MESSAGE FROM THE CHAIR

Colleagues,

Although it seems almost yesterday, over a year has already gone by since the last World Congress of the IASP was held in Sydney. Those of you who were lucky enough to attend probably recognized this Congress to be perhaps the best of all IASP Congresses. Not only was the scientific program outstanding, but the abstracts reflected the enormous enterprise and investment in basic science and clinical investigation into the pathophysiology and mechanisms of the many pain syndromes. In spite of the Australian winter, Sydney turned on its best face and some of the best weather for that time of the year.

This issue of SIG P&NS includes minutes of the SIG meeting that was held. Of interest is the fact that a consensus felt that complexities related to the nature of the sympathetic nervous system and syndromes like CRPS support continuation of the P&SNS as an independent Special Interest Group at this time and not, as had been suggested, its dissolution and incorporation within the SIG on Neuropathic Pain.

Two events are planned during the next 18 months. In addition to a business meeting of the P&SNS SIG to be held at the American Pain Society on May 2-5, 2007, will be a Round Table that will address the proposal that CRPS I may not be a neuropathic pain syndrome like CRPS II. A Satellite Meeting to the 12th IASP World Congress in Glasgow in 2008 will be held in Cardiff. The theme of this meeting will highlight implications of the most recent research that impact both diagnosis and treatment of patients with CRPS. Investigators taking part in these research projects will compose the faculty for this Satellite.

Although not a SIG activity, a Topical Workshop on CRPS presented by Professors Ralf Baron, Norman Harden and yours truly will be held at the WIP Congress in Budapest, September 24-28, 2007. The scientific program of this Congress chaired by Allen Basbaum and Martin Van Kleef is excellent and, of course, Budapest is one of the most beautiful Eastern European cities.

In this issue of the Newsletter our new Editor, Peter Wilson, has assembled and made editorial comments to recently published abstracts. As this is your newsletter, please send any comments, suggestions or changes that you would like to see made to the newsletter to Peter Wilson at the Mayo Clinic.

Following up on an observation that was made in Sydney, are there any members who would like to help set up a Web Site? Certainly this would be a much more rapid way of disseminating news and scientific abstracts pertaining to our SIG. Please, are there any volunteers? We have some funds that can be put to this purpose.

Michael Stanton-Hicks
Chair, IASP SIG on PSNS

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It is quite clear from a number of publications, only a few of which can be mentioned here, that CRPS is still an enigmatic but important disorder. Although there are components of neuropathic pain involved, I believe that it was a reasonable decision of this SIG to remain separate from the Neuropathic Pain SIG.

Jaenig and Baron posed the question of whether CRPS1 is a neuropathic pain syndrome in an editorial in Pain (120:227-229; 2006). They commented on the papers by Albrecht et al and Oaklander et al in the same issue (discussed separately below). It seemed premature to them to conclude that “[1] 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 pathophysiologic changes in the injured afferent neurons are the important events that initiate and maintain CRPS type I”. They preferred the hypothesis that “CRPS type 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.)….we are not convinced that there is a unitary mechanism that can explain CRPS.”


Abstract
CRPS-I consists of post-traumatic limb pain and autonomic abnormalities that continue despite apparent healing of inciting injuries. The cause of symptoms is unknown and objective findings are few, making diagnosis and treatment controversial, and research difficult. We tested the hypotheses that CRPS-I is caused by persistent minimal distal nerve injury (MDNI), specifically distal degeneration of small-diameter axons. These subserve pain and autonomic function. We studied 18 adults with IASP-defined CRPS-I affecting their arms or legs. We studied three sites on subjects’ CRPS-affected and matching contralateral limb; the CRPS-affected site, and nearby unaffected ipsilateral and matching contralateral control sites. We performed quantitative mechanical and thermal sensory testing (QST) followed by quantitation of epidermal neurite densities within PGP9.5-immunolabeled skin biopsies. Seven adults with chronic leg pain, edema, disuse, and prior surgeries from trauma or osteoarthritis provided symptom-matched controls. CRPS-I subjects had representative histories and symptoms. Medical procedures were unexpectedly frequently associated with CRPS onset. QST revealed mechanical allodynia (P<0.03) and heat-pain hyperalgesia (P<0.04) at the CRPS-affected site. Axonal densities were highly correlated between subjects’ ipsilateral and contralateral control sites (r=0.97), but were diminished at the CRPS-affected sites of 17/18 subjects, on average by 29% (P<0.001). Overall, control subjects had no painful-site neurite reductions (P=1.00), suggesting that pain, disuse, or prior surgeries alone do not explain CRPS-associated neurite losses. These results support the hypothesis that CRPS-I is specifically associated with post-traumatic focal MDNI affecting nociceptive small-fibers. This type of nerve injury will remain undetected in most clinical settings.

Editor’s comments: This is an elegant, invasive study of 18 CRPS patients with 7 control “chronic pain” patients without CRPS. The CRPS patients had mirror image 3 mm punch biopsies of the affected and unaffected sides. Quantitative sensory testing was carried out. The skin biopsies were immunolabeled and quantitated for epidermal neurite density. Only CRPS-affected skin had a loss of neurites [average 29%]. The authors compared these results with those of their post herpetic neuralgia [PHN] patients and found that the loss was higher in PHN skin [80%]. The results do not support “central” or “psychogenic” hypotheses.


Abstract
Complex regional pain syndromes (CRPS, type I and type II) are devastating conditions that can occur following soft tissue (CRPS type I) or nerve (CRPS type II) injury. CRPS type I, also known as reflex sympathetic dystrophy, presents in patients lacking a well-defined nerve lesion, and has been questioned as to whether or not it is a true neuropathic condition with an organic basis. As described here, glibrous and hairy skin samples from the amputated upper and lower extremity from two CRPS type I diagnosed patients were processed for double-label immunofluorescence using a battery of antibodies directed against neural-related proteins and mediators of nociceptive sensory function. In CRPS affected skin, several neuropathologic alterations were detected, including: (1) the presence of numerous abnormal thin caliber NF-positive/MBP-negative axons innervating hair follicles; (2) a decrease in epidermal, sweat gland, and vascular innervation; (3) a loss of CGRP expression on remaining innervation to vasculature and sweat glands; (4) an inappropriate expression of NPY on innervation to
superficial arterioles and sweat glands; and (5) a loss of vascular endothelial integrity and extraordinary vascular hypertrophy. The results are evidence of widespread cutaneous neuropathologic changes. Importantly, in these CRPS Type I patients, the myriad of clinical symptoms observed had detectable neuropathologic correlates.

Editor’s comment: This is a report of two cases in which limbs [one upper, one lower] were amputated for attempted symptom control and “general health issues”. The skin was analyzed with immunofluorescent techniques. They reported the changes in the peripheral nerves, sweat glands and blood vessels. The results were clearly abnormal, but the lack of controls or comparisons did not allow definitive conclusions to be made.

Sympathetic sprouting and changes in nociceptive sensory innervation in the glabrous skin of the rat hind paw following partial peripheral nerve injury.

Abstract
Previous studies have suggested that sympathetic sprouting in the periphery may contribute to the development and persistence of sympathetically maintained pain in animal models of neuropathic pain. In the present study, we examined changes in the cutaneous innervation in rats with a chronic constriction injury to the sciatic nerve. At several periods postinjury, hind paw skin was harvested and processed by using a monoclonal antibody against dopamine-beta-hydroxylase to detect sympathetic fibers and a polyclonal antibody against calcitonin gene-related peptide to identify peptidergic sensory fibers. We observed migration and branching of sympathetic fibers into the upper dermis of the hind paw skin, where they were normally absent. This migration was first detected at 2 weeks, peaked at 4-6 weeks, and lasted for at least 20 weeks postlesion. At 8 weeks postlesion, there was a dramatic increase in the density of peptidergic fibers in the upper dermis. Quantification revealed that densities of peptidergic fibers 8 weeks postlesion were significantly above levels in sham animals. The ectopic sympathetic fibers did not innervate blood vessels but formed a novel association and wrapped around sprouted peptidergic nociceptive fibers. Our data show a long-term sympathetic and sensory innervation change in the rat hind paw skin after the chronic constriction injury. This novel fiber arrangement after nerve lesion may play an important role in the development and persistence of sympathetically maintained neuropathic pain after partial nerve lesions.

Editor’s comment: The Bennett model is exploited in this excellent study to demonstrate peripherial nerve changes in the rat after chronic constriction injury of the sciatic nerve. It showed significant sprouting of both sympathetic and peptidergic sensory fibers in the upper dermis of the plantar surface of paw skin. Some of these were in close proximity to peptidergic sensory fibers. There was a decrease, then an increase in these sensory fibers. The authors speculate that this might be an explanation for hyperalgesia after such an injury.

The clinical role of the sympathetic nervous system is under increasing scrutiny. The Cochrane Database [below] concludes that there is a scarcity of published evidence.

Local anesthetic sympathetic blockade for complex regional pain syndrome. [Review] [20 refs]
Cepeda MS. Carr DB. Lau J. Javeriana University School of Medicine, Department of Anesthesia, Cra 4-70-69, Bogota, Colombia. scepda@javeriana.edu.co. Cochrane Database of Systematic Reviews. (4):CD004598, 2005.

Abstract:
Background: Local anesthetic blockade of the sympathetic chain is widely used to treat reflex sympathetic dystrophy (RSD) and causalgia. These two pain syndromes are now conceptualized as variants of a single entity: complex regional pain syndrome (CRPS). A recent meta-analysis of the topic has been published. However, this study only evaluated studies in English language and therefore it could have overlooked some randomized controlled trials.

Objectives: This systematic review had three objectives: to determine the likelihood of pain alleviation after sympathetic blockade with local anesthetics in the patient with CRPS; to assess how long any benefit persists; and to evaluate the incidence of adverse effects of the procedure.

Search Strategy: We searched the Cochrane Pain, Palliative and Supportive Care Register, the Cochrane Central Register of Controlled Trials, Medline, Embase, Lilacs, and conference abstracts of the World Congresses of the International Association for the Study of Pain. Bibliographies from retrieved articles were also searched for additional studies.

Selection Criteria: We considered for inclusion randomized controlled trials that evaluated the effect of sympathetic blockade with local anesthetics in children or in adult patients to treat RSD, causalgia, or CRPS.

Data Collection and Analysis: The outcomes of interest were the number of patients who obtained at least 50% of pain relief shortly after sympathetic blockade (30 minutes to 2 hours) and 48 hours or later. We also assessed the presence of adverse effects in each treatment arm. A random effects model was used to combine the studies.

Main Results: Two small randomized double blind cross over studies that evaluated 23 subjects were found. The combined effect of the two trials produced a relative risk (RR) to achieve at least 50% of pain relief 30 minutes to 2 hours after the sympathetic blockade of 1.17 (95% CI 0.80-1.72). It was not possible to determine the effect of sympathetic blockade on long-term pain relief because the authors of the two studies evaluated different outcomes.

Authors’ Conclusions: This systematic review revealed the scarcity of published evidence to support the use of local anesthetic sympathetic blockade as the ‘gold standard’ treatment for CRPS. The two randomized studies that met inclusion criteria had very small sample sizes, therefore, no conclusion concerning the effectiveness of this procedure...
could be drawn. There is a need to conduct randomized controlled trials to address the value of sympathetic blockade with local anesthetic for the treatment of CRPS. [References: 20]

**Editor’s comment:** A challenge!

**Endothelial dysfunction in cold type complex regional pain syndrome.**

**Abstract**
The authors examined endothelial function in cold type chronic complex regional pain syndrome (CRPS) I using acetylcholine- and sodium nitroprusside-induced vasodilation combined with laser Doppler flowmetry in 14 patients and 10 controls. On the affected side, acetylcholine-induced vasodilation was significantly reduced in comparison to controls and the unaffected extremity. No significant differences were found after application of sodium nitroprusside. The results demonstrate impaired endothelial function in chronic CRPS I.

**Editor’s comment:** This paper addresses the issue of sympathetically maintained pain [SMP] in a very sophisticated study. It showed that pain relief was variable [0% - 79%] and may have depended on blockade of the sympathetic nerves to deep structures rather than to skin. It also suggested that SMP was more prominent early in the course of the condition. There are clearly large areas of knowledge that need to be clarified. Unfortunately, the SIG will be needed for the foreseeable future.

**A reminder:** Sign up for the SIG PSNS when you send in your annual IASP dues. IASP dues can now also be paid online at: [www.iasp-pain.org](http://www.iasp-pain.org)

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**Minutes**

**SIG PSNS Triennial Business Meeting**
August 24, 2005 Sydney, Australia

Call to order: Michael Stanton-Hicks (Chair)
22 members in attendance

Minutes of the previous triennial meeting and current financial statements were presented and accepted.

1) Elections
a. The Chair called for nominations for the Board from the floor, and will forward those names to the IASP in time for the postal nominations and ballot of all SIG members
b. The Chair asked anyone present to indicate their interest in working on any of the SIG committees. These will be finalized by the incoming Board
e. The Chair asked for a volunteer to edit the newsletter.

2) Taxonomy
a. The Chair indicated that the taxonomy and diagnostic criteria from the consensus conference in Budapest would be presented to the IASP Taxonomy Committee for consideration in the next revision of the ‘official’ IASP taxonomy.
b. The new taxonomy committee would be charged with collecting data on specificity and sensitivity of the proposed changes.

3) Possible merger with Neuropathic Pain SIG
a. The Chair discussed the pros and cons of merging with another SIG. Pros would include a larger number of members, avoidance of duplication of membership, ability to “share” meetings. Cons would include loss of focus and autonomy, submersion by basic scientists and inability to maintain a forum for what are multidisciplinary clinical syndromes.
b. After spirited discussion, the show of hands indicated overwhelming support for the status quo.

4) Research Funding
a. The Chair indicated that there was a total of $50K available. Discussion did not indicate any consensus for the best use of the funds, as it is not yet sufficient to support any stand-alone research.

Meeting closed

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**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 September 30, 2006 the SIG has $61,402.00 in the account.

Please send your contributions, ideas and comments to PSNS SIG newsletter editor: Peter Wilson, MB BS, Dept. of Anesthesiology, Mayo Clinic, Rochester MN 55905, USA Email: wilson.peter@mayo.edu