PAIN MANAGEMENT

Pain by name, pain by nature

Pain, which is often chronic and unremitting, is the leading concern of patients with rheumatic diseases. Moreover, relief of pain is often the main reason why these patients seek medical attention. Despite this, the major focus of rheumatologists has not been pain relief, but rather control of inflammation, prevention of structural damage, and preservation of physical function. Although pharmacologic therapies are available that can effectively treat other aspects of rheumatic diseases, such as inflammation and bone erosion, patients are often left with unrelieved pain. This represents a major unmet medical need that has a considerable impact not only on a patient's quality of life and physical function, but also on healthcare resources. This Focus issue of *Nature Reviews Rheumatology* on pain management highlights the latest developments in pain-relief approaches for chronic musculoskeletal pain and discusses strategies that can be used to tackle the numerous management challenges in this field.

Even though it is well documented that in early rheumatoid arthritis the principle cause of loss of physical function is pain, focusing on achieving effective pain relief is difficult; in general, rheumatologists tend to believe that control of inflammation will alleviate pain and, therefore, devote little attention to understanding and controlling chronic pain *per se*. In this regard it is noteworthy that specific outcome measures in clinical trials of antirheumatic therapies, including the number of painful joints and levels of generalized pain, are standard, even when the agent tested has no intrinsic analgesic properties. Indeed, patients with musculoskeletal pain syndromes are often referred elsewhere by rheumatologists, even though these syndromes are common and often debilitating. Why is this the case and how can rheumatologists improve the management of pain in patients with musculoskeletal disorders? These questions are not just academic and ethical ones, but are also highly practical in an age when multiple consultations are often precluded. Failure to address issues of pain management could result in a large number of patients, who could best be managed by rheumatologists, being cared for by practitioners who focus on the relief of pain, but who might be less knowledgeable about rheumatic diseases.

One issue with pain management relates to education and knowledge. In 'Art of War', the Chinese philosopher Sun Tzu warned that, "If you know yourself but not your enemy, for every victory gained you will also suffer a defeat." How can rheumatologists focus on the alleviation of pain if they do not truly understand the nature of this multifaceted phenomenon? Until recently, pain management was not a central feature of most rheumatology training programs. Although the emphasis on it is greater now, the amount of time and energy devoted to a detailed understanding of pain and its management is still small. Even defining pain is not straightforward: the International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". This one-sentence description is obviously broad and is insufficiently mechanism-based to help understand the many aspects of pain experienced by patients with rheumatic diseases. The experience of pain is notoriously difficult to define, explain and understand, so it is hardly surprising that it is difficult to manage. As David Borenstein explains in his Perspectives article on page 227, in many rheumatic diseases, including osteoarthritis, the source of nociceptive pain is unknown. In addition, chronic pain is complex, comprising nociceptive, neuropathic, as well as central pathways. Understanding the interplay of these pathways and the appropriate approach to deal with the entire pain construct is just one of the many issues that make pain such a difficult management problem for rheumatologists.

A second issue is the tendency of rheumatologists to focus on targeting the inflammatory processes that result in tissue damage, rather than looking at the patient as a whole and taking into account neural pathways that can result in sensitization to pain, as well as emotional and psychological factors. The concepts of 'disease' (or the pathologic pathways that cause tissue damage) and of 'illness' (or the individual patient's response to disease) are complex and not well understood. Although sensitization of peripheral and central pain pathways by inflammatory mediators is clearly part of rheumatic diseases, the experience of chronic pain in these patients is much more complicated. Francis J. Keefe and Tamara J. Somers argue on page 210 that recognizing the involvement of emotional, cognitive, behavioral and societal variables can help rheumatologists understand the nature of the pain experienced by individuals. In addition, this approach could result in the development of novel psychological treatment strategies that might impact on the illness experience in some patients. However, at present, data on the efficacy of psychological treatments from clinical trials is limited. To increase the effectiveness of these programs, it will be necessary to understand how they work, to define ways to test them in clinical trials and also to develop ways of implementing any effective treatments in clinical practice.

> "...chronic pain is complex, comprising nociceptive, neuropathic, as well as central pathways"

Peter E. Lipsky is the Editor-in-Chief of *Nature Reviews Rheumatology*. **Jenny Buckland** is the Editor of *Nature Reviews Rheumatology*.

Competing interests
The authors declare no competing interests.

Yet another complicating factor is that there are limitations to the currently available pharmacological therapies for pain, which include NSAIDs, cyclo-oxygenase 2 inhibitors (coxibs) and opioids: they can be associated with adverse effects, tolerance and addiction issues, and in some people they simply do not work (or stop working). The reasons for this are varied, but it appears that loss of effectiveness does not always result from the drug losing its action (that is, coxibs continue to inhibit cyclo-oxygenase 2), but rather the pathway, for some reason, becomes less important. In many cases, drugs for chronic conditions stop working because the patient becomes tachyphylactic, or stops taking them, or because the nature of the patient-experienced illness changes. As discussed in the Review on chronic opioid therapy by Leslie J. Crofford on page 191, drugs need to be prescribed in a way that is safe and the benefits outweigh the potential risks associated with their use. Dr Crofford raises the issue of opioid-induced hyperalgesia—whereby pronociceptive pathways are activated by exogenous opioids which can result in central sensitization to pain—as an issue of importance to physicians treating chronic musculoskeletal pain. This phenomenon has mostly been studied in animal models, although there are some data from prospective clinical studies of people who received opioids for pain-relief, and is not fully understood. Of relevance to the practicing physician is the need to distinguish opioid-induced hyperalgesia from tolerance, as both of these processes could lead the clinician to increase the dose of opioids, but the biology behind them and the outcome for the patient could be very different.

With these three caveats in mind, what is the optimum treatment approach for the many manifestations of rheumatic diseases including pain? Developing individualized programs that combine pharmacological therapies that target the appropriate inflammatory pathways, an analgesic program directed toward the appropriate nociceptor, neuropathic and central neurologic pathways, and nonpharmacological approaches, including targeted surgery, self-management strategies, educational programs and exercise regimes, could be ideal. Obviously, the effects of such individualized programs are exceedingly difficult to validate with current clinical trials methodologies. One challenge in rheumatology, therefore, is to develop the means to validate the best approach to managing chronic pain is patients with rheumatic diseases. Only with good validation paradigms will new treatments be accepted as standard therapy and funded accordingly. For example, self-management approaches for patients with chronic low back pain or OA, which can include both exercise and educational programs, are outlined by Stephen May on page 199; the effectiveness of these approaches and barriers to successful application are discussed. As emphasized in this article, a multidisciplinary validated approach to pain involving a team of healthcare professionals centered on an understanding of individual patients' needs could be the best way forward.

Although the barriers for acceptance and funding of surgical procedures for pain control are usually lower than those for pharmacologic therapies, it is essential for the rheumatologist to be aware of surgical options in order to be in a position to integrate these adjunctive strategies into a comprehensive program of pain management. As an example, surgical options for patients with shoulder pain in whom conservative approaches have failed are discussed on page 217 by Salma Chaudhury, Stephen E. Gwilym, Jane Moser and Andrew J. Carr.

Rheumatologists face considerable challenges in developing and implementing novel treatment strategies that help patients with rheumatic disease to manage their pain effectively. We hope that the articles in this Focus issue of *Nature Reviews Rheumatology* will stimulate thought, promote discussion, and possibly encourage a more integrated approach to testing the validity of these approaches and incorporating them, when appropriate, into the management of patients with musculoskeletal pain.

doi:10.1038/nrrheum.2010.38