# CHRONIC PAIN: WHERE THE BODY MEETS THE BRAIN

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## ABSTRACT

Chronic musculoskeletal pain is one of the most intractable clinical problems faced by clinicians and can be devastating for patients. Central pain amplification is perceived pain that cannot be fully explained on the basis of somatic or neuropathic processes and is due to physiologic alterations in pain transmission or descending pain modulatory pathways. In any individual, central pain amplification may complicate nociceptive or neuropathic pain. Furthermore, patients with somatic symptom disorders may have alterations in their psychological or behavioral responses to pain that contribute significantly to the clinical presentation. Genetic, physiologic, and psychological factors associated with central pain amplification are beginning to be understood. One important contributor to chronic pain is perceived stress and stress response systems. We and others have shown a complex relationship between the physiologic stress response and chronic pain symptoms. Unfortunately, treatments for chronic pain are woefully inadequate and often worsen clinical outcomes. Developing new treatment strategies for patients with chronic pain is of utmost urgency. This essay provides a framework for thinking about chronic pain and developing new treatment approaches.

## INTRODUCTION

Perhaps no other symptom induces such fear and loathing as chronic pain. Most images of pain are focused on portraying negative emotions and the intrusive nature of the pain experience (Figure 1). Clinicians as people fear chronic pain, a symptom that demands attention and intrudes into every aspect of a person's life. Clinicians also loathe chronic pain, perhaps the symptom that brings more patients into our practices than any other but also the symptom most likely to make us feel helpless as healers.

The International Association for the Study of Pain defines it as "An unpleasant sensory and emotional experience associated with actual or

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FIG. 1.

potential tissue damage, or described in terms of such damage" (1). Pain is always subjective in that each individual learns the application of the word through their own experiences. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore a negative emotional experience. Many people report pain in the absence of tissue damage or any likely pathophysiological cause, and there is usually no way to distinguish their experience from that due to tissue damage. Thus pain has several important dimensions: a sensory dimension — where does it hurt and how much does it hurt; an emotional dimension — how unpleasant is the experience; and a cognitive dimension — how do we interpret the pain based on our previous experience, does it cause fear and anxiety, and how do we respond to the threat posed by pain. Any given individual could report a pain experience that is not easily understood by the clinician they encounter and to whom they turn for explanations and relief. Further, there is no distinct boundary between normalcy and disease. Most of us transiently experience pain symptoms. Many of us have chronic symptoms that do not rise to a level that interferes with function. The transition from normal to sick is a quantitative deviation that involves both primary (biologic) and secondary (psychological, social, and cultural) risk factors.

## CLASSIFICATION OF CHRONIC PAIN

Acute pain is likely to arise through tissue damage, termed nociceptive pain or "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors." That is, a signal is generated from abnormal peripheral tissues and transmitted by the dorsal horn pain transmission neurons to the regions of the brain that receive this input. Neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system." This requires a demonstrable lesion (seen on imaging, neurophysiology tests, biopsy results, laboratory testing) or a disease (stroke, vasculitis, diabetes, shingles) that satisfies established diagnostic investigations. Many times, however, the extent or intensity of the pain complaint cannot be easily explained by histological, anatomical, or biochemical processes. In these situations, we may invoke central amplification of pain or centrally maintained pain (2,3). The physiology of central amplification of pain is only now becoming understood, thanks in large part to advances in imaging (4).

Chronic pain is usually defined as pain lasting more than 3 months and almost certainly has some, albeit variable, element of central sensitization. However, any mechanistic combination — nociceptive, neuropathic, and central — may be present in a given individual. Chronic pain is a complex sensory and emotional experience that varies widely between people depending on the context and meaning of the pain and the psychological state of the person (5). Cognitive and emotional factors have a critically important influence on pain perception and these relationships lie in the connectivity of brain regions controlling pain perception, attention or expectation, and emotional states. Imaging studies have confirmed that activity of afferent and descending pain pathways are altered by attentional state, positive emotions, and negative emotions among many other factors unrelated to the pain stimulus itself. The physiology of central pain amplification at the level of the brain takes into account these important connections. There are now numerous studies that demonstrate that patients with chronic pain have alterations in brain regions involved in cognitive and emotional modulation of pain (5). This complex interplay may explain why patients with long-term chronic pain develop anxiety and depression, but also why those with cognitive distortion and psychological distress are at increased risk for chronic pain and central amplification of pain.

Chronic regional pain is present in 20% to 25% of the population and chronic widespread pain is present in approximately 10% of the population (6). Those patients with one pain condition are more likely to

develop another, more centralized form of pain. For example, patients with inflammatory or degenerative joint disease, for example, are almost four times as likely to also have fibromyalgia, the prototypical musculoskeletal central pain amplification syndrome (7). Centrally maintained pain, in contrast to nociceptive or neuropathic pain, is usually multifocal, difficult to precisely localize, moves from site to site, and may have variable pain descriptions.

Chronic pain syndromes, such as chronic headaches, temporomandibular disorder, fibromyalgia, irritable bowel syndrome (IBS), interstitial cystitis/irritable bladder, pelvic pain, and others, cluster together in an individual (8) (Figure 2). Often times, chronic pain syndromes wax and wane over time with one or the other dominant at a given point in time. It is not unusual, for example, for a patient to have a visceral pain syndrome, such as IBS dominate the overall symptom profile for a time then recede as fibromyalgia symptoms become more prominent. Chronic pain also clusters with other somatic symptoms including fatigue, unrefreshing sleep, dyscognition, and mood disturbances. We have shown alterations in sleep (9−11) and cognitive function (12,13) in patients with fibromyalgia. Other clinical syndromes, such as chronic fatigue syndrome/myalgic encephalomyelitis, have musculoskeletal pain as part of the diagnostic features. This leads to the frequent presence of multiple diagnoses and multiple providers interacting with a given patient, potentially leading to multiple testing that may increase anxiety and multiple drug treatments that may interact or cause adverse effects.

FIG. 2.

## BODY AND BRAIN: A HISTORICAL VIEW OF THE CHRONIC PAIN EXPERIENCE

There is much in the medical literature regarding the interplay between musculoskeletal pain and psychological distress, although only a few of these will be discussed. One starting point is the description of "psychogenic rheumatism" where one of the earliest case series was recorded in 1946 by Nobel Laureate Philip S. Hench and Edward W. Boland as they describe the characteristics of US Army veterans returning from war (14). Psychogenic rheumatism was one of the more common diagnoses, affecting approximately 20% of patients in specialized rheumatic disease centers. According to their report, "Psychogenic rheumatism — the musculo-skeletal expression of functional disorders, tension states, or psychoneurosis — is one of the commonest causes of generalized or localized aches and pains in muscles and/or joints in either civilian or military life." They identify that this condition may occur either alone, or as an overlay to rheumatoid arthritis or fibrositis, their term for soft tissue rheumatic disorders such as bursitis or tendonitis. They went on to describe that primary fibrositis "puts its victims at the mercy of changes in *external* environment: thus weather, heat, cold, humidity, rest, exercise, etc. characteristically influences most of them for better or for worse." On the other hand, psychogenic rheumatism "puts its victims at the mercy of changes in the *internal* environment: thus their symptoms may vary with mood or psyche, pleasure, excitement, mental distraction, worry, or fatigue." The description of psychogenic rheumatism included an attitude that was tense, anxious, defensive, and antagonistic. The chief symptoms were described as burning, tightness, weakness, numbness, tingling, queer or tired sensations that were often continuous day and night. They also describe severe fatigue causing disability, worsening of symptoms during and after exercise, and a "touch me not" reaction to examination.

Arthur J. Barsky and Jonathan F. Borus describe "functional somatic syndromes" characterized by higher levels of symptoms, suffering, and disability than by consistently demonstrable tissue abnormality (15). These authors indicate that the symptoms common to the functional somatic syndromes include fatigue, weakness, sleep difficulties, headaches, muscle aches and joint pain, problems with memory, attention, and concentration, nausea and other gastrointestinal symptoms, anxiety, depression, irritability, palpitations and racing heart, shortness of breath, dizziness or light-headedness, sore throat and dry mouth are highly prevalent in the population in general. Furthermore, patients often meet the criteria for other syndromes in

part because of the overlap in diagnostic criteria. In their analysis, these authors implicate "four psychosocial factors that propel symptom amplification including the belief that one has a serious disease, the expectation that one's condition is likely to worsen, the sick role including the effects of litigation and compensation, and the alarming portrayal of the condition as catastrophic and disabling" (15). The biological process of selecting sensations believed to have pathological significance for conscious attention lies in the realm of cognitions around these sensations and, certainly, pain is a symptom often selected for significance. There is also often an influence of negative memory of past symptoms and expectations of future symptoms that may play a role in the cognitive amplification processes.

More recently, Frederick Wolfe has been a proponent of the term "polysymptomatic distress" that incorporates multifocal musculoskeletal pain and neuropsychological symptoms of fatigue, unrefreshing sleep, dyscognition, and other functional somatic syndromes into a quantitative scale that allows for a flexible and continuous application in patients with any rheumatic disease and in the general population. It is clear from his work that individuals can have a variable degree of polysymptomatic distress that influences clinical outcomes no matter what other diagnoses may be present (16).

The American Psychiatric Association in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) has replaced the previous categories of somatoform disorder, hypochondriasis, pain disorder, and undifferentiated somatoform disorder with "somatic symptom disorder (SSD) with predominately somatic complaints" and "SSD with pain features" (17). This diagnosis is characterized by "distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms." Importantly, the previous requirement that symptoms had to be medically unexplained is removed and psychological symptoms surrounding the somatic symptoms have been added. These include excessive thoughts, feelings, or behaviors related to somatic symptoms or associated health concerns as manifested by rumination and/or high level of anxiety about health or symptoms and/or excessive time and energy devoted to symptoms or health concerns.

In all these ways of thinking about chronic pain and its associated multiple somatic symptoms, there is an underlying theme of the inability to objectively verify the symptoms expressed by the patient (Figure 3). Most of these frameworks explicitly indicate that chronic pain is associated with abnormal ways of perceiving and reacting to sensory information. Precisely because of the inherent subjectivity of


FIG. 3.

the symptoms and the observation that the symptoms are amplified beyond what is viewed as "normal," the clinician is placed into a situation that requires a judgment about the veracity of patient reports. This most uncomfortable position is augmented because the treatments available for chronic pain, particularly the use of opioid analgesics, are not effective and can be addictive, misused, abused, and diverted (18).

## GENETIC RISK AND ENVIRONMENTAL TRIGGERS FOR CHRONIC PAIN

An individual's risk for developing central pain amplification might be predicted by a personal or family history of chronic pain and, by virtue of shared genetic risk factors, anxiety and depression. Enormous strides have been made in the understanding of the genetics of pain. Pain sensitivity is strongly genetic in that it differs within inbred mice and rats and strongly runs in families in humans (19). Pain sensitivity, or the response to acute psychophysical testing, is present in a Bell shaped curve in the normal population (20).

A number of genes, including such genes as ion channels and genes in the monoamine metabolic pathway, are associated with pain sensitivity and there is imperfect overlap between these genes and chronic pain conditions. This may be related to the multiple overlapping pathways between pain and psychological responses to pain. For example,

two major neurotransmitter pathways have been repeatedly associated with musculoskeletal pain (19). The first is the adrenergic pathway, in which *COMT*, the gene encoding the enzyme catechol O-methyltransferase that is responsible for the catabolism of catechol neurotransmitters such as epinephrine, norepinephrine, and dopamine, is the most frequently associated with chronic musculoskeletal pain conditions. Most studies of *COMT* report an increased risk of chronic pain associated with a Val159Met (rs4680) that encodes a protein with lower enzymatic activity (19). More extensive studies have expanded the functional locus to three major haplotypes that modify expression and activity of the enzyme thus conferring low- and high-risk phenotypes for acute pain sensitivity as well as risk for developing chronic pain (20). Additional genetic variation in the $\beta_2$-adrenergic receptor gene (*ARDRB2*; rs1042713 and rs1042714) has been associated with an increased risk of fibromyalgia and chronic widespread pain. Haplotype variants that regulate $\beta_2$-adrenergic receptor expression and internalization are associated with differences in susceptibility to chronic pain (21). The second pathway associated with chronic pain syndromes is the serotonin pathway. Specific genes include the 5-hydroxytryptamin receptor 2A (*HTR2A*) and 5HT transporter (*SLC6A4*) (22−24). A 44-base pair insertion/deletion polymorphism in the promoter region of *SLC6A4* is most frequently associated with risk of chronic pain conditions (19). These genetic pathways are associated with "endophenotypes" or intermediate measurable phenotypes that are present in patients with chronic pain. These include autonomic dysregulation, altered pain processing and modulation, sleep dysfunction, and anxiety in the case of the adrenergic pathway (19). Personality and affective traits such as somatic awareness, depression, and anxiety have been associated with genetic variation in the serotonin pathway and are associated with risk for chronic pain (19).

It is quite clear that experiences or environmental triggers can be the proximate cause of chronic pain (that is, acute pain can transition to chronic pain). One interesting example is that of post-infectious IBS. Risk factors for developing IBS following infectious enteritis (which occurred in 15% of affected individuals) were female sex, younger age, prior anxiety/depression, and fever or weight loss during the acute enteric illness (25). However, even in this example in which a clear triggering event can be studied in a population, psychosocial factors are important risks. A history of childhood stress and current psychosocial stress increases the risk for developing chronic centrally maintained pain (26). In many longitudinal epidemiologic studies, chronic

pain and other somatic symptoms can be predicted by childhood abuse and traumas, low educational attainment, social isolation, depression and anxiety (27) (Figure 4). In a population-based study to determine psychosocial factors that predicted new-onset chronic widespread pain, investigators identified a random sample of subjects from socio-demographically disparate backgrounds then identified more than 3,000 who did not have pain at baseline and more than 300 that had new widespread musculoskeletal pain at follow-up examination (26). The strongest predictors were premorbid somatic symptoms, illness behaviors, and sleep problems. In another community-based study, perceived physical and emotional trauma as precipitating factors for fibromyalgia were associated with health-care seeking rather than pain severity (28). One can speculate both intrinsic factors and learning around the affected organ as important for the maintenance of symptoms. The biopsychosocial model of pain posits that pain experience and its impact of the individual is a function of interacting combinations of nociceptive input; psychological processes including beliefs, coping repertoire and mood; and environmental contingencies that would include family, community, and cultural rules or expectations (29). All of these factors are likely to play a key role on the clinical expression and health impact of chronic pain.

## STRESS, AROUSAL, AND CHRONIC PAIN

Because development of centrally mediated chronic pain is associated with stressful events and symptoms often wax and wane depending on perceived stress, there have been many studies focused on stress and stress response systems in patients with these syndromes. Our

FIG. 4.

original studies focused on the hypothalamic-pituitary-adrenal axis (HPA) in chronic pain and fatigue and we have demonstrated alterations in the dynamic function of this system (30,31). Because of the dynamic nature of stress and response, we have spent considerable effort modeling the function of the system in patients with chronic pain (32,33). We have found that the modeled stress-arousal parameters of HPA axis function may be related to symptom clusters such as fatigue-predominant or pain-predominant. Furthermore, somatic symptoms increase when, during the nocturnal period, cortisol is leaving the system at a faster rate than it is being produced (32). Studies in this realm have been highly variable likely due to the difficulty in defining phenotypes and comorbidities that may dramatically influence the physiology of the stress-arousal system.

We have also investigated the function of the autonomic nervous system (ANS) as affecting sleep and fatigue. Many investigators have discussed alterations in the sympathetic nervous system in patients with fibromyalgia and chronic fatigue syndrome (34). We found similar alterations in heart rate variability and also found peripheral effects of altered vascular reactivity during exercise that may be related to ANS function (9,35). The two branches of the ANS, however, have antagonistic effects on autonomic arousal. Arousal is under tonic inhibitory control of the parasympathetic branch via the myelinated vagus nerve (termed the "vagal brake" or "parasympathetic maintenance"), which allows for efficient upregulation of arousal via parasympathetic reduction (or "vagal withdrawal") (36). Parasympathetic maintenance promotes calm engagement, whereas vagal withdrawal facilitates quick escape from danger. Fibromyalgia and temporomandibular disorders are linked to higher baseline sympathetic activity or predominance, especially at night, and lower baseline parasympathetic activity. With regard to ANS reactivity in these disorders, some evidence points toward blunted sympathetic responding coupled with greater increases in arousal, from which one might infer greater parasympathetic reduction in response to the environment. We recently reported an exaggerated parasympathetic decline in a non-threatening situation, which was related to negative physical and psychosocial outcomes (36). This exaggerated response is associated with hypersensitivity to environmental danger and is a marker of emotional lability.

## SELF-REGULATION IN CHRONIC PAIN

It is often stated that illness behaviors accompany chronic pain. Successful adaptation to chronic pain conditions may depend on an

individual's ability to self-regulate, that is, ability to exercise control or guide and alter reactions and behaviors. The ability to self-regulate varies across people and situations, and self-regulatory strength appears to be an individual difference and a limited resource that can be fatigued (37). We hypothesized that patients with chronic pain may display adverse health behaviors because chronic pain may deplete this important resource. Experimentally, this can be measured by the ability to persist on a task following a high or low demand self-regulation task. Indeed, we were able to demonstrate experimentally that patients with fibromyalgia and temporomandibular disorder had a deficit in self-regulation that was evident following a low self-regulation task (38). Persistence was also associated with heart rate variability, linking the physiology of the stress response system to an important behavior. Another recent study of patients with fibromyalgia performed a cluster analysis based on pain characteristics and cognitive, affective, and behavioral responses to pain and stress (39). The study demonstrated that psychophysiological responses of blood pressure, heart rate, and skin conductance were associated with specific types of psychological coping and psychiatric diagnoses.

## MUSINGS ON THE TREATMENT OF CHRONIC PAIN

When you eliminate 90% of a patient's pain, the remaining 10% is 100% of what is left. This reminds us that any pain is still pain. Furthermore, when pain becomes chronic, the goal in most cases is management rather than elimination. One of the most distressing recent developments in medicine is the explicit focus on eliminating pain — manifested as pain as the fifth vital sign and relief of pain being used to measure the quality of a health care facility. Of course, relief of acute pain is an important function of health care, but too often there is no thought to the distinctions between acute and chronic pain and the negative outcomes of analgesics used for chronic pain. The institutionalized focus on eliminating pain is concomitant with the increase in use of opioids for chronic non-cancer pain (18,40).

Strategies for treatment of chronic pain include antidepressants that increase synaptic norepinephrine and serotonin, agents that reduce neuronal excitability, and analgesics. Simple analgesics are typically ineffective for centrally maintained pain. Opioids are also typically poorly effective and have many clinical and societal issues that make their use problematic (18). Concerns around opioid-induced hyperalgesia appear in the medical literature as early as 1870 when Clifford Albutt noted that "I have much reason to suspect that reliance on

hypodermic morphia only ended in that curious state of perpetuated pain" (41). From a clinical perspective, it is quite difficult to distinguish opioid-induced hyperalgesia from tolerance or merely inadequate analgesia. However, when patients on high-dose opioids continue to have high levels of pain that becomes more diffuse and difficult to localize with persistent treatment, it should trigger concerns. In truth, none of the available pharmacologic treatments for chronic pain are particularly effective and the non-pharmacologic treatments are difficult. Developing new treatment strategies for treatment of chronic pain is of utmost urgency and must start with a better understanding of the pathways that facilitate the transition from acute to chronic pain and maintenance of chronic pain.

Our patients are looking to us for help. When we have students in the clinic or participating in our research programs targeted towards understanding chronic pain and developing treatments, they often ask us how to handle patients with chronic pain — what do we say? It is essential that we understand what we as physicians can do and what is beyond the capabilities of medicine. Above all else, make sure that patients understand that we are hearing them, that we are thoughtfully considering their symptoms to be sure we do not miss a remedial cause of their symptoms, that we care about their suffering, and that we will help them to the best of our ability (Figure 5). This does not mean that we can make their pain go away. Often the factors that precipitate and maintain chronic pain are beyond the reach of medicine. It also does not mean that we will give them analgesic medications, in large part because these drugs are counterproductive for the

FIG. 5.

patient not to mention the society at large. Providing behavioral guidance is definitely more time consuming than ordering a test or writing a prescription. However, there is no treatment for patients with chronic pain that makes a bigger difference than our empathy and our time.

## REFERENCES


1. Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms, 2nd Edition*. Seattle, Washington: International Association for the Study of Pain (IASP) Press; 1994.
2. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004;140:441–51.
3. Crofford LJ, Casey KL. Central modulation of pain perception. *Rheum Dis Clin N A* 1999;25:1–13.
4. Napadow V, Harris RE. What has functional connectivity and chemical neuroimaging in fibromyalgia taught us about the mechanisms and management of 'centralized' pain? *Arthritis Res Therapy* 2014;16:425.
5. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. *Nat Rev Neurosci* 2013;14:502–11.
6. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2007;21:403–25.
7. Haliloglu S, Carlioglu A, Akdeniz D, et al. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. *Rheumatology Int* 2014;34:1275–80.
8. Kato K, Sullivan PF, Evengard B, et al. A population-based twin study of functional somatic syndromes. *Psych Med* 2009;39:497–505.
9. Chervin RD, Teodorescu M, Kushwaha R, et al. Objective measures of disordered sleep in fibromyalgia. *J Rheumatol* 2009;36:2009–16.
10. Burns JW, Crofford LJ, Chervin RD. Sleep stage dynamics in fibromyalgia patients and controls. *Sleep Medicine* 2008;9:689–96.
11. Thomas RJ, Mietus JE, Peng CK, et al. Impaired sleep quality in fibromyalgia: detection and quantification with ECG-based cardiopulmonary coupling spectrograms. *Sleep Medicine* 2010;11:497–8.
12. Park DC, Glass JM, Minear M, et al. Cognitive function in fibromyalgia patients. *Arthritis Rheum* 2001;44:2125–33.
13. Glass JM, Park DC, Minear M, et al. Memory beliefs and function in fibromyalgia patients. *J Psychosom Res* 2005;58:263–9.
14. Hench P, Boland E. The management of chronic arthritis and other rheumatic diseases among soldiers of the United States army. *Ann Rheum Dis* 1946;5:106–14.
15. Barsky AJ, Borus JF. Functional somatic syndromes. *Ann Internal Medicine* 1999;130:910–21.
16. Wolfe F, Brahler E, Hinz A, et al. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. *Arthritis Care Res* 2013;65:777–85.
17. Americal Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders - DSM-5*. Washington, D.C.: American Psychiatric Publishing; 2013.
18. Crofford LJ. Adverse effects of chronic opioid therapy for chronic musculoskeletal pain. *Nat Rev Rheumatol* 2010;6:191–7.

19. Diatchenko L, Fillingim RB, Smith SB, et al. The phenotypic and genetic signatures of common musculoskeletal pain conditions. *Nat Rev Rheumatol* 2013;9:340–50.
20. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005;14:135–43.
21. Hocking LJ, Smith BH, Jones GT, et al. Genetic variation in the beta2-adrenergic receptor but not catecholamine-O-methyltransferase predisposes to chronic pain: results from the 1958 British Birth Cohort Study. *Pain* 2010;149:143–51.
22. Bondy B, Spaeth M, Offenbaecher M, et al. The T102C polymorphism of the 5-HT2A-receptor gene in fibromyalgia. *Neurobiol Dis* 1999;6:433–9.
23. Offenbaecher M, Bondy B, de Jonge S, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis Rheum* 1999;42:2482–8.
24. Nicholl BI, Holliday KL, Macfarlane GJ, et al. Association of HTR2A polymorphisms with chronic widespread pain and the extent of musculoskeletal pain: results from two population-based cohorts. *Arthritis Rheum* 2011;63:810–8.
25. Marshall JK, Thabane M, Garg AX, et al. Eight year prognosis of postinfectious irritable bowel syndrome following waterborne bacterial dysentery. *Gut* 2010;59:605–11.
26. Gupta A, Silman AJ, Ray D, et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology (Oxford)* 2007;46:666–71.
27. Nicholl BI, Macfarlane GJ, Davies KA, et al. Premorbid psychosocial factors are associated with poor health-related quality of life in subjects with new onset of chronic widespread pain — results from the EPIFUND study. *Pain* 2009;141: 119–26.
28. Aaron LA, Bradley LA, Alarcon GS, et al. Perceived physical and emotional trauma as precipitating events in fibromyalgia. Associations with health care seeking and disability status but not pain severity. *Arthritis Rheum* 1997;40:453–60.
29. Blyth FM, Macfarlane GJ, Nicholas MK. The contribution of psychosocial factors to the development of chronic pain: the key to better outcomes for patients? *Pain* 2007;129:8–11.
30. Crofford LJ, Pillemer SR, Kalogeras KT, et al. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis Rheum* 1994;37:1583–92.
31. Crofford LJ, Engelberg NC, Korszun A, et al. Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. *Brain Behavior Immunity* 2004;18:314–25.
32. Aschbacher K, Adam EK, Crofford LJ, et al. Linking disease symptoms and subtypes with personalized systems-based phenotypes: a proof of concept study. *Brain Behavior Immunity* 2012;26:1047–56.
33. Liu Z, Cappola AR, Crofford LJ, et al. Modeling bivariate longitudinal hormone profiles by hierarchical state space models. *J Am Statistical Assoc* 2014;109: 108–18.
34. Martinez-Martinez LA, Mora T, Vargas A, et al. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. *J Clinical Rheumatol* 2014;20:146–50.
35. Shang Y, Gurley K, Symons B, et al. Noninvasive optical characterization of muscle blood flow, oxygenation, and metabolism in women with fibromyalgia. *Arthritis Res Therapy* 2012;14:R236.

36. Eisenlohr-Moul TA, Crofford LJ, Howard TW, et al. Parasympathetic reactivity in fibromyalgia and temporomandibular disorder: associations with sleep problems, symptom severity, and functional impairment. *J Pain* 2015;16:247–57.
37. Nes LS, Carlson CR, Crofford LJ, et al. Individual differences and self-regulatory fatigue: optimism, conscientiousness, and self-consciousness. *Pers Individ Dif* 2011;50.
38. Solberg Nes L, Carlson CR, Crofford LJ, et al. Self-regulatory deficits in fibromyalgia and temporomandibular disorders. *Pain* 2010;151:37–44.
39. Thieme K, Turk DC, Gracely RH, et al. The relationship among psychological and psychophysiological characteristics of fibromyalgia patients. *J Pain* 2015;16: 186–96.
40. Painter JT, Crofford LJ. Chronic opioid use in fibromyalgia syndrome: a clinical review. *J Clinical Rheumatol* 2013;19:72–7.
41. Albutt C. On the abuse of hypodermic injections of morphia. *Practitioner* 1870;5:327–31.

## DISCUSSION

**Gotto, New York:** I wanted to ask you about a form of chronic pain associated with depression. I've seen a few patients with depression, and there is a subgroup of patients whom the depressive episodes are associated with severe pain. It's not characteristically located in any part of the body, but it doesn't seem to be helped by electroshock therapy. I am wondering if you have any thought about etiology or treatment of this syndrome.

**Crofford, Nashville:** I don't have many thoughts about treatment because I don't think many of them work really well. I do think that it is very likely that patients who have what they call painful depression do have pain etiology that likely originates, in my view, in the fear centers within the central nervous system. These are overlapping; the genes are shared. I think it is incredibly common that — or certainly neurophysiologically feasible — that some of the biochemical etiologies of pain can arise specifically from dysfunction of the central nervous system rather than an anatomical or histological stroke-associated, for example, pain syndrome. But thank you for that question and I think it is a difficult problem.

**Palmer, New York:** I think it was Dr. Nuland who wrote at one point that pain is ubiquitous but suffering is optional. And we know that people who mark 7 on their pain scale out of 10 vary a lot on how that pain of seven is affecting them. Is there any way of quantitating the suffering or the response of patients to a given pain?

**Crofford, Nashville:** Well, the best way is to ask the patient. I think that is the crux of the problem. We, as physicians, bring our own understanding to the pain experience when we interact with an individual. It is so easy to look at the patient and say, well I don't think that that arthritis is bad enough to cause that much pain. But that is the filter in our own brain, and suffering is an intensely personal experience. A lot of it has nothing to do with physiology and has much more to do with that patient's previous experiences and their cognitive interpretation of the symptoms that they are feeling. So I think the only way that I know to quantitate suffering is to ask the patient and to believe the patient when they tell you how much they are suffering.

**Alpert, Tucson:** this is a huge problem. In last week's *JAMA* you probably saw the editorial that says there are a hundred million Americans suffering chronic pain. That is almost a third of the country. When I attend on inpatient ward medicine, there are lots of patients being admitted, as I am sure you have seen in Nashville. The ER does not want to deal with these patients and they just admit them to medicine. Actually, my

diagnosis is a little different from psychiatry literature, that it is psychosocial sexual dysfunction. It is the sum total of all the horrible things that have happened to this person that puts them exactly in the chronic fatigue and chronic pain and constantly seeking, of course, more and more narcotics. Of course that infuriates the house officers, and the whole situation just deteriorates. So that is a comment. I don't know what the solution is. When I was at University of Massachusetts, there was a young man named Jon Kabat-Zinn who was actually a DNA biophysicist who was a long life meditator. He came to me one day and said, you know, I'd like to try this. I hear that meditation can help with chronic pain. So eventually that led to Jim Dalen, who was the dean then and had a master's degree in psychology. With his agreement we did an experiment in which he went to the orthopedists and said, "I want you to send me the patients that you hide under the desk from when you see them coming." They have been operated on multiple times and all they are looking for is narcotics. He put them all through the program and there was a remarkably good response rate. The patients' remark was, just like the last comment: I still feel the pain, but it doesn't bother me as much. So it really is the difference between the pain fibers and the suffering.

**Crofford, Nashville:** I think that is a wonderful comment. I think, you know, we as a medical establishment have almost facilitated this concept that there is a pill for pain. There really isn't a pill for pain, exactly for the reasons that you point out. The more that we see more commercials on TV saying, if you take this pill you are going to be healed and feel wonderful. But the truth of the matter is that the more that we focus on a drug-based solution for these problems that surely they have something to do with the somatosensory pathways, but I don't think we are doing our patients a favor but pretending that these patients that have suffering in association with their chronic pain are going to be fixed by a pill.

**Alpert, Tucson:** Is there anybody doing deep brain stimulation for some of these very severe cases?

**Crofford, Nashville:** Yeah, there are people that have started looking at that. We had a little bit of conversation at the level of the NIH and whether or not this is something that we want to embark on. The truth of the matter is, as you point out, this is such a common disease that I am not even sure that I am enthusiastic about going there. Again, it gets to the concept that there is a medical answer for chronic pain, and I really don't think there is a medical answer for this problem. And the more we emphasize it the less likely we are going to address the root causes of the problem.

**Zeidel, Boston:** With more and more functional imaging and precise deep brain stimulation, you have to believe that a portion of the patients might respond very well to this. I guess the key would be figuring out which patients might have these reinforcing pathways that might be potentially interruptible. Those sorts of stimulations could be much more specific than, for example, narcotics.

**Crofford, Nashville:** I don't disagree. I think that you know people that have been looking at the central networks associated with chronic pain in animals as well as in people are finding really interesting differences between chronic pain patients and patients without chronic pain in terms of the degree to which the networks light up, particularly in these very deep amygdala fear centers. I think that is a large part of the issue that we just can't deal with in the usual ways. Certainly it is an experiment begging to happen. But I do worry about the next wave which is, "Woo! If I could get deep brain stimulation, I can be cured from my chronic pain."

**Zeidel, Boston:** It is going to be all about selection.

**Crofford, Nashville:** Exactly.

**Telen, Chapel Hill:** I am a hematologist, and I have spent a lot of my life taking care of sickle cell patients, which turns hematologists into pain doctors, especially if they take

care of adults. And it's become clear, I think as you describe, that all those different types of pain are involved in sickle cell pain. It's very hard when someone comes into the emergency room or the day hospital to decide if this is a vaso-occlusive pain episode or is this exacerbation of chronic pain. Somewhere between 30% and 50% of our population and in a lot of clinics in the United States are on daily opioid medicines, either short-acting or long-acting, or both. A recent study of vaso-occlusive episodes in a phase 2 study with a targeted drug that targeted mechanisms of vaso-occlusion had as its most obvious efficacy endpoint a huge reduction in opioid use, which was patient-controlled analgesia — a doctor had relatively very little to do with it. With this understanding of these multiple types of pain and the fact that they are often all there together, how do you see that really affecting how we deal with chronic pain, especially in patients who clearly have long standing tissue damage like sickle cell patients?

**Crofford, Nashville:** I think that is a great question. We deal with it often in our patients, for example, with osteoarthritis. There are some patients that have a peripheral pain generator that when you make it go away; even the elements of central pain that they are experiencing get better. So for example, if we have patients with osteoarthritis in the knee, no matter what kind of central elements of pain they have, you take out the old knee and give them a new knee and their pain goes away, and their pain syndrome goes away. But there are others in whom that does not happen. And trying to tease out what are the elements of pain that are peripherally maintained and what are the elements of pain that are centrally maintained is exceptionally challenging. There are a number of people that are working on trying to understand, particularly using psychophysical or functional MRI testing and how you tease that apart. It is not easy.

**Wenzel, Richmond:** Does acupuncture work? If so, what patients are likely to respond, and do you have an idea of how it might work?

**Crofford, Nashville:** So, many of our body-based therapies are very difficult to study. The studies that I am most familiar with are in patients with fibromyalgia where at least three or four large acupuncture studies have been done where sham acupuncture works as well as real acupuncture. I do think it works. This gets at the issue of what is placebo and what is the placebo effect, and can you stimulate the central pathways that are associated with how you think about chronic pain, because that does make a difference in the experience of chronic pain. Based on the studies where sham and real acupuncture work, I don't know if I can specifically tell you a peripheral mechanism for the efficacy of acupuncture. But I can tell that acupuncture works, and I use it in people who want it.

**Hochberg, Baltimore:** I would like to further comment on and amplify Leslie's response to Dr. Wenzel's question. So the studies in osteoarthritis of the knee — which I am familiar with, contributed to, and happen to analyze to a great extent — show that there is a small statistical difference between real acupuncture and sham acupuncture. But there is a large difference between sham acupuncture and standard of care, which in most of the studies involves an educational intervention. What that gets to is the need for practitioners — who take care of patients like Leslie is describing that present with chronic pain and other chronic somatic symptoms — to harness the placebo effect; in the interaction between the clinician and the patient, to listen to the patient, to be empathetic to the patient, and to stress the positives of the interventions which we will pursue as a team going forward. We know that sham acupuncture works a lot better than giving an oral placebo tablet. Injectable placebos work much better than giving an oral placebo tablet. Topical placebos work much better than giving an oral placebo tablet. So everything we do with the patient together as a team works to some extent in terms of improving their symptoms.

**Crofford, Nashville:** Thank you for those comments Mark, I couldn't agree more.