlands. The Academy of Occupational and Environmental Medicine (ACOEM) published its guidelines based on Cochrane methodology,¹² but the panel that conducted the review was not specifically dedicated to the study and care of CRPS. ACOEM's Guidelines are part of an omnibus volume of guidelines for the treatment of “Chronic Pain” and it treats CRPS as a monolith—making it unsuitable for use by most pain practitioners. On the other hand, all of the authors of the Dutch guidelines and Harden *et al*, are experienced and many are internationally-respected experts in the care of persons with CRPS. Anthony Kirkpatrick's Clinical Practice Guidelines is now a mixed-media, Internet publication, last formally updated in 2003 with frequent additions of illustrative material.¹³

Low Risk, Functional Restoration Therapies

While some of the treatments in Table 2 are controversial, the first cell of “low risk,” “functional restoration” treatments are not. It's axiomatic that pain practi-

tioners offer all patients with CRPS a combination of cognitive behavioral therapy (or something like it), neuro-PT and/or neuro-OT, vocational rehabilitation and recreational therapy. The concept of multi-modal, interdisciplinary care of patients with CRPS is now well-accepted. It was codified and refined by expert panels at conferences in Malibu (1987) and in Minneapolis (2001). The recommendations are supported by a growing body of controlled evidence.¹⁴ Each of these therapies addresses predispositions, capacities and skills that people need when coping with the pain and distress of CRPS—or of any illness, for that matter. Not all of them are necessary for every patient, but keeping them in view permits the practitioner to fill each need that may not be obvious at first.

In Table 2, I use the term “Neuro-PT” and “Neuro-OT” to distinguish them from the sorts of therapy that are useful for most orthopaedic and neurological disorders. For example, manual therapy like massage, manipulation and passive motion exercises can make patients with CRPS worse. Desensitization, edema control and active motor control are the hallmarks of PT and OT for CRPS.^{15,16} At the very least, recreational therapy may be no more than encouraging each patient to pursue former and potentially enjoyable and productive activities of which she or he may be fearful in the face of CRPS and now hesitating in anticipation of increased pain and failure.

Complementary and Alternative Medicine (CAM)

Someone should create a different name for “complementary and alternative medicine” or CAM. The name implies that therapies that we characterize as CAM fall outside mainstream medicine. For some practitioners, that might be viewed as an honorific characterization. For others, however, it may appear to be demeaning and pejorative. Many techniques of the established practice of “mainstream medicine” lack scientific validation, while there is good evidence for the effectiveness of some CAM modalities. When a condition is as troublesome as CRPS to diagnosis and to treat, there will be someone, somewhere, who will try almost anything to give their patients some relief of their suffering. Such treatments sometimes work, even though some of them amount to no more than supersti-

TABLE 2. Various Components of Multimodal Therapy for CRPS			
	Low Risk	Medium Risk	High Risk
Functional Restoration	<ul style="list-style-type: none"> • CBT • Neuro-OT/neuro-PT • Vocational rehabilitation • Recreational therapy • CAM 		
Symptom Control	<ul style="list-style-type: none"> • Topical DSMO • TENS • Amitriptyline, nortriptyline • Oral baclofen, diazepam, clonazepam • N-acetylcysteine • Ca++ channel blocker 	<ul style="list-style-type: none"> • Sympathetic blockade • Opiates, opioids • GABA antagonists • Carbamazepine 	<ul style="list-style-type: none"> • Sympathectomy* • SCS
Disease Control		<ul style="list-style-type: none"> • Sub-anaesthetic ketamine • IV ketanserine* • Corticosteroids (early) 	<ul style="list-style-type: none"> • Anaesthetic ketamine • Immunomodulation* • Glial modulation*
*Treatments about which there remain questions regarding their efficacy or safety.			

tious behavior. Telling the difference is sometimes difficult. Practitioners tread along the narrow boundaries among well-supported interventions and interventions that patients seek but which do neither harm nor demonstrable good. Along those boundaries the practitioner tries to keep the patient from being distracted from useful therapy by treatments that appear more attractive to the patient.¹⁷ A patient might pursue a time-consuming but ineffective treatment in lieu of attending, for example, neuro-modulatory occupational therapy in the hands of an experienced practitioner. I do not wish to imply that therapies without proof of efficacy uniformly lack value. “The absence of evidence of efficacy is not evidence of the absence of efficacy.”¹⁸

Some “non-traditional” therapies deserve special mention: Connectedness, storytelling, the “arts” and spiritual practice or counseling that includes contemplative practice. Anthropologists know that connectedness and storytelling are part of healing practices across cultures in all humankind. We often lose sight of the therapeutic effect of simple acts of profession.¹⁹ Connectedness and storytelling are what we do every day when we listen to our patients, when we let them know that we trust them, and when we provide opportunities to perceive that

they are part of the healing community of our office or clinic. We encourage patients to include their families, friends and community—particularly their religious community—in understanding their predicament and its treatment. We provide opportunities for “therapeutic alliance” with family therapy as well as individual therapy—particularly for pediatric patients with CRPS.²⁰

Storytelling, Narrative Medicine and Symbolic Representation of the Experience of Illness

Story telling as medical history is not just a recitation of facts and their chronology. The medical history is the symbolic representation of the patient’s illness, the narrative of the patient’s experience of suffering.^{21,22} Each patient can symbolically represent their experience in their own way. They can decrease the intensity of their own distress by focusing their awareness on representations of the subjectivity of the experience of pain as illness in stories and arts of every kind. Storytelling is first among “the arts.” For millennia, the storyteller was the repository of social values, a shaman and a healer. Storytelling can take the form of keeping a diary which can be more than the useful task of relating the experience of pain to activities, to medications or to

the weather. Like storytelling, the other “arts” provide an opportunity for patients to express the subjectivity of their experience of CRPS in ways they cannot reveal in words.²³

Access to Spirituality and “The Arts”

I have characterized the experience of CRPS as representing not only a medical crisis, but also an existential and, often, a spiritual crisis. For persons who suffer the pain and distress of CRPS, opportunities to hope may be few and far between. It’s a fact of life that practitioners seldom take a spiritual history but, for people of faith and for those who have no religious belief system, access to spirituality can make the difference between an effective treatment protocol and one that languishes in hopelessness and helplessness.^{24,25} “Believers” have many practices and rituals that provide access to spiritual experience; but spirituality is independent of religion,²⁶ which is why we encourage our patients to partake of “the arts” to whatever extent their up-bringing, experience and predispositions permit. Recreational therapists help patients to find such opportunities with instruction, supervision and encouragement.

Spiritual experience evoked by “the arts” need not be a matter of seriousness. Ecstatic experience can be as simple as a good laugh. Few of our patients can laugh their way to wellness watching Marx Brothers movies as did Norman Cousins²⁷ but we can encourage them to seek opportunities to do something close. Intuitively we think of our patients who suffer from chronic pain as a humorless lot. Their condition is not one that they can take lightly. Encouraging them to find opportunities to focus their awareness on the humorous ironies of the human condition is never amiss.^{28,29}

It’s neither within the scope nor the capacity of this article to comment on all of the therapies listed in Table 2. Some of them are controversial. Some are yet unproven in well designed trials. I present Table 2 here only as one way of organizing a complicated set of treatment alternatives for a complicated condition. Each practitioner creates her or his own way of organizing CRPS care. What’s important is that CRPS care is organized in a coherent way. In the months to come I’ll invite a series of experts in the diagnosis and care of patients with CRPS to present detailed discussions of some of the treat-

ments listed here. Of particular interest is ketamine—long and curiously used as a dissociative anaesthetic—which appears to block the NMDA mediated pathways of nociception. Several articles in coming months will address the theory and practice of this CRPS treatment that is both promising and controversial.

Elusive and Emerging Therapies

Several other treatments that appear in Table 2 warrant mention here. Immunomodulation remains elusive. The acute administration of high dose corticosteroids continues to be theoretically desirable since emerging mechanisms of the disease appear to include immune-mediated pathways.³⁰ But corticosteroids are ineffective for the middle and late stages of the condition and their use requires acute phase diagnosis and administration. There is good reason to think that a close relative of reincarnated thalidomide³¹ would be helpful against CRPS, but, as of this writing, the search for an immune modulator that is effective in treating CRPS continues.

Recent reports that reveal a relationship between the activation of spinal cord glia and the enhanced transmission and experience of neuropathic pain foretell of possible future treatments.^{32,33} Immune-mediated mechanisms will one day be a target of CRPS therapy.³⁴ The science is incomplete and there is no practical application of this work presently. There is a special irony in the observation that a potent antagonist to glial activation is a medication whose patent protection has long ago expired. There can be no com-

mercial incentive for a pharmaceutical manufacturer to sponsor complex and expensive clinical trial of the modulation of glial activity for neuropathic pain in general and for CRPS in specific. One hopes that not-for-profit foundations and public funding agents will take up the cause. Stay tuned.

The Pain Practitioner as Conflict Manager

Observations about the difficulties in understanding and in funding the study and care of people who suffer from CRPS lead me to consider the “stakeholders” in the process of evaluating a particular patient’s condition and of providing care. The term “stakeholder” is typically used in the field of dispute management in which a resolution to a conflict may be incomplete if the interests of each and every party to the dispute, or stakeholder, are not satisfied. It is sometimes said of dispute management that the best resolution to a conflict is when all parties are equally unhappy.³⁵ For example, a group of workers declares that they won’t work for less than 10 dollars per hour. Management declares that it cannot pay more than 5 dollars per hour; and both parties will be reasonably satisfied, and equally unhappy, if they conclude their negotiation with an hourly rate somewhere between 7 and 8 dollars per hour.

The analogy between pain management and conflict resolution is useful. For chronic pain patients in general, and for the CRPS patient in particular, a cure is both elusive and, often enough, illusory. Satisfactory control of symptoms permits a level of comfort and function that may

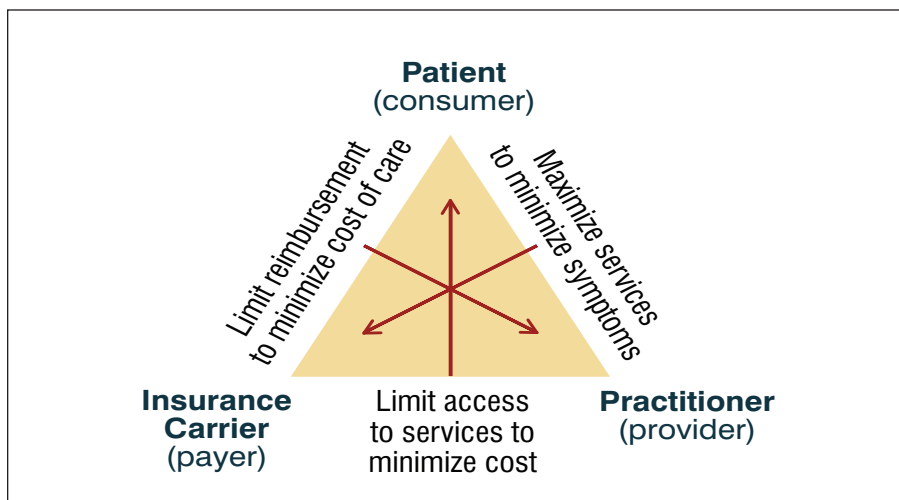


FIGURE 1. Potential conflicts of interest in the three-way relationship among “stakeholders” in healthcare including ways in which two parties can join interests against the third party.

not be ideal, but it might be sufficient and “feel right” for both the patient and the practitioner. The practitioner often feels as though she or he is “mediating” between the patient and the painful disease process. The practitioner’s “client” in this analogy is, of course, the patient. The contract and covenant for proper care is with, and for, the patient. Nonetheless, if the “mediator” ignores or neglects any of the other “stakeholders,” then the “resolution” may not be satisfactory. One simple example is a conflict between organ systems in the use of medication that the practitioner recommends for control of the “conflict” between the patient and the experience of pain. Acetaminophen is an easy recommendation but the integrity of liver function is a “stakeholder” whose tolerance must be considered.

Thinking of internal organ systems as “stakeholders” in a disease process might seem a bit farfetched; but thoughtfulness about the sensibilities of family, friends, an employer and other treating practitioners is never out of place and can only enhance the care of the patient. But how the practitioner helps the patient navigate her or his relationship with an insurance carrier, being a “stakeholder” in CRPS care, is another question. In our health care system in general and in the workers’ compensation system in specific, there exists a three-way conflict that is universal and fraught with danger. We are, none of us, immune to such conflicts.

Figure 1 represents this triangular relationship among the patient, as consumer of healthcare; the practitioner, as provider; and the insurance carrier, as the private or public payer for healthcare. Potential conflicts of interest arise when two parties join against the third. Such conflicts are often cited in criticism of “managed care,” when the practitioner is viewed as an agent of the payer or insurance carrier. Practitioners in occupational medicine clinics and consultants to utilization managers for workers’ compensation carriers are often and one hopes, mistakenly, viewed in this way. In another potential conflict, payers offer coverage to their enrollees for lower premiums if they are willing to limit their access to specialty practitioners and expensive services and medications. A provider may be tempted to stretch or falsify the facts of “medical necessity” in order to obtain services for a patient

whose certificate of coverage does not provide payment for a desired service or medication. No stakeholder in healthcare, no less in pain management, is ever free of such conflicts. Being mindful of them is the least we can do.

Summary

This article is one practitioner’s overview of CRPS and CRPS care. During 2010, I look forward to facilitating contributions from experts in the field who will present both the theory of CRPS care and practical information that readers can use for patients who suffer from CRPS, as well as for patients with other types and sorts of severe and chronic pain. ■

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Notes and References

1. Attributed to Mary Beth Kenny Ludington, columnist and advocate for RSD/CRPS patients.
2. Van Hilten JJ. Presented in conference at the Erasmus U Med Cent. Rotterdam, The Netherlands. 2007.
3. de Mos M, de Bruijn A, Huygen F, et al. The incidence of complex regional pain syndrome: A population-based study. *Pain*. 2007. 129(1): 12-20.
4. <http://www.rsdsonline.org/>. Accessed 1/4/2010.
5. The author is a member of the Board of RSDSA, sits on its Scientific Advisory Committee and is the principal investigator of the 20-year longitudinal study of CRPS. <http://www.crpsurvey.org/>
6. Stanton-Hicks M, Janig W, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. 1995. 63: 127-133.
7. Janig W and Stanton-Hicks M. *Reflex Sympathetic Dystrophy: A Reappraisal*. IASP Press. Seattle, Washington. 1996.
8. Harden R and Bruhl S. Diagnostic criteria: the statistical derivation of the Four Criterion Factors. In Wilson PR. CRPS: Current Diagnosis and Therapy. *Progress in Pain Research and Management*. 2005. Vol. 32. IASP Press. Seattle, Washington. pp 45-58.
9. Harden R, Bruhl S, Stanton-Hicks M and Wilson P. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Medicine*. 2007. 8(7): 326-331.
10. Geertzen JHB, Perez RSGM, et al. *Guideline, Complex Regional Pain Syndrome type I*. Van Zuiden Communications B.V. Alphen aan den Rijn. 2006.
11. Harden R, Bruhl S, Burton A, et al. *Complex Regional Pain Syndrome: Treatment Guidelines*. RSDSA Press. Milford, Conn. 2006.
12. Hegmann K. *Occupational Medicine Practice Guidelines 2nd Edition*, Evaluation and Management of Common Health Problems and Functional Recovery in Workers, Chronic Pain. Am Col of Occupational and Environmental Med. Elk Grove Village, Illinois. Revised 2008.
13. Kirkpatrick A. *Clinical Practice Guidelines, Third Edition*, Reflex Sympathetic Dystrophy/Complex

14. Regional Pain Syndrome (RSD/CRPS). International Research Foundation for RSD/CRPS. Tampa. 2003.
15. Harden R, Swan M, et al. (2006). Interdisciplinary management. In Harden R. *Complex Regional Pain Syndrome: Treatment Guidelines*. RSDSA Press. Milford, Conn. pp 12-24.
16. Severens J, Oerlemans H, et al. Cost-effectiveness analysis of adjuvant physical or occupational therapy for patients with reflex sympathetic dystrophy. *Archives of Physical Medicine and Rehabilitation*. 1999. 80(9): 1038-1043.
17. Hughes B. How should clinical psychologists approach complementary and alternative medicine? Empirical, epistemological, and ethical considerations. *Clinical Psychology Review*. 2008. 28(4): 657-675.
18. After an expression attributed to Carl Sagan, astronomer, 1934-1996.
19. Bertelsen P. *Free Will, Consciousness and Self: Anthropological Perspectives on Psychology*. Berghahn Books. New York. 2005.
20. Berde C, Lebel A, and Olsson G. (2003). Neuro-pathic pain in children. In Schechter N, Berde C, and Yaster M. *Pain in infants, children, and adolescents (2nd Edition)*. Lippincott Williams & Wilkins. Hagerstown, Maryland. 2003. p 631.
21. Moskovitz P. A theory of suffering. *The Pain Practitioner*. 2006. 16(1): pp 74-81.
22. Charon R. *Narrative medicine: Honoring the stories of illness*. Oxford University Press. New York. 2006.
23. Nainis N and Paice J. Relieving Symptoms in Cancer: Innovative Use of Art Therapy. *J Pain and Symptom Management*. 2006. 31(2): 162-169.
24. Gropman J. *Anatomy of Hope: How people prevail in the face of illness*. Random House. New York. 2005.
25. Puchalski C. Spirituality. In Berger A, Shuster J, and Von Roenn J. *Principles and practice of palliative care and supportive oncology, 3rd Edition*. 2006. Lippincott Williams & Wilkins. Hagerstown, Maryland. pp 633-645.
26. Harris S. *The end of faith: Religion, terror, and the future of reason*. W.W.Norton. New York. 2004.
27. Cousins N. *Anatomy of an Illness As Perceived by the Patient*. Norton. New York. 1979.
28. Cousins N. *The Healing Heart: Antidotes to Panic and Helplessness*. Norton. New York. 1983.
29. Adams E and McGuire F. Is laughter the best medicine: A study of the effect of humor on perceived pain and affect. In Foster P. *Therapeutic Activities with the Impaired Elderly*. 1986. The Haworth Press. New York. pp 157-176.
30. Christensen K, Jensen E, and Noer I. The reflex dystrophy syndrome response to treatment with systemic corticosteroids. *Acta Chir Scand*. 1982. 148(8): 653-655.
31. Schwartzman R, Chevlen E, and Bengtson K. Thalidomide has activity in treating complex regional pain syndrome. *Arch Intern Med*. 2003. 163: 1487-1488.
32. Watkins L. Spinal cord glia: new players in pain. *Pain*. 2001. 93(3): 201-205.
33. DeLeo J, Sorkin L, and Watkins L. *Immune and Glial Regulation of Pain*. IASP Press. Seattle. 2007.
34. Costigan M, Moss A, Latremoliere A, et al. T-cell infiltration and signaling in the adult dorsal spinal cord is a major contributor to neuropathic pain-like hypersensitivity. *J Neuroscience*. 2009. 29(46): 14415-14422.
35. Sometimes, and perhaps incompletely, attributed to Mary Margaret Golten, internationally respected mediator and consultant in conflict management and founding partner of CDR Associates, Boulder, Colo.