Complex regional pain syndrome (CRPS) is the current taxonomic label for a syndrome previously known by many names (reflex sympathetic dystrophy, causalgia, Sudeck’s atrophy, shoulder-hand syndrome, neuroalgodystrophy, reflex neurovascular dystrophy, etc). It is an inflammatory and neuropathic pain disorder, often involving both peripheral and central sensitization, but principally characterized by regional dysfunction of the autonomic nervous system. It involves a full measure of bio-psycho-social features and it can be significantly disabling. CRPS remains one of the most enigmatic and difficult to treat of all pain conditions probably in large part due to the fact that the pathophysiology remains poorly characterized. In fact, there is increasing consensus that CRPS is unlikely to be caused by a single, simple pathophysiological mechanism. Rather, it is likely to be the result of multiple interacting systems throughout the neuroaxis, with varying relative contributions of these various mechanisms across different patients at different times.

There are several animal models that shed light on the mechanisms of CRPS, especially the chronic constriction injury model in rat that was first described by Bennett and colleagues. There are human models such as the intracutaneous injection of capsaicin and the controlled heat injury model which induce features of CRPS such as burning pain, cutaneous allodynia, and hyperalgesia, and as such may represent useful models to study certain aspects of CRPS. Other methodologies such as whole body cooling induce sympathetic activation and allow the study of the role of the sympathetic nervous system in “maintaining” the pain in CRPS.

One clear standout in the study of CRPS pathophysiology is cytokine activity, particularly IL-6 and TNF-alpha. Animal and human sympathetic manipulations demonstrate that the sympathetic nervous system can influence the intensity of these inflammatory processes. Some evidence also suggests that “neurogenic inflammation” is facilitated in CRPS patients, again mediated by cytokine balance. CRPS is characterized by “disproportionate” spontaneous and evoked pain (e.g., hyperalgesia, thermal, and mechanical allodynia). Whether these sensory symptoms are due to peripheral and/or central sensitization is the subject of considerable debate and investigation. Psychophysical techniques, such as Quantitative Sensory Testing, frequently reveal positive and negative sensory signs and symptoms commonly ipsilateral and occasionally contralateral to the affected part. These effects are more likely to occur with greater CRPS chronicity, suggesting centralization of the pathology over time. Skin biopsies have revealed decreased C-fiber and A-delta fiber axonal densities in the affected limb of CRPS Type I patients compared with the unaffected side. It is not known whether such changes are primary to the disease or a consequence of nutritional changes and ischemia caused by chronic vasoconstriction and inflammation. Although older diagnostic criteria do not mention motor or movement disorders, newer statistically derived criteria and clinical experience feature prominent motor system abnormalities such as weakness, spasm, tremor, bradykinesia, range of motion abnormalities, and occasionally dystonia. Finally, data regarding possible genetic contributions to CRPS are rather limited, but are sufficient to justify further exploration of this very plausible contribution to pathophysiology.

There is a critical need to extend and corroborate these hypothetical mechanistic considerations, as without a coherent understanding of pathophysiology there can be no rational approach to treatment, or gold standard diagnostic test. Dr Stanton-Hicks et al. have arranged several transformative international symposia and workshops over the years with the goal of developing consensus and direction in the effort to approach these goals. We are grateful for the leadership and editorial skill of Dr. Peter Wilson, who has assembled reports of the presenters at the latest of these “satellite” conferences (sponsored by the IASP Special Interest Group on Pain and the Sympathetic Nervous System in Cardiff Wales, before the World Congress in August 2008) in this issue, regarding status and progress in several research areas, as above. We are finally making good progress in delineating the pathophysiology of this most complicated pain disorder, as you may judge from this monograph.

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