Editorial

The fibromyalgia conundrum

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This monothematic issue of *Clinical and Experimental Rheumatology* dedicated to fibromyalgia is the first of an annual issue on this subject. That a whole issue of the journal is being applied to this subject annually is emblematic of the growing importance of fibromyalgia and central pain mechanisms in rheumatology and in clinical medicine in general and speaks to the increasing number of studies and publications about this condition. Yet unlike disease states such as rheumatoid arthritis or spondyloarthropathy, wherein research on pathophysiologic mechanisms, clinical manifestations, assessment, and treatment is well established and highly regarded in rheumatology, the same is not true for fibromyalgia, which is still struggling to become a respectable area of research and clinical care within a medical specialty that the condition can call "home". As exemplified by the articles in this issue, on topics ranging from specific genetic markers in fibromyalgia, to disease risk factors, to the psychometric properties of assessment tools, to treatments, the state of research respectability is changing. Indeed, when one tracks articles on fibromyalgia in PubMed, there has been a surge of research in recent years which appears to be synergistically increasing our understanding of the illness and the development of rational approaches to its assessment and management.

A brief review of the history of fibromyalgia demonstrates how far we have come and the importance of very recent developments in our understanding and treatment of fibromyalgia. Although descriptions of illness characterised by chronic widespread pain, fatigue, sleep disturbance, and mood disorder go back to Biblical times, designations such as "muscular rheumatism" and "neurasthenia" were employed in the 1800s to characterise the condition we now know as fibromyalgia (1). Sir William Osler, in Principles and Practice of Medicine (1896), writes "Neurasthenia appears to be the expression of a morbid, unhealthy reaction to stimuli acting on the nervous system" and goes on to note that "sleeplessness is a frequent concomitant"…"the majority are moody or depressed"…"the aching pain in the back of the neck is the most constant complaint"…"and there are spots of local tenderness in the spine"(2). In 1904, Gowers coined the term "fibrositis" based on the mistaken notion that there was evidence of inflammation in musculoskeletal sites of tenderness (3). Through much of the 20th century, this condition was alternately thought of as a true inflammatory condition or more commonly, a form of psychogenic rheumatism observed in depressed females or soldiers traumatised psychologically by war.

In the 1970s, Moldofsky and Smythe described specific abnormalities in slow wave deep sleep electrophysiologic patterns in "fibrositis" patients and also considered the term a misnomer, since no peripheral inflammation could be documented, thus ushering in the current era of understanding of the neuropathophysiologic mechanisms of the condition (4). Yunus, in 1981, described the multi-symptom complex, including fatigue, sleep disturbance, and headache, in addition to chronic widespread pain and tenderness which characterises the syndrome (5). In 1990, a group of investigators led by Fred Wolfe published the ACR classification criteria of chronic widespread pain and 11/18 tender points to establish a standard for research work in the field. It was recognised that the condition could occur on its own, or it could be a significant accompaniment of other diseases, such as rheumatoid arthritis, lupus or other chronic diseases, suggesting that central pain is part of the clinical experience in a number of disease states. Subsequently,

a number of investigators in the US and Europe began to describe a number of neuropathophysiologic findings which were different in fibromyalgia patients compared to control subjects. Several centres described elevations of substance P, a nociceptive neurotransmitter, in cerebrospinal fluid of fibromyalgia patients as well as deficiencies in certain pain modulatory biogenic amines(6). Gracely and colleagues demonstrated cortical and subcortical augmentation of pain processing using functional magnetic resonance imaging in fibromyalgia patients (7, 8). Harris, Clauw and colleagues at the University of Michigan have performed multiple studies demonstrating changes in glutamate (nociceptive) processing in the central nervous system as well as differences in mu-opioid receptor function in fibromyalgia patients (9). Kosek, Staud and others have demonstrated deficiencies in inhibitory pain pathways, partly related to a deficiency of norepinephrine and serotonin function (10). Manuel-Lavin, Crofford, Holman, and Woods, among others, have described dysautonomia and neurohormonal abnormalities such as dopamine dysregulation (11). Diatchenko, Maixner, Buskila, Russell, and others have described specific genetic profiles, many related to genes which control sensory processing pathways, which are more common amongst fibromyalgia patients, as well as patients with related central amplification syndromes such as irritable bowel syndrome or other chronic pain states (9). Several centres have identified the concerning finding that chronic pain states, including fibromyalgia, appear to result in diminished grey matter volume of the brain (12). The clinical correlates of this observation and the potential for reversibility have not yet been determined. In recent years at both rheumatology and pain meetings, there are whole oral abstract sessions devoted to the emerging neuroscience of fibromyalgia in which investigators from both sides of the Atlantic are sharing their findings.

In parallel with discoveries in neuroscience, a number of other areas of work have been advancing simultaneously. In the last decade, neuromodulatory drugs which specifically target the dysregulated neural pathways in fibromyalgia and other chronic pain states, and which are better tolerated than some of the more traditional pain medicines, have been developed and show efficacy in large controlled trials in fibromyalgia patients (13-17). Not only are these drugs addressing the clinical domain of pain, but they are also demonstrating benefit for domains such as fatigue, sleep disturbance, and dyscognition. In conjunction with these trials, there has been a great deal of interest in the application and development of reliable and feasible measures of symptom severity and improvement of the various clinical domains of fibromyalgia. Specifically, the OMERACT (Outcome Measures in Rheumatology Clinical Trials) association has convened an ongoing fibromyalgia working group which over the last six years has conducted patient focus groups, analysed clinical trial data, and developed consensus amongst clinician-investigators to establish a "core set" of clinical domains, such as pain, tenderness, fatigue, and sleep disturbance which should be measured in fibromyalgia studies. This group has also evaluated the performance of outcome measures used to assess these domains employing the OMERACT "filter" (truth, discrimination, and feasibility) (18-21). At the current time, the majority of these measures are patient-reported outcomes, although we are beginning to see functional neuroimaging techniques beginning to be employed. There has also been a significant increase in research on non-pharmacologic approaches to the treatment of fibromyalgia, including exercise and psychosocial modalities such as cognitive behavioural therapy. It is acknowledged that there are often complicating psychosocial issues which beset individuals with fibromyalgia which effect the quality of their family, social and work relations as well as their relationships with health care providers. In this year's ACR (2009) meeting, Fred Wolfe introduced a new *diagnostic* criteria for fibromyalgia, intended to complement the 1990 classifcation criteria. Based on a study of more than a 1000 fibromyalgia and control patients with a pain condition, it was demonstrated that using a quantitative index of chronic widespread pain coupled with a quantitative symptom severity index (fatigue, sleep disturbance, cognitive dysfunction and other symptom domains), both patient reported indices, that a diagnosis of fibromyalgia could be made with a high degree of sensitivity and specifity (22). It is anticipated that this diagnostic criteria will facilitate diagnosis of, or at least suspicion about, fibromyalgia by primary care and other clinicians who are not particularly knowledgeable about the tender point exam. It also acknowledges the importance of the varied symptom domain of fibromyalgia (23).

Given the current state of maturity of the science of pathophysiology, assessment and treatment of fibromyalgia, why is there still skepticism about the validity of the construct of the condition, resistance by some rheumatologists to be willing to evaluate and/or manage patients with fibromyalgia, and significantly, reluctance of the European drug regulatory agency (EMEA), to give formal approval to three medications (pregabalin, duloxetine, and milnacipran) now approved in the US for the treatment of fibromyalgia based on substantial clinical trial data? One key point has to do with the rate of development and dissemination of knowledge and the factors which determine how new knowledge changes ingrained assumptions. Much of our current knowledge about the mechanisms of fibromyalgia have emerged in the last decade and indeed, in the last few years. Yet many clinicians have ingrained impressions about the psychoemotional substrate of fibromyalgia from years prior to this time. Unless a clinician is curious and motivated to learn about new pathophysiologic data and neuromodulatory treatment effects, or has an unopen mind, this knowledge will not be accessible to them. Numerous analogies can be suggested regarding the evolution of our understanding of diseases which now are well-accepted regarding pathophysiology and treatment. Another factor is the discrepancy between symptom severity and absence of tissue pathology (other than the emerging data about grey matter volume). How

can a condition which can cause such suffering and disability without tissue damage be taken seriously? Numerous other significantly impactful conditions share this feature, including irritable bowel syndrome, headache, depression, and others. These are generally well accepted, have a medical "home" (gastroenterology, neurology, psychiatry), and have a plethora of approved drugs for treatment, to try to lessen the burden of symptomatology on the individual and society. In time, this will be true of fibromyalgia as well. Indeed, research is showing overlapping genetic and pathophysiologic features amongst these conditions. Some clinicians feel that patients with fibromyalgia are malingering or are simply demonstrating somatic manifestations of depression. As in any disease, there will be patients with that disease who have features of hysteria, are malingering, and do have significant depression, all of which magnify their symptom expression. Some patients with fibromyalgia do have those psychoemotional features, especially if they have been frustrated by years of living with a condition in which there has been diagnostic uncertainty and for which there has been little effective treatment. These may be the individuals that stick out in a clinician's mind as being truly representative of the condition. This results in unfair characterisation of the great majority of patients who are more quietly suffering, are motivated to improve, and who are not malingering or depressed. Some clinicians fear that a diagnosis of fibromyalgia provides a patient with a medical "badge" that leads to greater consumption of medical resources and greater illness behaviour. In fact, the preponderance of studies show the opposite effect, *i.e*. that once a diagnosis of fibromyalgia is made, that diagnostic test seeking and medical resource consumption actually decrease and patient satisfaction with health increases.

This issue of the journal is part of an effort to disseminate some of the interesting research findings from centres in Europe and North America on fibromyalgia. It is hoped that this knowledge will help to increase our understanding, openness and interest in the consideration, evaluation, and treatment of this vexing problem for patient and clinician alike. In time, it is our hope that with further research and understanding, we will be on a better foundation to effectively diagnose and assess, both with patient reported measures as well as biomarker such as functional neuroimaging, as well as treat with targeted therapies and multidisciplinary treatment, fibromyalgia and related syndromes characterised by central sensory dysregulation.

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