Complex Regional Pain Syndrome

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Editors

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Preface

Pain associated with dysfunction of the autonomic nervous system has a rich, complicated, and confusing history. The latest chapter in this history unfolded last year in Cardiff, Wales, at the 2000 IASP Research Symposium sponsored by the International Association for the Study of Pain, where specialists from all over the world gathered to share the latest knowledge on complex regional pain syndrome (CRPS).

For a day and a half, 28 researchers presented their work to a diverse multidisciplinary audience from 32 countries. The first day's presentations addressed the state of basic and clinical science in CRPS, and the next day we focused on diagnosis. Either by hard work or good luck, we had brought together a near-perfect collaboration of minds, and we made good progress toward the goal of airing new concepts and ideas that cut across institutional bias and tradition. Each representative of the various laboratories brought a unique piece of the puzzle to the table. Young researchers and veteran faculty members alike believed in the preeminent value of their own work in pursuing an understanding of the syndrome. However, when all the pieces were laid out and examined as a whole, it was obvious that we had been functioning like blind men examining the elephant: we understood and believed in our own piece, but we could not conceptualize the big picture.

It is now apparent that CRPS can at different times and by different pathologies affect the entire neuraxis. Certainly we see patients who seem to be primarily affected by inflammation, swelling, and other tissue changes in the traumatized limb (Chapters 13 and 14). These changes may be associated with an apparent afferent neuropathic dysfunction or regional sensitization characterized by allodynia and hyperpathia (Chapters 3, 4, 13, and 15). The pathological contribution of reactive bracing and disuse in the face of intense pain cannot be underestimated (Chapter 11), nor can the development of a neglect-like phenomenon (Chapter 10). The nociceptive barrage on the dorsal horn may cause central sensitization or hyperexcitability, which ultimately may be the essential common element to the development and perpetuation of CRPS (Chapter 15). Functional and neuroplastic changes can extend into the brainstem (Chapter 15) and possibly into the cerebral cortex (Chapter 16). The efferent side of these phenomena is mediated primarily by the sympathetic nervous system, which interacts with the pathology in the extremity (Chapters 4 and 7), but motor abnormalities are noted as well (Chapters 8, 9, and 10). The hypothesis that multiple sites, both

afferent and efferent, are affected along the neuraxis is corroborated by the animal models (Chapters 2–6) and by human "models" (Chapters 12 and 13). Aside from direct involvement of the neuraxis, genetic factors might be involved (Chapter 17).

Several participants emphasized the need for more specific diagnostic criteria to complement the high level of sensitivity achieved by the first permutation of CRPS as a specific diagnostic entity. These criteria, formulated at a conference in Orlando, Florida, in 1993 and presented in *Reflex Sympathetic Dystrophy: A Reappraisal* (W. Jänig and M. Stanton-Hicks [Eds]; Seattle: IASP Press, 1996), were formally codified in the second edition of the *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms* (H. Merskey and N. Bogduk [Eds]; Seattle: IASP Press, 1994). Drs. Pieter Dijkstra, Jan Geertzen, Michael Stanton-Hicks, Stephen Bruehl, and Norman Harden all highlighted information relevant to our need for better diagnostic accuracy and suggested ways to achieve this. Clearly, much work remains to be done.

This book describes various aspects of CRPS that have been systematically investigated in human and animal experiments since the publication of *Reflex Sympathetic Dystrophy,* which triggered many of the experimental investigations on humans and animals reported in this volume. These aspects include:

- Analysis of neural regulation of blood flow through skin under various experimental conditions.
- Analysis of neural regulation of sweating.
- Analysis of sympathetically maintained pain under controlled conditions.
- Analysis of changes in motor functions.
- Analysis of changes in sensory functions of the skin.
- Genetic aspects of CRPS.
- Inflammatory processes in CRPS.
- Development of quantitative tests to characterize CRPS.
- Development and critical evaluation of new human and animal models simulating components of CRPS.
- The role of immobilization.
- Directions for improving diagnostic specificity.
- The role of regional anesthesia in diagnosis.
- Assessment of impairment.
- Psychological issues.

The level of communication and the rapid progress seen at this meeting are very encouraging. We are nearing an understanding of the basic and clinical pathophysiological elements involved in the syndrome and can glimpse how these elements may interrelate in different individuals. Perhaps our confusion regarding the different manifestations of CRPS can be ascribed to the fact that we were observing the syndrome at different times and in different settings, reflecting our biases as to how we think the syndrome works and the different ways in which individual patients respond over time. This meeting has given the research community a better understanding of what is occurring in the various laboratories working on CRPS. It is our hope that this type of collaboration will continue and that the ultimate prize will soon be attained. Systematic investigation of multiple aspects of CRPS should lead to deeper insight into the mechanisms underlying CRPS, to appropriate subclassifications of CRPS, to more stringent diagnostic criteria, and ultimately to better mechanism-based therapeutic strategies.

Dr. Bradley Galer originally proposed this symposium to IASP. Subsequently, his professional responsibilities prevented him from continuing with the organization of this international, multidisciplinary meeting. At that point Dr. Harden assumed leadership, together with the organizing committee consisting of Drs. Ralf Baron, Stephen Bruehl, and Galer. Drs. Wilfrid Jänig, Michael Stanton-Hicks, and Michael Bennett provided invaluable support in their capacity as members of the Scientific Advisory Board for the symposium. The task of organization proved to be tremendously complex and we are particularly indebted to Dr. Bruehl for his tireless efforts. Without the thoroughly professional and knowledgeable help of Wales Trade International in the persons of Antonia Uys, Gus Noble, and Denis Turner, and the unparalleled skills of our organization guru, Don Olson, the meeting could not have occurred.

Acknowledgment must be made of the hard work and patience of the authors in bringing this work to press. We are deeply indebted to the section editors for all their hard work, especially to Dr. Bruehl, who managed the largest and most complicated section. We would also like to acknowledge the assistance of the IASP Press staff. In particular, the editorial professionalism of Elizabeth Endres added immensely to the finished quality of this volume, and Editor-in-Chief Howard Fields provided insightful comments throughout the process. Most of all, we wish to acknowledge our patients, who have taught us so much and who await the fruit of our efforts so patiently.

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Part I

Overview

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CRPS-I and CRPS-II: A Strategic View

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The mechanisms of pain and associated changes occurring in patients with complex regional pain syndrome (CRPS) types I and II are still unclear, despite considerable efforts and many experiments performed on humans and animals both in vivo and in vitro (Jänig and Stanton-Hicks 1996; see Baron and Jänig 1998).

The key clinical symptoms of CRPS include pain (spontaneous pain, hyperalgesia, and allodynia); abnormal regulation of blood flow and sweating; edema of the skin and subcutaneous tissues; trophic changes of the skin, appendages of the skin, and subcutaneous tissues; and active and passive movement disorders, including increased physiological tremor (Blumberg et al. 1994; Blumberg and Jänig 1994; Jänig and Stanton-Hicks 1996; Harden et al. 1999; see Baron and Jänig 1998, 2001). The disturbances may be restricted to one extremity and generally are confined to its distal part. However, symptoms occur not only at the site of the trauma but also in nontraumatized parts of the affected extremity, or in disparate regions of the body ipsilateral to the trauma. Patients may have different combinations of symptoms.

How does this painful disease fit into our modern concepts of the biology and pathophysiology of pain? Its mechanisms might include the somatic and visceral sensory systems, the central endogenous (antinociceptive) control systems, the sympathetic nervous system (SNS), the somatomotor system, and the neuroendocrine systems (Fig. 1). In this chapter, I will argue that CRPS is a complex neurological disease involving various levels of integration of the brain. I will not concentrate on peripheral processes such as mechanisms of sympathetic-afferent coupling or inflammation.

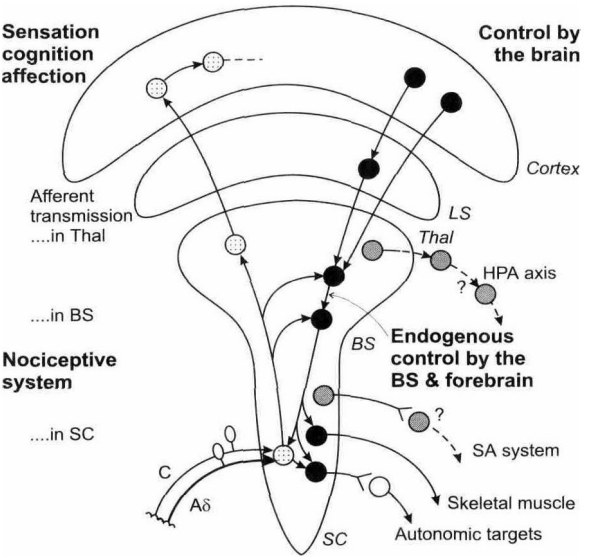

Fig. 1. Biology and pathobiology of pain. The nociceptive system, its endogenous control system(s), the sympathetic system, the somatomotor system and the neuroendocrine systems (hypothalamo-pituitary-adrenal [HPA] axis, sympatho-adrenal [SA] system). All these systems are principally involved in the generation of pain and may also mediate CRPS-I and CRPS-II, although no data are available regarding the involvement of the HPA axis and the SA system. BS = brainstem, LS = limbic system, SC = spinal cord, Thal = thalamus.

CRPS AND SYMPATHETICALLY MAINTAINED PAIN

The SNS may be involved in generating pain under certain pathophysiological conditions. Pain dependent on activity in the sympathetic neurons is called *sympathetically maintained pain* (SMP; Stanton-Hicks et al. 1995; Jänig and Stanton-Hicks 1996). Under normal (healthy) conditions, activity in the SNS innervating somatic tissues does not generate pain (Jänig and Koltzenburg 1991). SMP is a syndrome that usually includes both spontaneous pain and pain evoked by mechanical and cold stimuli. It is often, but not always, present in CRPS types I and II, and sometimes in other neuropathic pain syndromes (Stanton-Hicks et al. 1995; Jänig et al. 1996; Jänig 1999).

The concept that the (efferent) SNS is involved in pain is based on long-standing clinical observations (Sweet and White 1969; Bonica 1990; Blumberg and Jänig 1994; Baron et al. 1996, 1999). Three groups of experimental clinical studies are representative of this extensive work.

First, in a study of patients with SMP who probably would be diagnosed with CRPS-II, Torebjörk et al. (1995) showed that spontaneous pain,

mechanical allodynia, and cold allodynia in the hand could be alleviated by stellate ganglion block. The pain could be rekindled, under proximal sympathetic block, by injection of norepinephrine into the area of skin that was painful before sympathetic blockade. In patients with chronic pain, the authors demonstrated that SMP can persist for many years (Wahren et al. 1995). These results have been fully confirmed, reproduced, and extended by Ali et al. (2000), in CRPS patients with SMP. Intradermal injection of norepinephrine, in physiological concentrations (0.1–1 μM) that did not produce vasoconstriction or were just suprathreshold for inducing it, evoked greater pain in the injected region of the painful limb than in the contralateral unaffected limb in patients or in limbs of healthy control subjects. Under proximal sympathetic block, local injection of norepinephrine rekindled the pain in most patients. In most cases, intravenous infusion of phentolamine significantly reduced the pain.

Second, in a double-blind crossover study in CRPS-I patients with SMP, Price et al. (1998) found that local anesthetic applied to the appropriate sympathetic paravertebral ganglia generated pain relief in the affected extremity for a significantly longer period than did saline injected close to this site in the same group of patients. This remarkable study clearly demonstrates that the pain relief generated by blockade of sympathetic activity exceeds that produced by a similar placebo "block." This study confirms others in showing that the duration of pain relief greatly outlasts the conduction block generated by the local anesthetic. Thus, the pain-relieving effect of sympathetic blocks cannot be explained simply by temporary blockade of activity in the sympathetic neurons.

Third, R. Baron and coworkers (unpublished manuscript) demonstrated that a physiological intervention that increases the activity of sympathetic neurons can heighten pain. In patients with chronic CRPS-I with SMP, spontaneous pain and mechanical allodynia increased in an extremity that was maintained at a constant temperature of 35°C when the rest of the body was cooled to enhance activity in cutaneous vasoconstrictor neurons. The increased pain in the extremity may be independent of a vascular component.

These clinical experiments clearly argue that (1) activity in sympathetic neurons can be involved in generating pain, (2) blockade of sympathetic activity can relieve pain, and (3) norepinephrine injected intracutaneously can rekindle pain. These results lead to the following hypothesis: Nociceptors are excited and possibly sensitized by norepinephrine released by the sympathetic fibers (Fig. 2). The nociceptors may have expressed functioning adrenoceptors, or the excitatory effect may be indirectly mediated by the vascular bed or by other components of the microenvironment of the nociceptive terminals. Sympathetically maintained activity in nociceptive neurons

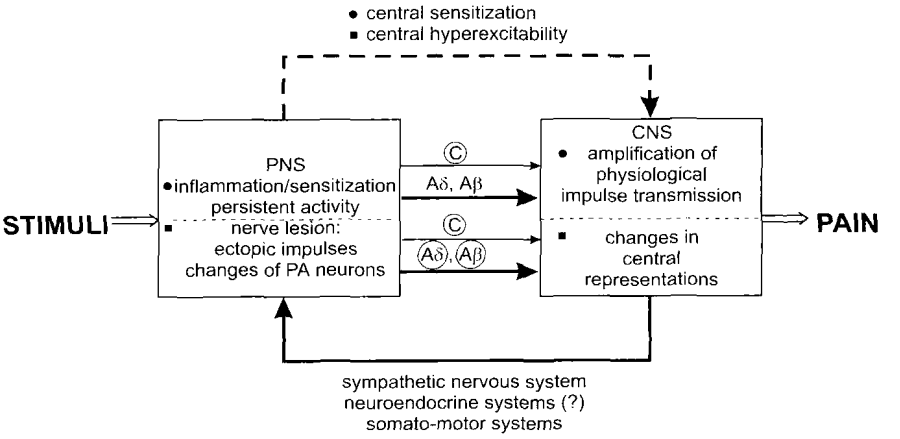

Fig. 2. Generation of peripheral and central hyperexcitability during inflammatory pain and neuropathic pain. The upper interrupted arrow indicates that the central changes result from changes in the primary afferent neurons induced by inflammation or persistent stimulation (central sensitization) and of trauma associated with nerve lesion (*central hyperexcitability and changes in central representations*). The lower interrupted arrow indicates the efferent feedback via the sympathetic nervous system, the somatomotor system, and the neuroendocrine systems. Primary afferent nociceptive neurons (in particular those with C fibers) are sensitized during inflammation. The biochemical and physiological changes occurring in these neurons during sensitization are principally reversible. After nerve lesion *all* lesioned primary afferent neurons (both unmyelinated and myelinated) undergo biochemical, physiological, and morphological changes that become irreversible over time. These changes entail central irreversible changes if there is no regeneration of primary afferent neurons to their target tissue. The central changes, induced by persistent activity in afferent nociceptive neurons or after nerve lesions, are reflected in the efferent feedback systems. CNS = central nervous system, PA = primary afferent, PNS = peripheral nervous system. Reprinted from Jänig and Baron (2001), with permission.

may generate a state of central sensitization or hyperexcitability that can cause spontaneous pain and secondary evoked pain (e.g., mechanical and cold allodynia). These and other less well-controlled experiments and clinical observations suggest that the (efferent) SNS may be involved in generating pain. Thus, the pain-relieving effect of sympathetic blocks reveals an abnormal direct or indirect communication from the sympathetic postganglionic neurons to the afferent neurons and shows that activity in sympathetic neurons is important in generating SMP. However, these studies have been unable to clarify the basic underlying mechanisms or to reveal whether this abnormal communication involves only nociceptive afferent neurons or includes other groups of afferent neurons. Furthermore, they do not reveal whether SMP depends on special functional constellations of the SNS that are clinically expressed in other phenomena, particularly in CRPS-I (changes