MESSAGE FROM THE CHAIR

Colleagues,

The proposal to change the IASP World Congress to a Biennial event will be beneficial for the SIG groups. Apart from enabling a SIG meeting every two years, the IASP staff would also be available for help in planning other meetings such as satellites. Also, if the SIG decided to develop its own website, the IASP could help develop a cost analysis and aid in its development. An Ad Hoc Subcommittee on Special Interest Groups (SIGs) has been constituted to review activities of the different SIGs and any input from the membership that I can take to the subcommittee will be solicited.

A SIG meeting was held in conjunction with the annual American Pain Society (APS) meeting in Washington on May 4, 2007. A roundtable discussion on the role of minimal distal nerve injury as a possible mechanism of complex regional pain syndrome (CRPS) was presented by Wade Kingery, MD, R. Norman Harden, MD and yours truly. Unfortunately, as the meeting was not announced in the APS newsletter or program, attendance was poor. Minutes of this meeting are included in the body of the newsletter.

Of interest to North American SIG members is a proposal by Case Western Reserve University to initiate an annual meeting devoted entirely to complex regional pain syndromes. The subject material would obviously comprise contemporary research mechanisms, epidemiology and management of complex regional pain syndromes. As soon as further information in this regard is received, it will be published in the next newsletter.

Upcoming activities already mentioned are the approaching Topical Symposium entitled, “CRPS: The Case for Minimal Distal Nerve Injury,” to take place at the World Institute of Pain World Congress in Budapest September 24-28, 2007. A satellite meeting sponsored by the SIG PSNS under the auspices of IASP will be held in Cardiff before the World Congress on August 14-15, 2008, allowing a day and a half to travel between Cardiff and Glasgow for the World Congress from August 17-22, 2008. This satellite will be devoted to the most recent investigations into CRPS and its impact on current and future treatment.

As always, members are asked to provide any input concerning the nature and purpose of this SIG.

Michael Stanton-Hicks
Chair, IASP SIG on PSNS
The editorial by Jaenig and Baron [below] [Pain 120:227-229, 2006] generated two letters. This editor does not doubt that CRPS is a neuropathic pain syndrome, and also believes that it may not be possible to separate cause and effect in peripheral, central and autonomic systems. Events in any one of these inevitably causes physiological and anatomical changes in the other two.

Editorial by Jänig and Baron, PAIN 2006, 120, 227-229

There is still considerable disagreement as to the mechanisms underlying complex regional pain syndrome (CRPS). This is probably related to the lack of quantitative clinical data, which would allow the formulation of precise testable hypotheses, and to the lack of animal models and experimental approaches using the human patient as the model (Baron et al., 2002, Jänig and Baron, 2002, Jänig and Baron, 2003 and Jänig and Baron, 2004). Observations on CRPS patients clearly show that sympathetic, somatomotor, and somatosensory systems contribute to this pain syndrome and we can distinguish peripheral and central nervous systems factors. There are two types of CRPS. CRPS type I may develop after trauma, without nerve lesion (although some damage of nerve fibers usually occurs). CRPS type II develops after trauma with nerve lesion. It is important to emphasize that the severity of symptoms of CRPS type I, which is much more common than CRPS type II, is disproportionate to the severity of the trauma. Moreover, the patterns of symptoms, as variable as they may be, are not related to the type and degree of trauma. In fact, in rare cases, remote trauma in the viscera or in the CNS can trigger CRPS I in an extremity.

Based on this seemingly confusing and complex clinical situation and on preferences of different groups of investigators, primary mechanisms underlying CRPS include:

- Peripheral mechanisms, e.g., CRPS is considered to be primarily an inflammatory disease in the periphery or a consequence of nerve damage, including all other changes observed in the CRPS patients.

- Central mechanisms, e.g., reorganization of somatosensory, somatomotor, and autonomic systems triggered by a peripheral input (McCabe et al., 2003, Moseley, 2004 and Pleger et al., 2005). An extreme view is that CRPS I is a pseudoneurological disease, i.e., that many features of CRPS are manifestations of somatoform disorders, malingering, and psychiatric pathology (Ochoa, 1995). This view is now generally disregarded.

We prefer the hypothesis that CRPS I is a syndrome in which the CNS representations of the somatosensory, somatomotor, and sympathetic systems are altered and that this occurs concomitantly with important peripheral changes (such as edema, signs of inflammation, sympathetic-afferent coupling, trophic changes, etc.). The manner in which the peripheral and central changes interact is only partly understood. However, we are not convinced that there is a unitary mechanism that can explain CRPS. For example, we do not believe that it can be reduced to a peripheral inflammatory disease, to a peripheral adrenoceptor disease or to a psychoneural disease (Jänig and Baron, 2002 and Jänig and Baron, 2003).

The present issue of PAIN contains two papers in which it is hypothesized that the primary underlying mechanism of CRPS type I is a persistent, minimal distal nerve injury (Oaklander et al., 2006) or that it involves widespread changes of the cutaneous innervation by small-diameter afferent and postganglionic sympathetic efferent fibers (Albrecht et al., 2006).

In 18 CRPS patients, Oaklander and coworkers studied the innervation density of the epidermis of the CRPS-affected site (location of maximum pain), of a nearby (pain-free) control site, and of a mirror-image, contralateral control site. They immunolabeled the nerve fibers in sections of skin biopsies with a polyclonal antibody that recognizes the pan-axonal enzyme, ubiquitin hydrolase (PGP9.5, protein–gene product 9.5). They found on average, a reduction of the axonal density by 29% in the CRPS-affected skin sites compared to the control skin sites, with a huge interindividual variance. They propose that CRPS type I is triggered by nerve injuries predominantly affecting small diameter axons. They further propose that CRPS type I is maintained by ectopic activity generated in these injured afferent fibers, together with other (transcriptional) changes that occur in these afferent neurons. Thus, they clearly take the position that CRPS type I is a neuropathic pain syndrome.

Albrecht et al. (2006) studied the innervation of CRPS-affected glabrous and hairy skin and in corresponding skin samples not affected by CRPS (as defined by the relatively normal sensations). Their studies were performed in two surgically amputated extremities (upper and lower extremity) from two patients with CRPS type I. They labeled the innervation of epidermis and dermis, including blood vessels, sweat glands, and hair follicles,
using double immunostaining with antibodies directed against neuron-related proteins and transmitters. In CRPS-affected skin areas, they found impressive changes of the innervation of the different target tissues, as well as changes of the target tissue itself (e.g., blood vessels). These authors also concluded that CRPS type I can be associated with peripheral pathological changes of the innervation of skin, i.e., that CRPS type I may indeed be a neuropathic pain syndrome.

We suggest that considerable caution must be taken in evaluating these conclusions, as they are based only on the changes of the innervation of CRPS-affected skin areas. The following factors must also be taken into account:

• Almost all patients diagnosed as having CRPS type I were very chronic and went through many medical, and most importantly interventional, procedures. Thus, the conclusions drawn by the authors can only apply to potential mechanisms that maintain chronic CRPS, not to those that operate at the beginning of acute CRPS, i.e., in the first 1–6 months.

• There is increasing evidence that secondary tissue changes occur in the course of the disease, i.e., severe vasoconstriction, blood supply redistribution due to abnormal blood flow shunting with hypoperfusion in nutritive vessels, hypoxia, lactate increase, and acidosis (Birklein et al., 2000, Koban et al., 2003 and Schattschneider et al., 2006). All of these could contribute to the small fiber damage that is observed.

• A reduction of the innervation density of the epidermis of CRPS-affected skin by about 30% does normally not lead to clinically detectable changes of sensation, e.g., in patients with diabetic and other neuropathies.

• Most patients with CRPS type I have had trauma in the deep somatic tissues, a few in the viscera, and a few in the CNS. In these patients, the innervation of the skin is not primarily affected. Of course, the patients may have cutaneous allodynia and hyperalgesia as well as other changes, possibly associated with sympathetic vasoconstrictor and sudomotor innervation. In fact, most CRPS type I patients locate the spontaneous pain in deep somatic tissues.

• As noted above: The initiating events leading to CRPS type I are typically out of proportion with the pain (disease) that is experienced. One of the cardinal clinical features of CRPS I is the generalized distribution of all signs at the distal extremity. The patients described by Oaklander obviously had a more territorial distribution, with nearly normal skin areas (as assessed by counts of nerve fibers in the epidermis, quantitative sensory testing, and absence of pain evoked by non-pain stimuli) in close proximity to the painful-affected area. This observation makes one question whether there was an undetected nerve lesion leading to the fiber loss in the affected area.

In our opinion, therefore, it is premature to conclude, based on the data described in these two papers, (1) that the development of CRPS type I can be reduced to persistent minimal nerve injuries and their functional consequences and (2) that CRPS type I is a typical neuropathic pain syndrome, i.e., that nerve injury and the pathophysiological changes in the injured afferent neurons are the important events that initiate and maintain CRPS type I.

We do not deny that pathological changes (and their pathophysiological consequences) as described here may contribute to the maintenance of chronic CRPS type I. Furthermore, pathophysiological changes as described here in special subgroups of CRPS type I patients are not at all at variance with our hypothesis that CRPS type I is a disease of the CNS, with peripheral features contributing. However, we question whether the results presented in these two papers can explain the initiation and maintenance of CRPS type I and their underlying mechanisms.

Two letters in response to this editorial:

1. **Title:** Comment on editorial: Is CRPS I a neuropathic pain syndrome?

**Source:** PAIN, Rocco 2007, 128, 3, 285–286

The editorial by Jänig and Baron entitled “Is CPRS I a neuropathic pain syndrome?” is provocative (Jänig and Baron, 2006). Our response is no. CRPS is best understood as a disease of the autonomic nervous system. Neuropathic pain, on the other hand, is usually understood as a disease provoked by injury to the peripheral nervous system with secondary changes in excitability and firing of somatic systems centrally. Although CRPS can also be initiated by a trivial injury to the periphery, it is maintained by the central autonomic nervous system. This is exemplified in our recently published case report (Rocco and Raymond, 2005). Allow us to put this case in context. CRPS can be considered a quasi-persistent or regenerative process (like a memory) that can diminish or worsen. In some patients the disease may remit spontaneously in others it can progress relentlessly. In the patient we described the dystonia involved every segment/nuclei with both sensory and motor components. A single sympathetic block can put the disease in some patients into remission. In others it is only of temporary benefit. After a period of years the periphery may no
longer be sensitive to adrenergic agonists (Torebjork et al., 1995). At this point in the disease one may miss the diagnosis if only the periphery is checked with a regional intravenous block (Wall, 1995).

In some patients the process remains dormant, like an imprint of the disease in the CNS. It is possible to suddenly intensify the process and the disease can recur with the original severity, at the original location. This triggering of dormant CRPS has been seen in patients who have had surgery under general anesthesia (Rocco, 1993), and could be provoked by focal mechanical or thermal stimulation (Rocco and Raymond, 2005).

We are pleased that Jänig and Baron have asked this key question, because we think clinicians who approach CRPS as an autonomically driven, persistent process will be more likely to make their patients better than those who treat CRPS as a neuropathic pain.

2. Title: Is CRPS I a neuropathic pain syndrome?

Source: PAIN, Ochoa, 2006, 123, 3, 334–335

Congratulations to Drs. Jänig and Baron, Scientist and Neurologist, on an insightfully negative Editorial focused on two papers recently published in Pain (Albrecht et al., 2006 and Oaklander et al., 2006). Those papers show that, in some CRPS I patients, regressive structural pathology of cutaneous unmyelinated fibers may be discerned in painful body parts. Of course, there are multiple reasons why CRPS I patients may carry pathology in their symptomatic parts, and Albrecht et al., gallantly address such caveat in their Discussion. Arguably, the presence of primary pathology might validate a structurally based local mechanism for the pain, etc. In addition, it might be taken to support the tandem hypotheses that, in these patients, there would be occult chronically sensitized primary nociceptors, which would in turn induce and sustain a secondary hyperexcitable state in pain signaling cord neurons. While the second hypothesis remains to be tested directly in humans, the first is painstakingly explorable through microneurography (see Örstavik et al., 2003, Bostock et al., 2005 and Ochoa et al., 2005), a method just beginning to be applied to CRPS patients. Until nociceptors in CRPS I and II patients are tested functionally with the scientific rigor of the single fiber physiological method, all else is conjecture. In a critique of Weddel’s Pattern theory of sensation, the legendary P.W. Nathan once remarked: “Why should he judge the function of those nerve fibers in the cornea from the way they look? He might as well have judged them from the way they taste…”

Judgmentally, however, Jänig and Baron arbitrate: “An extreme view is that CRPS I is a pseudoneurological disease, i.e. that many features of CRPS are manifestations of somatoform disorders, malingering, and psychiatric pathology (Ochoa, 1995). This view is now generally disregarded.” For sure, the Neurologist is aware of publications on malingerers feigning RSD/CRPS I, and on cured somatizers that displayed such non-specific profile as the legitimate expression of a respectable biopsychosocial disorder (necessitating no spinal cord stimulator) (Walters, 1961, Shaw, 1964, Rodriguez-Moreno et al., 1990, Kurlan et al., 1997, Mailis et al., 2001, Mendelson, 2004 and Verdugo et al., 2004). For the benefit of the Scientist, in its Program Announcement for CRPS research, the NIH stipulates (PA No. 03-120) “The disorder could result from peripheral afferent mechanisms, peripheral efferent mechanisms, central mechanisms (including psychological mechanisms), or combinations of more than one mechanism. While theories abound, there has been a paucity of research to elucidate the pathophysiology of CRPS/RSD.” Jänig and Baron are forgiven for misquoting Ochoa (and Verdugo, 1995). Our clinical-basic group does not maintain that all CRPS I is pseudoneurological (DSM IV) and thus psychogenic. We write that patients meaninglessly invested with such “emperor’s new clothes” (Max and Gilron, 1999), a by default “diagnosis,” and treated invasively but ineffectively, await and deserve neurological differential diagnosis. Patients so labeled constitute a heterogenous group and may harbor any of several possible underlying neuropathological or psychopathological disorders (Walters, 1961, Ochoa, 1999, Ochoa and Verdugo, 2001, Ochoa, 2002 and Ochoa, 2006).

The pathophysiologies of neuropathic pains lie anywhere between skin and brain (Ochoa, 2004). Actually, between skin and psyche. The psyche is neuronal. It would be myopic not to agree with Jänig’s (2001) formidable writing in a publication through the IASP: “Critical evaluation of the changes occurring in CRPS-I patients in the somatosensory, sympathetic, and somatomotor systems shows that CRPS-I can only be understood as a pain syndrome or disease that is actively generated by the brain.” Other authors demonstrate: “In chronic ‘neuropathic’ ‘SMP’ patients, painful thermal stimuli evoked abnormal prefrontal and cingulate changes during functional MRI. Effective sympathetic blocks removed pain and rectified the MRI, while … effective placebo resulted in similar changes” (Apkarian et al., 2001b). Remarkably, a similar pattern of abnormal cortical activation is found in hysterical paralysis and hysterical anesthesia (Spence et al., 2000, Vuilleumier et al., 2001 and Mailis-Gagnon et al., 2003). Thus, for many CRPS I patients, every finger points to the brain. CRPS I is neither primary nor secondary nociceptor sensitization. It is certainly not “Sympathetically Maintained Pain” (SMP). In the past, our group disagreed with Jänig’s
initial “SMP” theory. Today, I am not sure I can identify at what level our group and Dr. Jänig’s disagree.

Role of Radionuclide Imaging in the Orthopedic Patient


Abstract: Since its introduction more than 40 years ago, nuclear medicine has played an important role in the diagnosis and detection of soft tissue and skeletal disorders. Skeletal scintigraphy or bone scanning is a diagnostic study used to evaluate the distribution of osteoblastic activity or active bone formation within the body. Because no single imaging technique is ideal in all clinical situations, selecting an appropriate imaging test depends on understanding the pathophysiology of the suspected condition and limitations of each technique. This article provides a brief overview of bone scintigraphy, infection imaging, and positron emission tomography in the context of current, adult orthopedic practice.

The orthopedic physician often encounters complex regional pain syndrome (CRPS) type I in the post-traumatic period. It is characterized by diffuse, chronic nondermatosomal pain, accompanied by trophic and autonomic changes. The pain is usually out of proportion to the level expected from the initiating event, and in contrast to CRPS II or causalgia, there is no identifiable damage to any major peripheral nerve. Untreated, CRPS I can spread proximally and lead to permanent limb atrophy and loss of joint mobility. Nuclear medicine can be useful to confirm initial clinical suspicion so that a neurologist may be involved early to optimize treatment. The pathophysiology of CRPS I is still incompletely understood. At the moment, the most widely accepted theory is that CRPS I is mediated by a process of “neurogenic inflammation.” This theory suggests that at a critical level of sensory afferent excitation neuropeptides are released at nerve fiber terminals. These peptides lower the pain threshold and trigger vasodilation and increased vascular permeability, which act to excite more sensory afferents. This “inflammatory” process also may be a stimulus for synovial proliferation and fibrosis.

Sympathetic dysfunction no longer is considered to play a major role in the pathogenesis of CRPS, which is why the term reflex sympathetic dystrophy is being phased out.

CRPS I is a clinical diagnosis; however, scintigraphy has an adjunct role in the diagnostic confirmation and disease staging. The scintigraphic findings depend on the stage of the disease, but classically are associated with increased periarticular activity in the affected limb (Fig. 18). The reported sensitivity and specificity in the literature range from 75% to 100% and 80% to 100%. Scintigraphy also has a prognostic value in CRPS I in predicting response to therapy; patients with a higher degree of tracer uptake had a higher likelihood of a positive response to therapy.

![Fig. 18](image_url) Palmar flow, blood pool, and delayed static images show diffuse hyperemia and periarticular increased activity within the left hand as a result of reflex sympathetic dystrophy. The patient also had an amputation of the distal left second digit.

Editor’s comment: These papers indicate that scintigraphy has limited value in the diagnosis of CRPS, and previous studies [e.g, Mailis] have shown that sympathetic block can mimic these changes. Bone scan may be useful in evaluating the presence of other pathology, for example, occult fracture or infection.

Reminder: Sign up for the SIG when you send in your IASP dues. You can now sign up online at: www.iasp-pain.org

Official Satellite Symposia

| PSNS SIG Satellite Symposium August 13-15, 2008: Cardiff, Wales, United Kingdom |
| To be held before the 12th World Congress on Pain. For information please contact organizers: Anne Louise Oaklander: aoaklander@partners.org and Michael Stanton-Hicks: stantom@ccf.org |
MINUTES
SIG Ad Hoc Meeting at APS Annual Meeting May 4, 2007, Washington DC, USA

Present: Drs. Stanton-Hicks, Haddox, Harden, Covington, Kingary, Raja, Scheman, Wilson, Mr. Jim Broatch

1. Dr. Stanton-Hicks suggested that the SIG request time on the 2008 APS program. This will require coordination with the appropriate committee.

2. AMA Guide to the Evaluation of Permanent Impairment. My Broatch and others pointed out the proposed criteria for CRPS in the 5th Edition are the figment of the editor’s imagination, and there is no reference to IASP criteria or those of Harden et al which have an evidence base. It would not seem possible for any patient to satisfy the new AMA criteria. The insurance industry and their attorneys must be delighted. Input is being attempted. The AMA guides, as a whole, are without any evidentiary basis, but some parts may have been derived by consensus.

3. IASP taxonomy. Dr. Harden reported that the previous taxonomy committee wanted “prospective” data to validate the proposed criteria. There are recruitment problems for this endeavor. The patient base will need to be from multiple centers. Members of the PSNS SIG are asked to contact Dr. Harden to become involved in this process.

4. SIG communication. Various methods of timely communication and discussion were proposed, including a SIG web site, chat room, blog site, list serve and regular emails. These are all time-consuming [and beyond the capability of your newsletter editor], so in the absence of other volunteers, I would suggest that we utilize the good offices of the IASP and expand the PSNS SIG site:

   http://www.iasp-pain.org/AM/Template.cfm?Section=Sympathetic&Template=/CM/HTMLDisplay.cfm&ContentID=1598

   This might include a copy of the newsletter and information about upcoming meetings.

5. Free papers:
   a. Dr. Stanton-Hicks addressed the question of whether CRPS is a central disease state, and concluded that it was not possible to separate central and peripheral components.
   b. Dr. Harden reviewed Dr. Oaklander’s research on small fiber loss in CRPS. This research has shown that CRPS in humans is associated with peripheral fine fiber loss. There is concomitant loss of CGRP in cutaneous arterioles. The changes were identical in both historic categories of CRPS [I and II]. Further work needs to be done to determine cause, association or effect.
   c. Dr. Kingery reviewed his studies on the rat fractured tibia/leg cast model, and indicated that there were still many questions about peripheral mechanisms, including neurogenic inflammation.

SIG Objectives
- To provide a forum for members to engage in free and frank communication on the diagnosis and management of pain syndromes of the sympathetic nervous system.
- To bring focus to new developments in the field in basic and clinical research.
- To assimilate the views on pain and the SNS of the different medical disciplines and the expressions of the patients.

SIG Information
The SIG PSNS currently has 238 members in 32 countries representing 30 disciplines
Financial Statement: As of May 30, 2007 the SIG has $64,945 in the account.

Please send your contributions, ideas and comments to PSNS SIG newsletter editor:
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