

**Campbell JN, Basbaum AI, Dray A, Dubner R, Dworkin RH, Sang CN, eds. *Emerging Strategies for the Treatment of Neuropathic Pain*. Seattle: IASP Press, 2006. ISBN 0-93109261-2; 2514 pages; US\$80; IASP member price US\$64**

This book is the result of a five-day meeting in Scottsdale, Arizona, in April 2005, with the purpose of developing new ways to treat neuropathic pain (NP). It is divided into four parts: peripheral nervous system targets, central nervous system targets, disease-specific targets, and measurement and new technologies. It is the intent that the book represents the state of the art and a blueprint for the future.

Part I (chapters 1 to 4) contains chapters on peripheral targets, generators and receptors, and discusses the role of sensitization of primary afferents in NP. Some examples of consensus are for the term dynamic mechanical allodynia, the meanings of the term 'mechanisms', ectopic activity, central sensitization, the induction of central sensitization by C fibers, dynamic mechanical allodynia being signalled by A-beta fibers, and that physiological central sensitization does not usually outlast peripheral provoking stimuli for more than one day. Research questions are whether injured A-beta fibers can induce central sensitization, the role of mechano-insensitive afferents, under what circumstances peripheral NP becomes independent of the periphery input, how quickly it develops and whether C-fiber activity is essential for the induction/maintenance of neuropathic pain. Targeted monotherapy versus polypharmacy and the future of genetics are important issues raised here. An important question is whether focusing aggressively on the periphery can arrest central changes and prevent chronicity. There is a stimulating review of current systemic drug actions pointing out that many effective agents act as membrane stabilizers on ion channels suppressing ectopia. Plasma membrane receptors are exhaustively detailed. The section comes up somewhat short on topical agents admittedly of very limited effect currently and excludes reference to the several trials of opioids in neuropathic pain. Finally, peripheral sensitization is emphasized as an important mechanism and therapeutic target for the prevention of sensitization.

Part II (chapters 5 to 10) is entitled *Central Nervous System Targets*. The relevant topics chosen in the first chapter of this section are central sensitization, plasticity, neuronal-glial interaction, competition in the brain, descending modulation, pain experience, animal models, genomics and proteomics and therapeutics. Important research questions are identified, with particular regard to central sensitization. Chapter 6 discusses descending modulatory circuitry and begins with a superb review of research into the descending inhibition of pain. The

chapter then proceeds to a thorough discussion of descending inhibitory and facilitatory modulation, the effects of injury and clinical implications. Chapter 7 concerns *Opioids and Neuropathic Pain*. It reviews the controversies about chronic opioid therapy in neuropathic pain and clinical research. A plea is made for more long-term studies and evaluation of how well the design of preclinical investigations have provided guidance to clinical investigations. Chapter 8 discusses the role of *Neuroimmune Activation in Chronic Neuropathic Pain and Possible Future Therapies*. It addresses approaches to treating NP involving the immune system and highlights the role of cytokines and neuroimmune activation and treatment strategies. Chapter 9 is entitled *Signaling Pathways in Pain Neuroplasticity in the Spinal Dorsal Horn*. This chapter begins with a nice summary of the physiology and pathophysiology of the dorsal horn, emphasizing plasticity and the emerging role of microglia and pain hypersensitivity following nerve injury. It nicely discriminates 'wind-up' versus classical 'central sensitization' and goes on to discuss persistent enhancement of excitatory synaptic neurotransmission and suppression of inhibition. Chapter 10 deals with *Ascending and Descending Facilitatory Circuits in Neuropathic Pain States*. It reviews sensitization of the dorsal horn by primary afferents and the current evidence that initial discharges cause central sensitization but that neuroplastic changes in the central nervous system maintain central sensitization. It then goes on to discuss primary afferent input and spinal sensitization in some detail and then ascending pathways of possible importance. Of interest is the discussion of descending pain facilitatory pathways that maintain central sensitization and the involvement of serotonin. We have long thought about descending pain inhibitory systems, but we now need to think from a therapeutic point of view about this facilitatory system. The chapter finishes with a nice synthesis which suggests points at which pharmacological manipulation may be considered.

Part III (Chapters 11 to 16): Chapter 11 will be of interest not only to basic researchers, but also to clinical scientists doing controlled trials. It is entitled *Disease Specific Targets* and highlights three general issues of importance to clinical research. The section on novel diagnostic approaches includes good discussions of quantitative sensory testing, skin biopsy, biomarkers, microneurography, imaging techniques, autopsies and drug challenges. The clinical trials section includes a discussion of innovations in trial design and addresses the issue of mechanism-based versus disease-based approaches, trials of concomitant analgesics and the need for long-term studies. The section on disease-specific targets discusses in detail the benefits of using models such as diabetic neuropathy, postherpetic neuralgia and others. The chapter concludes with recommending natural history

studies, early treatment studies, interdisciplinary interactions, the need for long duration studies, especially of opioids, the need for head to head trials and the importance of registration, timely publication and the publication of negative trials. Chapter 12 is entitled *The Role of Growth Factors in Painful Length-Dependent Axonal Neuropathies*. I have seldom read a better or more succinct account of the types of painful neuropathy than in the beginning of this chapter. It discusses at length two basic patterns that may account for pain in neuropathies. Although the chapter would have benefited from a summary section at the end, the table in part compensates for that. Chapter 13 discusses *Pain Related to Inflammatory, Infectious and Toxic Neuropathies – Mechanisms and Perspective on Treatment*. This chapter is a comprehensive discussion of the different types of HIV-associated neuropathies, the mechanisms of pain in antiretroviral toxic neuropathy and also of chemotherapy-induced neuropathies, such as cisplatin, taxanes and vincristine. Although the purpose of the chapter focuses on pathophysiological mechanisms, there have been some recent randomized controlled trials showing that tricyclic antidepressants do not relieve HIV-associated neuropathy but there is no discussion of these or any other published literature. Chapter 14 is entitled *The Depression Pain Complex: Overlap Between the Two Problems and Implications for Neuropathic Pain*. Three of the authors work for Lilly Pharmaceutical Company, which may explain the emphasis on duloxetine in the chapter, but it is a reasonable account of the relationship between pain and depression, epidemiological data on both, the contribution of serotonin and norepinephrine and although it is a good review of clinical studies, it does not include early research and the research in postherpetic neuralgia. It does not mention the dearth of comparative trials which are the best way of determining whether new drugs such as duloxetine and venlafaxine are any better than the older tricyclics, as we are led to believe by advertising. One of the conclusions could have been the crying need for comparative trials. Chapter 15 is entitled *Dissecting Molecular Causes of the Components of Chronic Neuropathic Pain Syndrome*. This chapter looks at the potential links among pain, mood, sleep and substance abuse disorders, molecular epidemiology of chronic neuropathic pain, genetics, quantitative sensory testing, measurement of neurotransmitters, brain imaging and environmental influences. It concludes that to better understand and treat the 'disease' of NP, we must use large prospective studies to determine causal relationships among pain, mood and substance abuse disorder. It concludes that preliminary evidence suggests that the risk of chronic pain in humans, as well as animals, may be partially determined by common genetic variants but cautions that because of the expense of large cohort studies researchers may need to piggyback their questions into other studies funded by more established researchers. It

also concludes that advances may be more rapid if there is a focus on more common neuropathic conditions and suggests the need for briefer measures of variables, such as sleep, mood and substance abuse. There follows an Appendix which will be of great use to those interested in genetics and pain. Chapter 16 deals with tailoring pharmacotherapy to diagnostic subgroups in NP. This is a succinct chapter that reviews current treatment options and provides a table of drugs that are approved in the United States. This might give the impression that treatment is limited to these drugs, but many patients are treated off-label with drugs such as tricyclic antidepressants and opioids. There are concise tables of investigational compounds for NP with approval for other diseases to stimulate investigators. There is a third table indicating newer approaches to the treatment of NP in terms of potential targets. Chapter 17 is entitled *Measurements and New Technologies*. The consensus is that new developments are held back because of limitations in these areas. Although numerous targets have been identified, validation has been difficult and as a result molecules are inappropriately rejected based on animal testing while other molecules that appear useful in animals are not effective in the clinic. The chapter addresses the issue of what NP is and the role of uninjured primary afferents, injured afferents and dorsal horn changes. It specifically addresses whether we should be targeting the disease or the pain and then addresses measurement and pain models and psychophysics. With animal models it addresses the issue of whether drug studies in animals predict efficacy in humans, whether withdrawal reflexes are a valid measure of pain in animals and the role of operant tests. There is a brief discussion of the chronicity of NP and opioid sensitivity and the placebo effect and of a variety of technologies such as functional brain imaging, DNA, gene screens and proteomics. The summary of the chapter is that there are no shortages of new technologies or new targets for pain treatment, but there is a pressing need for the development of new behavioural screening tests and reiterates that many molecules are inappropriately discarded or inappropriately studied and proceed to later phase testing and that 80% of centrally acting drug candidates ultimately fail. The conclusion is that if we discover new treatments it will be important to combine progress in basic science with better screening techniques in early phase human trials. Chapter 18 deals with brain imaging as a surrogate measure of pain in humans and animals. The chapter concludes that brain imaging in both humans and animals has great potential and can be used as a tool to examine the site of actions of new pharmaceutical agents and to provide an overview of brain areas affected by analgesic manipulation. Some caveats are expressed with regard to the possibility of false-negative imaging and the chapter concludes that the technology is advancing at a great rate in terms of spatial and temporal

resolution and sensitivity. Chapter 19 is entitled *Microarray Studies in Pain* and gives an overview with relevance to pain, describing them as powerful tools for the molecular analysis of tissues with the potential ability to assay the expression of every gene in a biological sample. Chapter 20 is entitled *Psychophysical Models of Neuropathic Pain*. This chapter focuses on the potential of human surrogate models of NP and explores the role of these models in translational research on mechanism based treatment. It concludes by stating that human surrogate models of pain are already very useful for the investigation of pharmacological mechanisms of action and therapeutic efficacy because they are based on the same assessment techniques used in clinical studies. Chapter 21 deals with psychophysical tests that characterize pain mechanisms and discusses their utility in aiding diagnosis, understanding mechanisms and matching treatment to mechanisms. Chapter 22 is about biomarkers in pain. The authors point out that correct usage depends on the principle of close association of a molecule or a pattern of expression of several molecules with the disease. The chapter is divided into sections on proteomic patterns and biomarkers in experimental pain, rheumatoid arthritis, osteoarthritis and NP syndromes. The authors state that it is too early to judge the results of these pilot studies, but based on experience in other fields, the authors are confident clinical pain studies will increasingly turn to this powerful technique for insight into pain mechanisms and better pain management. The final chapter is entitled *Animal Studies of Pain: Lessons for Drug Development*. The chapter give a thorough examination of the pros and cons of reflex measures and operant testing paradigms. The authors propose operant testing as an alternative to reflex testing.

In conclusion, this book is a valuable resource for both the basic and clinical scientist. It will probably be of more value to the former, but any clinician who wants to be current with the state of the art and to gain insight into future trends in basic and clinical research in NP will find a wealth of information here. The book is good value, as is usual for IASP publications.

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**P Beaulieu, ed. Pharmacologie de la Douleur. Les Presses de l'Université de Montréal, 2005. ISBN 2-7606-1951-6; 616 pages.**

Le docteur Merskey, rédacteur précédent de la revue *Pain Research & Management*, m'a demandé en décembre dernier d'écrire une brève revue en français sur l'ouvrage collectif de Beaulieu. Ma première réaction a été... encore un autre livre sur la douleur! Mille excuses au professeur Beaulieu et à ses 29 collaborateurs d'Amérique et d'Europe. Je dois immédiatement souligner que j'ai été enchanté par la facture de l'édition, la qualité du langage et des informations colligées. Ce recueil est, selon moi, le texte le plus à jour sur la pharmacologie clinique et fondamentale de la douleur. Il est accessible aussi bien au clinicien qu'au chercheur en formation ou à celui qui découvre, sur le tard, le monde de la gestion de la douleur. De plus, il sera une ressource de premier choix pour les vulgarisateurs scientifiques et communicateurs. Cet ouvrage contient des informations qui sont utilisables autant en Amérique qu'en Europe. Le professeur Beaulieu a su internationaliser les textes en s'assurant que les termes sont compréhensibles des deux cotés de l'océan Atlantique. Trop souvent les Franco-Canadiens utilisent des adaptations venant des États Unis et les Franco-Européens utilisent des termes nationaux qui réduisent la facilité des échanges.

Pour la deuxième édition, je formule quelques souhaits. Un chapitre sur la pharmacogénétique serait bienvenu; les connaissances actuelles contribuent à expliquer les effets secondaires ou le manque d'efficacité de certains analgésiques entre autre par l'action des cytochromes. Le chapitre sur les modèles animaux pour tester la douleur est excellent, l'équivalent chez l'humain est toutefois absent. Les chapitres 12 à 17 gagneraient à être regroupés sous une section « applications cliniques » bonifiée entre autre de chapitres nouveaux sur la douleur post-opératoire, les céphalées et douleur orofaciale, la douleur arthritique-musculosquelettique, les médecines alternatives et complémentaires de nature chimique-pharmacologique. Probablement due à des biais personnels, il m'apparaît pertinent d'ajouter des informations sur l'altération de la vigilance diurne par les analgésiques, sur l'action potentiellement délétère des opiacés sur le sommeil et les troubles respiratoires, ainsi qu'une brève section sur les différences raciales et le faible accès aux analgésiques dans les pays économiquement défavorisés. Ces derniers commentaires n'enlèvent en rien au plaisir que j'ai eu à lire ce livre qui sera disponible sur les rayons de mon département pour le bien des patients! Vivement j'en recommande la lecture à mes étudiants et à mes collègues cliniciens.

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**Mailis-Gagnon A, Israelson D. Beyond Pain: Making the Mind Body Connection. Viking Canada (Pearson Canada/Penguin), Toronto, 2003. ISBN 0472030825; 274 pages; \$25.00.**

In this book, Dr Mailis-Gagnon relates her own experience – indeed journey as a person and as a professional and investigator – in her work with patients with chronic pain. It is written well and interestingly, and is full of case histories, told in a sympathetic and engaging manner, of many pain sufferers she has dealt with over many years. It also describes the unique approach she has evolved in assessment and diagnosis of patients with apparently bizarre complaints. The book is warmly endorsed in the Forward by Dr Oliver Sacks, who had himself once experienced unexplained pain and sensory symptoms. Dr Sacks points out that the function of the central nervous system is far more complex than we might have imagined a few decades ago, and that the concept of ‘plasticity’ may have much relevance to phenomena such as phantom limb pain and neurologically unexplained pain disorders.

Dr Mailis-Gagnon has specialized in study of and treatment of patients with complex presentations and poor outcomes, and has evolved a protocol of extensive sensory testing and examinations using intravenous placebo and amytal. While these approaches may seem foreign to the usual practice of doctors, her recommendations for multidisciplinary and cognitive behavioural therapy in rehabilitation for chronic pain patients with psychological comorbidity is based on good evidence, and she is a respected clinician who has often had good results when to everyone else the case seemed hopeless.

The strong point of this book is her sense of warmth and good humour and optimism, and profound respect for her patients, no matter what their history or complaint. Her feistiness, that much characterizes her in reality, also comes across with her infectious good humour, and that gives great human interest to the narrative. Another strong point is the biopsychosocial perspective. There is a great variety of fascinating personal stories, even including that of Dr Mailis-Gagnon herself, and most patients will find patients’ stories that would speak to them.

Perhaps the greatest endorsement is that in the past two months three patients have come to me with this book in hand and have said that it was reassuring and helpful to read this, and that one or other patient story in it was particularly meaningful.

Clinicians involved in treatment of chronic pain, and especially clinicians who see patients with medically unexplained or ‘nonorganic’ symptoms, will find her approach and her concepts on this subject interesting and engaging.

It is not a textbook of diagnosis, of theory, or a how-to book, but it will likely appeal to patients who have chronic pain and who are looking for a way to understand that the biopsychosocial perspective is relevant and palatable for

them as patients. It will also appeal to clinicians who have struggled with interpreting medically unexplainable complaints in their pain patients.

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**Filligim RB. Concise Encyclopedia of Pain Psychology, 2005. Haworth Press, New York. ISBN 978-0-7890-1893-9/978-0-7890-1894-6; 204 pages; soft cover \$24.95, hard cover \$44.95.**

This short volume gives well referenced discussions of major topics in psychology with particular reference to pain. The statements made are clear and well supported. This is a well informed and interesting small volume, although inevitably not all topics covered can be dealt with to the same level of knowledge and skill. On the other hand, every item is clearly written and the overall approach is very balanced and reasonable.

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**McCracken LM. Contextual Cognitive-Behavioral Therapy for Chronic Pain, 2005. IASP Press, Seattle, Washington. ISBN 0-931092-83-3; 148 pages; \$67.00.**

Many people with chronic pain develop elaborate strategies to control their pain. These often involve avoidance of thoughts, activities and experiences that have been associated with increased pain or distress in the past. Paradoxically, in the long run, these strategies can restrict life enjoyment and the pursuit of meaningful goals. In the extreme, avoidance of pain can become one of the major organizing principles of daily life. This provocative new book argues that a more promising approach may be to help people with chronic, refractory pain create and experience meaningful, value-based lives despite ongoing pain. This is a powerful thesis, yet it is easy to imagine many patients and psychotherapists balking at it in favour of more traditional approaches which focus on pain control. However, as is cogently argued, waiting for complete pain relief before pursuing life goals may be unrealistic for many patients and may contribute to ongoing distress.

Dr Lance McCracken is a Consultant Clinical Psychologist and Clinical Lead of the Pain Management Unit, Royal National Hospital for Rheumatic Diseases,

Bath, United Kingdom. He is the sole author of this slim volume (148 pages) in the *Progress in Pain Research and Management Series*. Without question, Dr McCracken is the leading authority on the acceptance of pain. In this volume, he brings together several years of clinical and research experience on psychological approaches to pain and acceptance of pain to propose a shift from traditional cognitive behavioural pain management towards a more integrated, contextually based approach. The first chapter of the book describes the magnitude of the problem of chronic pain and highlights the need for multidisciplinary intervention. Several chapters follow which provide an excellent overview of behavioural and cognitive behavioural theories and management strategies. The second half of the book outlines the author's functional contextualist approach which he describes as an integration of some of the key features of operant and cognitive behavioural approaches with new features such as acceptance, mindfulness, spirituality, self and willingness.

The theoretical description is supplemented with discussion of various treatment goals and group therapy techniques. However, the volume is not a treatment manual, so implementation and clinical scenarios are not described in detail. The line between describing a psychotherapeutic approach and providing a treatment manual is blurred at times; for instance, when patient activity sheets are provided. Nonetheless, it is my opinion that the complexity of this approach would require specialized training – for instance, in mindfulness meditation – and that the information provided in the book is insufficient to allow adoption as a therapeutic tool. Ample references to empirically supported treatments, such as Acceptance and Commitment Therapy, which inform the proposed approach are provided.

As a pain psychotherapist and researcher and a student of insight meditation, there are many additional topics

that I would have liked to see Dr McCracken tackle. For instance, he focuses only on adults with chronic, nonmalignant pain; it would have been interesting to consider how the approach could be tailored to special groups including adolescents, the elderly and those with progressive disease. In addition, there is only superficial consideration of the role of the therapeutic relationship and little discussion of working with family members. Developing a new relationship with one's pain and letting go of many years' avoidance and control undoubtedly trigger changes throughout the patient's life, both positive and negative, but this issue is not addressed. Perhaps I am asking too much from a book that introduces a new approach and instead will look forward to these topics being addressed as the approach matures.

On the whole, I found Dr McCracken's book to be a valuable, thought-provoking resource. It is very well written, and the author's compassion for and understanding of people with chronic pain is evident. I highly recommend it to anyone involved in the psychology of chronic pain, whether in research or the provision of clinical services.

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