History of Fibromyalgia: Past to Present

Fatma Inanici, MD and Muhammad B. Yunus, MD

Address
Department of Medicine, University of Illinois College of Medicine at Peoria, One Illini Drive, Peoria, IL 61605, USA.
E-mail: yunus@uic.edu

Current Pain and Headache Reports 2004, **8:**369–378
Current Science Inc. ISSN 1531-3433

Fibromyalgia syndrome (FMS) is now a recognized clinical entity causing chronic and disabling pain. For several centuries, muscle pains have been known as rheumatism and then as muscular rheumatism. The term fibrositis was coined by Gowers in 1904 and was not changed to fibromyalgia until 1976. Smythe laid the foundation of modern FMS in 1972 by describing widespread pain and tender points. The first sleep electroencephalogram study was performed in 1975. The first controlled clinical study with validation of known symptoms and tender points was published in 1981. This same study also proposed the first data-based criteria. The important concept that FMS and other similar conditions are interconnected was proposed in 1984. The first American College of Rheumatology criteria were published in 1990 and neurohormonal mechanisms with central sensitization were developed in the 1990s. Serotonergic/norepinephric drugs were first shown to be effective in 1986.

Introduction

The history of a disease provides us an interesting clinical, pathophysiologic, and therapeutic perspective. This article examines a chronologic evolution of the concepts and descriptions of fibromyalgia syndrome (FMS) throughout the past 150 years. Original nomenclature used by the authors (*eg,* fibrositis) is retained while discussing a particular article. The focus of this paper is to narrate important historic developments, emphasizing the first authors of original ideas. In selecting the importance of a paper or idea, there is always a personal bias; a particular contribution may influence one researcher, but not the other. However, we have tried to be as objective as possible.

Discussion

Descriptions of musculoskeletal aches and pains can be found in the European literature dating back to the late 16th century. The French physician Guillaume de Baillou first introduced the term rheumatism to describe clinical manifestations of muscular pain and acute rheumatic fever in 1592 [1]. By the 18th century, physicians started to distinguish articular rheumatism with deforming features from painful but nondeforming soft tissue musculoskeletal disorders, which generally were called muscular rheumatism [2].

Since the 19th century, various forms of muscular rheumatism under different nomenclature have been described [1,3–6,7•,8–21] (Table 1). The early definitions were vague and it is almost impossible to distinguish between generalized and regional/localized types. Important chronologic developments that have had an impact on FMS literature are shown in Table 2.

Literature on muscular rheumatism was published by German, Scandinavian, and British physicians from the beginning of 1800s. In 1815, William Balfour [22], a surgeon from Edinburgh, described nodules and suggested that inflammation in muscle connective tissue is the cause for nodules and pain. Balfour also first reported focal tenderness, referred to as tender points, in 1824 [5]. In 1827, another British physician, Scudamore [23], identified rheumatism as "pain of a peculiar kind, usually attended with inflammatory action, affecting the white fibrous textures belonging to muscles and joints, such as tendons, aponeuroses, and ligaments; the synovial membranes of the bursae and tendons; and nerves…." He endorsed the idea of inflammation in fibrous tissue asserted by Balfour [22].

In the following years, Valleix [3] set forth the referred pain/trigger point concept. He described painful points in various parts of the body, which caused referred pain to other regions on palpation. He noted that these painful points were closely related to the route of different nerves. He proposed muscular rheumatism as a form of neuralgia.

In 1858, Inman [24] remarked that the radiation of pain was independent of the course of nerves. He proposed a functional change in muscles and explained nodules as hypertonus or spasm of the muscle. In 1903, Cornelius [25] opposed Valleix's [3] idea of referred pain via nerves. He suggested that local points of tenderness were related to hyperactive nerve endings, which he called nerve points. He attributed nerve point hyperactivity to external influences, such as climatic, emotional, or physical exertion. However, he insisted that the radiation pathway was different from nerve routes. He explained referred pain on reflex mechanisms [25].

Unlike the British and French physicians, the German/Scandinavian school assumed that there was an exudative, proliferative process of muscle itself, rather

Table 1. Chronologic appearance of terms used to describe musculoskeletal pain conditions

Author [reference number]	Year	Terminology
Guillaume de Baillou [1]	1592	Muscular rheumatism
Valleix [3]	1841	Neuralgia
Froriep [4]	1843	Muscle calluses (muskelschwiele)
Helleday [5]	1876	Chronic rheumatic myitis
Beard [6]	1880	Neurasthenia
Gowers [7•]	1904	Fibrositis
Telling [8]	1911	Nodular fibromyositis
Schade [9]	1919	Muscle gelling (myogelosen)
Lange and Everbusch [10]	1921	Muscle hardening (muskelharten)
Albee [11]	1927	Myofacitis
Murray [12]	1929	Myofibrositis
Clayton [13]	1930	Neurofibrositis
Rowe [14]	1930	Allergic toxemia
Halliday [15]	1937	Psychogenic rheumatism
Gutstein-Good [5]	1940	Idiopathic myalgia
Good [5]	1941	Rheumatic myalgia
Mayo Clinic [16]	1950	Tension myalgia
Randolph [17]	1951	Allergic myalgia
Travell *et al.* [18]	1952	Myofascial pain syndrome
Gutstein [5]	1955	Myodysneuria
Muller [19]	1970	Generalized tendomyopathy
Awad [20]	1973	Interstitial myofibrositis
Hench [21]	1976	Fibromyalgia syndrome

than the connective tissue [4]. Froriep [4] reported on 80 patients with regional pain who had palpable muscle hardness that was painful to pressure. He used the term muscle calluses.

Virchow and Vogel supported Froriep's [4] exudation and muscle calluses theory. Virchow [26] ascribed exudation to local vascular atony and dilation of the blood vessels as a result of diminished nerve activity and attributed calluses to muscle fiber atrophy and replacement of the fibers by proliferated connective tissue as a result of nutritional alterations caused by exudation. Vogel suggested fibrinous exudates could persist and become clinically detectable as callus [27]. However, these theories later were denied by two other German physicians, Strauss [28] and Port [29].

In the 1850s, Dutch physician Mezger, who was considered the father of massage therapy, taught his massaging technique to a large number of his students from all over Europe [30]. Mezger strengthened the concept of nodules and taut bands in muscles.

In 1880, Beard [6], a neurologist from the United States, mentioned widespread pain (in addition to fatigue and psychologic disturbance) in what he called neurasthenia/myelasthenia. He attributed these symptoms to the daily stresses of modern life.

In 1893, Graham [31], a Boston physician, stated that "muscular rheumatism is probably coagulation of the semi-fluid contractile muscular substance and adhesion of muscular fibrils." This concept was approved in the 1920s by European physicians who advocated colloidal change from sol to gel, causing increased cytoplasmic viscosity in muscle tissue involved in trigger points. Schade [9] referred to it as myogeloses and Lange and Everbusch [10] referred to it as muscle hardening.

The term "fibrositis" was first introduced by the British neurologist Sir William Gowers [7•] in 1904. He stated, "We are thus compelled to regard lumbago in particular, and muscular rheumatism in general, as a form of inflammation of the fibrous tissues of the muscles…(and thus)...we may conveniently follow the analogy of 'cellulitis' and term it 'fibrositis'." In his article, he mentioned spontaneous pain and asymptomatic sensitivity to mechanical compression, fatigue, sleep disturbances, and aggravation of symptoms by exposure to acute and chronic cold and muscular overstrain. For treatment, he suggested manipulation, counterirritation, and cocaine injections and noted the failure of salicylates [7•].

In the same year, Stockman [32] reported patchy inflammatory hyperplasia, fibroblast proliferation, serofibrinous exudates, thickening of nerves and blood vessel walls, and capillary proliferation on biopsies of excised myalgic nodules. His findings subsequently could not be confirmed [33–36], but he provided a pathologic basis for Gower's [7•] fibrous inflammation theory. Thus, the term fibrositis became entrenched and was used for the next 72 years.

Stockman's [32] original sections were re-examined by Collins [35] at the Mayo Clinic and were reported to be essentially normal. Several muscle biopsy reports later [36] claimed inflammatory or degenerative changes, but these were found to be invalid because of a lack of appropriate design [37••].

In 1909, Sir William Osler [38], the best-known physician in the English-speaking world at that time, considered muscular rheumatism to involve "neuralgia of the sensory nerves of the muscles." However, uncertainty of physical signs, inconsistent histologic changes, and a lack of specific laboratory tests hindered a wide recognition of fibrositis by North American physicians.

In 1913, Llewellyn and Jones [39] wrote an elaborate book, wherein they lumped diverse clinicopathologic entities, including rheumatoid arthritis and gout, into a catch-all term of fibrositis. They classified fibrositis as articular, bursal, neural, muscular, gouty, infective, traumatic, or rheumatic and mentioned aggravating factors such as overexertion and cool weather. Various therapeutic interventions were recommended (*eg*, aperients, purgation,

Table 2. Important chronologic developments with emphasis on the first published report that made a subsequent impact on FMS literature*

First author [reference number]	Year	Important developments
Guillaume de Baillou [1]	1592	Initial naming of muscular rheumatism
Gowers [7•]	1904	First use of the term fibrositis
Copeman [55]	1945	First controlled study showing that fibrositic nodules are as frequent in patients with FMS as in control subjects
Traut [57]	1968	First near-modern description of FMS with systemic features
Smythe [61••]	1972	First modern description of FMS with widespread pain and multiple tender points at specified sites, along with a set of working criteria that stimulated clinical interest and research
Moldofsky [62••]	1975	First EEG sleep study showing a disturbance of non-rapid eye movement sleep by an intrusion
Hench [21]	1976	First use of the term fibromyalgia
Smythe [63]	1977	Brought into focus the importance of sleep with sleep EEG findings and suggested a revised set of criteria for FMS that generated further interest in research
Yunus [64••]	1981	First description of a controlled clinical study validating previous anecdotal symptoms and tender points; addition of new symptoms (*eg*, subjective swelling and paresthesia); first data-based suggested criteria; beginning of a new concept of FMS association with other functional syndromes (*eg*, irritable bowel syndrome); popularization of the term fibromyalgia
Yunus [68••]	1984	First depiction (by a Venn diagram) of the important modern concept that FMS and other functional syndromes have overlapping features, have mutual associations, and are interconnected
Wolfe [74]	1984	First report of a high prevalence of FMS in rheumatoid arthritis
Yunus [72]	1985	First description of juvenile FMS by a controlled study
Carette [104], Goldenberg [105]	1986	First report of efficacy of amitriptyline by randomized, controlled trial
Vaeroy [99•]	1988	First report of elevated substance P in cerebrospinal fluid of patients with FMS
Bennett [106]	1988	First report of efficacy of cyclobenzaprine by randomized control trial
Yunus [37••]	1989	First blinded, controlled study of muscle biopsy showing normal results, resulting in a new focus on the central nervous system
Bennett [102]	1989	First demonstration of a lack of aerobic fitness in patients with FMS compared with normal control subjects with implications for research findings (*eg*, muscle studies)
Hudson [69•]	1989	Suggested overlaps between functional and psychiatric syndromes by affective spectrum mechanism
Wolfe [58••]	1990	Publication of the American College of Rheumatology criteria for classification of FMS in a well-designed, blinded study
Burckhardt [86••]	1991	Development of a validated questionnaire (Fibromyalgia Impact Questionnaire) for assessing physical and psychologic functions in FMS
Bennett [95]	1992	Demonstration of a low-serum somatomedin C (growth hormone)
Yunus [73•]	1992	Proposal of a new model for fibromyalgia pathogenesis with emphasis on central aberrant pain mechanisms
Granges [87], Arroyo [88]	1993	First demonstration of central sensitization on FMS
Griep [93]	1993	First demonstration of hypothalmic-pituitary-adrenal axis abnormalities in a well-designed study showing exaggerated ACTH release with relative hyporesponsiveness
Crofford [94]	1994	Important confirmation of hypothalmic-pituitary-adrenal axis dysfunction
Russell [1]	1994	Important confirmation of elevated substance P in cerebrospinal fluid of patients with FMS
Wolfe [75]	1995	First US population study showing 2% prevalence of FMS
Mountz [91]	1995	First study of brain imaging by SPECT showing decreased cerebral blood flow in thalami and caudate nuclei
Buskila [103]	1997	Report of a controlled study showing the role of trauma (cervical spine injury) in FMS
Yunus [97]	1999	First report of genetic linkage (unlike less reliable association studies) of FMS (with HLA) with later confirmation
Yunus [71•]	2000	An important review of evidence for central sensitization in FMS and other related syndromes; coined the term central sensitization syndromes
Staud [89•]	2001	Well-designed study demonstrating temporal summation

*Other important historic developments are described in the text.
ACTH—adrenocorticotropic hormone; EEG—electroencephalogram; FMS—fibromyalgia syndrome; SPECT—single photon emission computed tomography.

massage, counterirritants, and a prudent combination of rest and exercise). They even published a picture of their new type of treatment, a large metal cylinder, in which the patients lay with only their head exposed. It seemed to be some kind of "heating device" [39].

Approaching the middle of the 20th century, Slocumb [40] initiated a growing interest in fibrositis. During the second half of the century, a distinctive American and Canadian contribution appeared on regional fibrositis, which now is called myofascial pain syndrome, and generalized fibrositis, now known as FMS. Slocumb [40] stated that fibrositis was the most common form of acute and chronic rheumatism, giving the example that 60% of 2500 insurance cases of rheumatic diseases in the British Ministry of Health were based on fibrositis.

A particular interest in regional muscle pain with referral patterns grew in the 1930s. Charts of tender spots and their referral patterns were published based on clinical [41–43] and experimental studies [44,45]. These reports documented pain relief by local anesthetic injections of tender spots.

Kellgren's [44,45] experiments of hypertonic saline injections into deep muscle tissue on healthy volunteers provided significant data on referred muscle pain. He showed that irritation of paraspinal ligaments caused referred pain peripherally on the trunk or proximal limb, while proximal limb muscle injection could induce pain in the area of the wrist or ankle. His concept is still held by many researchers.

Kelly [46,47] proposed the somatovisceral reflex theory to explain the nature of tender points causing referred pain. According to this theory, central connections of neurons were responsible for heterotopic pain mechanisms. When a noxious stimulus from the periphery, either visceral or somatic tissues, reached the central nervous system (CNS), it generated an antidromic signal to the neurons and produced cutaneous or deep pain and hyperalgesia. This may be the first mention of the CNS involvement in muscle pain disorders. He recommended deactivation of these tender areas by local injections [46,47].

At the same time, Travell and Rinzler [48] published a paper on myofascial trigger points and myofascial pain syndromes, the terms they later popularized. They described the clinical features and treatment of chronic shoulder pain. Subsequently, they defined individual myofascial trigger point pain syndromes and their specific referral pattern. They proposed that when several syndromes developed concomitantly, the pain was generalized. In 1952, Travell and Rinzler [48] described details of these syndromes with illustrations.

During and after World War II, a high occurrence of fibrositis among soldiers drew attention. Approximately 70% of rheumatic patients admitted to a British Army Hospital were diagnosed with fibrositis [49]. In the US military hospitals, similar muscle pain syndromes were reported, with a prevalence of 5.8% among 450 hospitalized patients [50,51]. In the absence of inflammation or degeneration and an association with depression and stress, Boland and Corr [51] labeled the condition as "psychogenic rheumatism." A similar view also was held by Ellman *et al.* [52].

In 1937, Halliday [15,53] wrote that muscular rheumatism was a minor manifestation of chronic psychoneurotic state. He suggested discarding the term fibrositis and using a syndrome name of pain, stiffness, and soreness. This organic versus psychogenic polemic continues to persist today.

Graham [54] revived particular interest in FMS in the 1950s and 1960s by his contribution in a chapter on fibrositis in the well-known textbook of rheumatology, *Arthritis and Allied Conditions*, which was published in 1949. He emphasized that "there can no longer be any doubt concerning the existence of such a condition." He described acute, subacute, and chronic painful conditions involving muscles, subcutaneous tissues, ligaments, tendons, or fasciae "arising independently of gross anatomic disease from which pain might be referred," along with local tender points and referred pain. The etiology was stated to be infective, traumatic/occupational, weather factors, and psychologic disturbance. Nodules were mentioned, but Graham [54] referenced a study by Copeman and Pugh [55], who observed 500 soldiers in whom frequency of nodules were equal among those with and without fibrositis, although tender nodules/trigger points were much more frequent in those with fibrositis (30%) than in those without it (3%). Referring to a paper by Ellman *et al.* [52] in 1942, Graham [54] correctly described pain characteristics as burning, piercing, gnawing, excruciating, and nagging long before Leavitt *et al.* [56] described such descriptors assessed by the 1975 McGill Pain Questionnaire in a study that used rheumatoid arthritis as a control group. However, the overall concept of fibrositis remained a jumble of acute, chronic, and multiple regional pain conditions of diverse etiology. Among non-musculoskeletal symptoms, physical fatigue, psychologic distress, and headaches were described, but poor sleep was not [54].

The next important paper was by Traut [57] of the University of Illinois whose description of fibrositis in 1968 is fairly similar to the one used today. Traut [57] described female gender almost exclusively, generalized aching and stiffness, aching all over, fatigue, headaches, colitis, poor sleep, being "worry worts," and tender points on physical examination. Using a diagram, he demonstrated the common sites of tender point locations (*eg*, occipital muscles, paraspinal muscles, and the origin of the gluteus muscle at the posterior iliac crest). Traut [57] described generalized pain, but also regional ones including carpal tunnel syndrome and Dupuytren's contracture. He further recognized the importance of mind-body interaction in fibrositis. He made a correct observation that "nonarticular rheumatism most commonly originate various levels of the spinal axis," considering that axial pain is now a criteria item for the

classification of FMS [58••]. He properly noted that men have more localized symptoms (pain) and signs (tender points) given that recent data have shown that men have fewer pain symptom sites and tender points than women [59,60]. Traut [57] discredits Stockman's [32] histologic observations, stating that such findings "had little substantiation." His important contribution was to bring into focus the systemic features of FMS (*eg,* fatigue, poor sleep, headache, and colitis). He also explained the role of mind-body interaction in the pathogenesis of FMS.

It may be fair to say that Smythe [61••] is the grandfather of modern FMS. His elaborate 10-page chapter on fibrositis syndrome in a popular textbook of rheumatology influenced many fibromyalgia researchers in the late 1970s and the 1980s. It seems that he was the first one to describe FMS exclusively as a generalized pain syndrome, along with fatigue, poor sleep, morning stiffness, aggravating and relieving factors, emotional distress, and multiple tender points. Smythe [61••] also provided an anecdotal, but working set of criteria for diagnosis. He specified sites of tender points, many of which were still used in the 1990 American College of Rheumatology (ACR) criteria [58••]. For the first time, the role of sleep was properly emphasized, describing real patient experience and providing sleep electroencephalogram (EEG) findings of absent stage-4 and near-absent stage-3 sleep, citing the unpublished work of his colleague, Dr. Harvey Moldofsky. Smythe [61••] provided a pathophysiologic frame work for FMS by describing the possible role of deep tissue reflex hyperalgesia and its referral pattern of pain, differentiating it from cutaneous hyperalgesia and establishing the true global hyperalgesic state in FMS by mentioning bone as a site of pain and tenderness. At the same time, he integrated the role of nonrestorative sleep, trauma, and emotional distress in causing FMS symptoms. He suggested mechanical stress in the deep structures of the cervical and lumbosacral spine region as a factor for sustained reflex hyperalgesia. His personal astute observations, written elegantly from personal observation and conviction [61••], are a triumph for clinical bedside medicine.

The preliminary unpublished sleep EEG findings by Moldofsky *et al.* [62••], as mentioned by Smythe [61••], were confirmed by a sleep EEG study of 10 FMS patients and six healthy control subjects in a pioneering work. Stage-4 and very little stage 3-sleep and contamination of non-rapid eye movement (NREM) sleep by α rhythm (α-δ sleep) were reported; α-δ sleep was suggested to be an indication of arousal (external, internal, or both) during non-rapid eye movement sleep. All of the subjects also showed an overnight increase in pain symptoms, hyperalgesia by dolorimetry, and worse mood symptoms. The stage-4 sleep of the six healthy male and younger volunteers were disturbed by auditory stimuli, producing α-δ sleep. After overnight induction of such disturbed sleep, the volunteers complained of aches and stiffness, fatigue, increased tenderness, and worse mood symptoms the next morning. Thus, FMS essentially was created in the sleep laboratory by sleep deprivation. The authors also suggested serotonin deficiency as a cause for such sleep anomalies in FMS. These findings later were corroborated by better designed studies by Moldofsky *et al.* and others.

The subsequent paper by Smythe and Moldofsky [63], regarded "seminal" by some [58••], essentially is a modification of the earlier book chapter by Smythe [61••]. It effectively summarized the earlier sleep study by Moldofsky *et al.* [62••], better identified the tender point sites, and proposed a refined but anecdotal set of criteria, which included symptoms of chronic pain, disturbed sleep, morning stiffness, fatigue, and the presence of 12 tender points among 14 specified sites. In this paper, the authors correctly asserted that "the existence of exaggerated tenderness at anatomically reproducible locations is central to acceptance and recognition of the syndrome."

However, the clinical characterization of FMS without a controlled study remained in question. What is fibromyalgia after all? Don't many in the normal population have pain, fatigue, and poor sleep? Doesn't everyone have sore muscles and tender insertions if enough pressure is applied? The answers to these important questions were provided in 1981 when the first controlled study of the clinical characteristics of this syndrome by a formal protocol was published by Yunus *et al.* [64••]. This study, which included 50 FMS patients and 50 matched healthy control subjects, confirmed that previously described symptoms of pain, fatigue, and poor sleep were significantly more common in patients with FMS than in age- and gender-matched healthy control subjects. Moreover, it was shown for the first time that the number of tender points was significantly greater in FMS patients than in control subjects. In addition, several other previously undescribed symptoms (*eg,* subjective swelling of tissues, paresthesia, and associated syndromes of irritable bowel syndrome [IBS]), tension-type headaches, and migraine were found to be significantly more common in patients with FMS than in the control group. This documentation of multiple symptoms raised fibromyalgia to a syndrome level. This paper also provided the first data-based criteria for FMS, providing a sensitivity of 96% and a specificity of 100% against healthy control subjects [64••]. These criteria were used most frequently in the literature until the 1990 ACR criteria were published [58••]. Since then, a large number of controlled studies have been published to confirm these musculoskeletal and associated features of fibromyalgia [58••,59,60,65,66•].

Based on the earlier observation that FMS is associated with headaches and IBS [64••], the idea that several other conditions similar to FMS (*eg,* IBS, headaches, and primary dysmenorrheal) are similar to and clinically overlap with FMS was first proposed by Yunus in 1984 [68••], demonstrating their overlaps and interrelationship by a Venn diagram (Fig 1). The connecting thread of these syndromes was suggested to be muscle spasm,

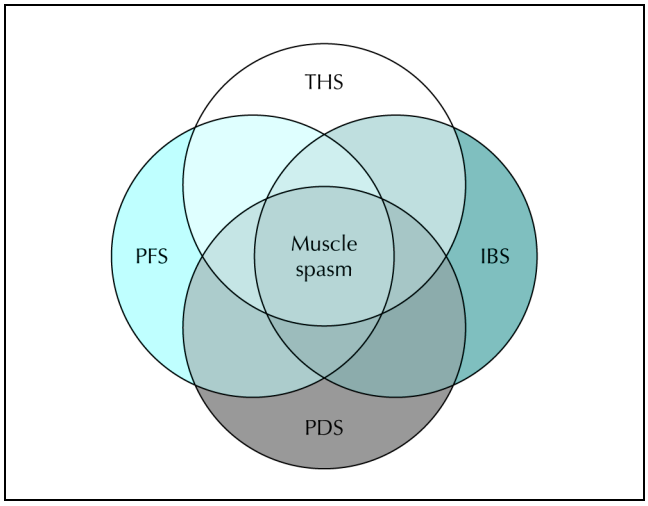

Figure 1. An important and enduring new concept of clinical overlaps and interconnectedness between fibromyalgia and other similar syndromes was first clearly depicted in this Venn diagram in 1984. Statistical associations between them and their presence in the same patient also were described. The common pathophysiologic binder between them was proposed to be muscle spasm (unlike central sensitization as we understand it now). IBS—irritable bowel syndrome; PDS—primary dysmenorrhea syndrome; PFS—primary fibromyalgia syndrome; THS—tension-type headache. *Reproduced with permission from* Yunus [68••].

according to the prevailing concept; central sensitization generally was not recognized at that time. After initial skepticism, such a paradigm is now universally accepted and deemed to be a very important concept for internal medicine. These conditions previously were thought to be generally discrete under the loose and non-specific terminology of "functional" or "somatic functional" syndromes, mostly implying psychiatric/psychologic and psychosocial mechanisms [66•]. Subsequently, in 1989, Hudson and Pope [69•] published an important paper suggesting that some of the previously mentioned functional medical syndromes and several psychiatric disorders (including depression, panic disorder, bulimia, and obsessive-compulsive disorder) are all interconnected through "affective spectrum disorder" mechanism. Yunus [66•] later accepted this model of an overlap between medical-psychiatric conditions, including depression, through the suggested neural mechanism of central sensitization. Many studies of associations between FMS and other similar overlapping syndromes, including chronic fatigue syndrome, have been carried out since the first paper was published [64••], as has been reviewed [66•].

In 1999, Bennett [70•] published a review paper showing evidence of central sensitization (CS) in FMS based on published articles. In 2000, Yunus [71•] reviewed the evidence for CS in FMS and other overlapping syndromes, including myofascial pain syndrome, temporomandibular disorder, tension-type headache, migraine, and chronic fatigue syndrome, and suggested that CS is the binding glue of these syndromes. He also coined the term central sensitivity syndromes as a group terminology for these overlapping syndromes [71•]. Direct or indirect evidence for CS in multiple chemical sensitivity, post-traumatic stress disorder, and depression later was provided [66•]. The important significance of the concept of central sensitivity syndromes has been described [66•,71•].

Fibromyalgia syndrome among children was not generally recognized until 1985 when the first controlled study of juvenile fibromyalgia (JF) was published [72]. Numerous articles on JF since have been published and it is now accepted that JF is a clinical entity that causes much disability among children.

The issue of histologic findings in FMS, first described in 1904 [32], remains a controversy. Although several controlled muscle biopsy studies were published in the 1980s showing non-specific changes, they were criticized because of flaws in methodology. An electron microscopic study of biopsy specimens from the trapezius muscles from 21 patients with FMS and 11 healthy control subjects (who were similar in age, gender, and physical activity) showed no significant difference between the two groups [37••]. This is the only study that evaluated muscle histology in FMS in a blinded manner without any knowledge of the diagnosis (patients or control subjects). With a general acceptance that there was no significant histologic changes in the skeletal muscles, attention was drawn to the CNS and an aberrant central pain mechanism was suggested to be the main pathophysiologic mechanism in FMS [73•]. Such a model was readily embraced by the researchers and most of the studies on the pathophysiology of FMS since then have been directed at the neurohormonal mechanisms.

The study of multicenter ACR criteria for classification of fibromyalgia, spearheaded by Wolfe *et al.* [58••], was the most important study published in the 1990s and it continues to have an impact. Unlike other ACR criteria for rheumatologic diseases, the examiners were blinded with regard to diagnosis (*ie*, FMS patients [n = 293] vs control subjects [n = 265] with other chronic pain/rheumatology diseases). This multicenter study confirmed previous findings [64••] and suggested a disarmingly simple set of criteria for the classification of FMS (*ie*, a combination of widespread pain and the presence of 11 or more tender points at 18 specified sites) [58••]. These criteria were most helpful for a uniform classification of FMS for research all over the world and in clinical practice. Another important outcome of this study was that a differentiation between primary and secondary/concomitant FMS could be abandoned. Remarkably, unlike the criteria for many other functional conditions, no exclusion criteria were suggested.

An association of FMS with various connective tissue diseases is an important concept for clinical, therapeutic, and pathophysiologic significance. The first such association was published by Wolfe *et al.* [74] in 1984, which showed an increased prevalence of FMS (14%) among patients with

rheumatoid arthritis; associations with other connective tissue diseases (*eg,* systemic lupus erythematosus, Sjogren's syndrome) followed and have been reviewed [65].

Epidemiological studies on FMS using ACR criteria were first carried out among a population in Wichita, Kansas showing a prevalence of 2% [75] and later in London, Ontario, Canada, which reported a prevalence of 3.3% [76]. Common age (55–79 years) and much higher prevalence in women also were demonstrated [75,76]. Other population studies showed an association of psychologic distress with widespread pain [77] and tender points [78]. However, such an association between tender points and psychologic distress was not found in clinic patients [79]. Another study of non-FMS patients in the community concluded that psychiatric disorders were not intrinsic to FMS [80]. The prevalence of anxiety, stress, and depression in FMS compared with rheumatoid arthritis have shown inconsistent results [81]; however, depression most likely is associated with FMS compared with rheumatoid arthritis [82], with a familial aggregation [83].

Subgrouping has clinical, therapeutic, and pathophysiologic implications. Turk *et al.* [84] classified FMS into three subgroups based on psychosocial status and found that such subgrouping influences the outcome of an interdisciplinary treatment. Giesecke *et al.* [85] found three subgroups by cluster analysis: moderate psychologic distress with moderate control over pain and low tenderness (51.5%); high psychologic distress, low control over pain, and high tenderness; and low psychologic distress, high control over pain, and high tenderness (15.5%).

Gender difference is an important topic in current medical research. Two studies describing FMS in men, both in the general population [59] and in the clinic [60], showed that men with FMS have fewer symptoms, symptom sites, tender points, and IBS.

An instrument (Fibromyalgia Impact Questionnaire) for assessing physical and psychologic functions was developed by Burckhardt *et al.* [86••] in 1991. This well-validated questionnaire has been used widely in research and clinical practice and has been validated in numerous non-English languages.

The most significant advance in the area of disease mechanisms in FMS is the recognition that FMS essentially is a disease of the CNS, although peripheral factors may initiate or perpetuate the central mechanisms [73•]. Of similar significance is further characterization of the central mechanism (*ie,* CS) [66•,70•,71•], which is influenced by other factors (*eg,* psychologic, hormonal, autonomic, trauma, and genetic). The clear evidence of CS in FMS was presented in 1993 by Granges and Littlejohn [87] using algometric pressure stimulus and by Arroyo and Cohen [88] using innocuous cutaneous electric stimulus in the same year. Further evidence of central sensitization subsequently was provided by many other investigators [66•,70•,71•]. Among these, important are the demonstration of temporal summation by Staud *et al.* [89•] and a decreased spinal nociceptive flexion reflex, in addition to decreased pain threshold to pressure, heating, and cooling by Desmeules *et al.* [90•]. Decreased nociceptive flexion reflex would suggest that central sensitization in FMS is independent of self-reported pain.

The first imaging study (by single photon emission tomography) in support of CS was published by Mountz *et al.* [91] showing decreased cerebral blood flow in thalami and caudate nuclei, which are structures known to modulate pain; more direct evidence of central augmented pain processing following a peripheral stimulus was presented by Gracely *et al.* [92] using functional magnetic resonance imaging. An abnormality of hypothalamic-pituitary-adrenal axis showing hyperactive pituitary release of adrenocorticotropic hormone and relative hyporesponsiveness of the adrenal cortex was reported first by Griep *et al.* [93] and then by Crofford *et al.* [94]. Significantly decreased somatomedin C/growth hormone level was reported first by Bennett *et al.* [95], with further confirmation by several other studies; however, its role in the pathogenesis of FMS is unclear. The role of the autonomic nervous system, particularly sympathetic overactivity, was discussed by Martinez-Lavin and Hermosillo [96] in a review that included their own significant contributions in this area.

Since 1989, several studies showing associations of FMS with genetic markers and familial aggregations have been published. However, association studies have limitations because of multiple biases, including the selection of patients and control subjects. Genetic linkage studies by evaluation of multicase families are free from such bias. Such a study of 40 multicase FMS families showing a genetic linkage of FMS with *HLA* was first published in 1999 [97]; these results were confirmed using 80 multicase families, showing a greater significant linkage with the *HLA* gene [98].

Central sensitization is mediated through neurochemicals (*eg,* substance P and serotonin). An increased substance P level in the cerebrospinal fluid of patients with FMS was first published by Vaeroy *et al.* [99•] and then by Russell *et al.* [100•], who showed other neurochemical abnormalities, including low serotonin [101].

Significant deconditioning in FMS has been demonstrated [102]. Lack of physical fitness likely plays a role in the pathogenesis of FMS, with therapeutic implications. However, it seems important that physical fitness among patients with FMS and control subjects be assessed to ensure that deconditioning is not a confounding factor in muscle [37••] or cerebral blood flow studies in FMS. The role of trauma in FMS was first shown convincingly by Buskila *et al.* [103] in 1997.

Relatively few significant contributions have been made in the therapeutic area in FMS. Efficacy of amitriptyline in FMS by randomized, blinded, controlled trials was first shown by Carette *et al.* [104] and then by Goldenberg *et al.* [105] in 1986. Similar efficacy of cyclobenza-

prine [106] and of tramadol [107] by randomized, controlled studies subsequently have been shown by Bennett *et al.* [106,107]. The success of multidisciplinary treatment and of cognitive behavioral therapy by appropriate randomization and control groups have not been definitely determined. Physical exercise seems to be of value, but results have been inconsistent. Important chronologic developments in FMS are shown in Table 2.

Conclusions

Fibromyalgia syndrome now is a generally well-recognized clinical condition that causes much chronic pain and disability. It evolved from a non-descript muscular rheumatism some 500 years ago. The term "fibrositis" was used in 1904. However, it represented local or regional musculoskeletal pain. The characteristic generalized pain in FMS was suggested by Smythe [61••] in 1972, setting the stage for the modern picture of this disorder. In the past 25 years or so, numerous controlled clinical and neuroendocrine studies have established FMS as a recognizable entity by its own right on a pathophysiologic basis. The pathogenesis of this disorder now is accepted to be an aberration of central neurohormonal functions, particularly central sensitization. Serotonergic and norepinephric medications are the main pharmacologic treatment options at this time.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Ruhman W: **The earliest book on rheumatism.** *Br J Rheumatol* 1940, **2:**140–162.
2. Block SR: **Fibromyalgia and the rheumatisms: common sense and sensibility.** *Rheum Dis Clin North Am* 1993, **19:**61–78.
3. Valleix FL: *Traite Des Nervalgies ou Affections Douloureuses Des Nerfs.* Paris: JB Bailliere; 1841:266–594.
4. Froriep R: *Ein Beitrag zur Pathologie des Rheumatismus.* Weimar: 1843.
5. Baldry PE: **The evolution of current concepts.** In *Myofascial Pain and Fibromyalgia Syndromes.* Edited by Baldry PE. Edinburg: Churchill Livingstone; 2001:3–15.
6. Beard GM: *A Practical Treatise on Nervous Exhaustion (Neurasthenia).* New York: William Wood and Co; 1880.
7. • Gowers WR: **Lumbago: its lessons and analogues.** *BMJ* 1904, **i:**117–121.

First coining of the term fibrositis, which was used for the next 72 years.

8. Telling WH: **Nodular fibromyositis: an everyday affliction and its identity with so-called muscular rheumatism.** *Lancet* 1911, **1:**154–158.
9. Schade H: **Untersuchungen in der Erkaltungsfrage. III: Ueber den rheumatismus, insbesondere den muskelrheumatismus (myogelose).** *Munch Med Wschr* 1921, **68:**418–420.
10. Lange F, Everbusch G: **Die Bedeutung der Muskelharten fur die allgemeine Praxis.** *Munich Med Wochenschr* 1921, **68:**418–420.
11. Albee F: **Myofasciitis: a pathological explanation of any apparently dissimilar conditions.** *Am J Surg* 1927, **3:**523–533.
12. Murray G: **Myofibrositis as simulator of other maladies.** *Lancet* 1929, **1:**113–116.
13. Clayton EG: **Fibrositis.** *Lancet* 1930, **1:**420–1423.
14. Rowe AH: **Allergic toxemia and migraine due to food allergy.** *Calif West Med J* 1930, **33:**785.
15. Halliday JL: **Psychological factors in rheumatism.** *BMJ* 1937, **i:**213–217, 264–269.
16. Thompson JM: **Tension myalgia as a diagnosis at the Mayo Clinic and its relationship to fibrositis, fibromyalgia, and myofascial pain syndrome.** *Mayo Clin Proc* 1990, **65:**1237–1248.
17. Randolph T: **Allergic myalgia.** *J Michigan State Med Soc* 1951, **50:**487.
18. Travell J, Rinzler S, Herman M: **Pain and disability of the shoulder and arm: treatment by intramuscular infiltration with procaine hydrochloride.** *JAMA* 1942, **120:**417–434.
19. Raspe H: **Rheumatism epidemiology in Europe.** *Soz Praventivmed* 1992, **37:**168–178.
20. Awad EA: **Interstitial myofibrositis: hypothesis of the mechanism.** *Arch Phys Med Rehabil* 1973, **54:**449–453.
21. Hench PK: **Nonarticular rheumatism, 22nd rheumatism review: review of the American and English literature for the years 1973 and 1974.** *Arthritis Rheum* 1976, **19(suppl):**1081–1089.
22. Balfour W: **Observations on the pathology and cure of rheumatism.** *Edinb Med Surg J* 1815, **11:**168–187.
23. Scudamore C: *A Treatise on the Nature and Aure of Rheumatism.* London; 1827:II.
24. Inman T: **Remarks on myalgia or muscular pain.** *BMJ* 1858, 407–408.
25. Cornelius A: **Narben und nerven: deutsche militatarztlische.** *Zeitschrift* 1903, **32:**657–673.
26. Virchow R: **Ueber parenchymatose entzundung.** *Arch Pathol Anat* 1852, **4:**261–279.
27. Reynolds MD: **The development of the concept of fibrositis.** *J History Med Allied Sci* 1983, **38:**5–35.
28. Strauss H: Uber die sogenannte "rheumatische muskelschwiele." **Klin Wochenschr** 1898, **35:**89–91, 121–123.
29. Port K: **Eine fur den orthopaden wichtige gruppe des chronischen rheumatismus (Knotchenrheumatismus).** *Arch Orthop Unfallchir* 1920, **17:**465–506.
30. Haberling W: **Johan Georg Mezger of Amsterdam: the founder of scientific massage.** *Med Life* 1932, **39:**190–207.
31. Graham D: **Massage in muscular rheumatism and its possible value in the diagnosis of muscular rheumatism from neuritis.** *Am J Med Sci* 1893, **106:**190–198.
32. Stockman R: **The causes, pathology, and treatment of chronic rheumatism.** *Edinb Med J* 1904, **15:**107–116.
33. Schmidt A: **Der muskelrheumatismus (myalgie) auf grund eigener beobachtungen und untersuchungen gemeinverstandlich dargestelli.** *Bonn* 1918, 46–47.
34. Abel O Jr, Siebert WJ: **Fibrositis.** *J Mo Med Assoc* 1939, **36:**435–437.
35. Collins DH: **Fibrositis and infection.** *Ann Rheum Dis* 1940, **2:**114–125.
36. Slocumb CH: **Fibrositis.** *Ann Rheum Dis* 1943, **2:**169–178.
37. •• Yunus MB, Kalyan-Raman UP, Masi AT, Aldag JC: **Electron microscopic studies of muscle biopsy in primary fibromyalgia syndrome: a controlled and blinded study.** *J Rheumatol* 1989, **16:**97–101.

The first controlled and blinded evaluation of muscle histology in FMS showing normal results. The findings helped to focus on central mechanisms.

38. Osler W: *The Principles and Practice of Medicine,* edn 7. New York: Appleton; 1909.
39. Llewellyn LJ, Jones AB: *Fibrositis.* London: William Heinemann; 1913.
40. Slocumb CH: **Differential diagnosis of periarticular fibrositis and arthritis.** *Proc Staff Meet Mayo Clin* 1936, **11:**363–368.
41. Reichart A: **Reflexschmerzen auf grund von myoglosen.** *Dtsch Med Wochenschr* 1938, **64:**823–824.
42. Gutstein M: **Diagnosis and treatment of muscular rheumatism.** *Br J Phys Med* 1938, **1:**302–321.

43. Steindler A: **The interpretation of sciatic radiation and the syndrome of low back pain.** *J Bone Joint Surg* 1940, **22:**28–34.
44. Kellgren JH: **Observations on referred pain arising from muscle.** *Clin Sci* 1938, **3:**175–190.
45. Kellgren JH: **On distribution of pain arising from deep somatic structures with charts of segmental pain areas.** *Clin Sci* 1939, **4:**35–46.
46. Kelly M: **The treatment of fibrositis and allied disorders by local anesthesia.** *Med J Aust* 1941, **1:**294–298.
47. Kelly M: **Local injections for rheumatism.** *Med J Aust* 1962, **1:**4–7.
48. Travell J, Rinzler S: **Myofascial genesis of pain.** *Postgrad Med* 1952, **11:**425–434.
49. Bach F: **Physical medicine in the treatment of rheumatic diseases in the armed forces an impression of the war years.** *Arch Phys Med* 1947, **27:**734–737.
50. Beeson P, Scott T: **Clinical epidemiological and experimental observations in an acute myalgia of the neck and shoulders: its possible relation to certain cases of generalized fibrositis.** *Proc R Soc Med* 1942, **35:**733–740.
51. Boland P, Corr W: **Psychogenic rheumatism.** *JAMA* 1943, **123:**805–809.
52. Ellman P, Savage OA, Wittkower E, Rodger TF: **A biographical study of fifty civilian and military cases from the Rheumatic unit, St Stephen's Hospital (London County Council), and a military hospital.** *Ann Rheum Dis* 1942, **3:**56–76.
53. Halliday JL: **The obsession with fibrositis.** *BMJ* 1942, **1:**164.
54. Graham W: **Fibrositis.** In *Arthritis and Allied Conditions,* edn 4. Edited by Hollander JL. Philadelphia: Lea & Febiger; 1949:622–647.
55. Copeman WS, Pugh LG: **Effect of artificial dehydration in rheumatism.** *Lancet* 1945, **2:**553–555.
56. Leavitt F, Katz RS, Golden HE, *et al.*: **Comparison of pain properties in fibromyalgia patients and rheumatoid arthritis patients.** *Arthritis Rheum* 1986, **29:**775–781.
57. Traut EF: **Fibrositis.** *J Am Geriatr Soc* 1968, **16:**531–538.
58.•• Wolfe F, Smythe HA, Yunus MB, *et al.*: **The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: report of the Multicenter Criteria Committee.** *Arthritis Rheum* 1990, **33:**160–172.

This multicenter study set the criteria for uniform classification of FMS for research purposes that have been used all over the world. These criteria also are helpful for clinical diagnosis.

59. Wolfe F, Ross K, Anderson J, Russell IJ: **Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms.** *J Rheumatol* 1995, **22:**151–156.
60. Yunus MB, Inanici F, Aldag JC, Mangold RF: **Fibromyalgia in men: comparison of clinical features with women.** *J Rheumatol* 2000, **27:**485–490.
61.•• Smythe H: **Nonarticular rheumatism and psychogenic musculoskeletal syndromes.** In *Arthritis and Allied Conditions,* edn 8. Edited by McCarty DJ. Philadelphia: Lea & Febiger; 1972:881–891.

The first description of modern day fibromyalgia with widespread pain and multiple tender points that generated research interest.

62.•• Moldofsky H, Scarisbrick P, England R, Smythe H: **Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects.** *Psychosom Med* 1975, **37:**341–351.

The first study of sleep encephalogram in FMS showing arousal in non-REM sleep.

63. Smythe HA, Moldofsky H: **Two contributions to understanding of the "fibrositis" syndrome.** *Bull Rheum Dis 1977*–1978, **28:**928–931.
64.•• Yunus M, Masi AT, Calabro JJ, *et al.*: **Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls.** *Semin Arthritis Rheum* 1981, **11:**151–171.

This is the first controlled study of the clinical characteristics of FMS that provided the first data-based criteria for FMS. It also confirmed previous anecdotally described symptoms and a high number of tender points in FMS and added new features, including association of fibromyalgia with IBS and headaches.

65. Yunus MB: **Symptoms and signs of fibromyalgia syndrome: an overview.** In *Text Book of Fibromyalgia and Other Non-neuropathic Chronic Pain Syndromes.* Edited by Wallace DJ, Clauw DJ. Philadelphia: Lippincott Williams & Wilkins; in press.
66.• Yunus MB: **The concept of central sensitivity syndromes.** In *Text Book of Fibromyalgia and Other Non-neuropathic Chronic Pain Syndromes.* Edited by Wallace DJ, Clauw DJ. Philadelphia: Lippincott Williams & Wilkins; in press.

An important chapter that describes the concept of central sensitivity syndromes and reviews all of the currently available evidence for mutual associations and central sensitization among FMS and related conditions.

67. Yunus MB: **Fibromyalgia: a need for uniform classification.** *J Rheumatol* 1983, **10:**841–844.
68.•• Yunus MB: **Primary fibromyalgia syndrome: current concepts.** *Compr Ther* 1984, **10:**21–28.

The first article that depicts the interconnectedness between FMS and similar syndromes by a Venn diagram.

69.• Hudson JI, Pope HG Jr: **Fibromyalgia and psychopathology: Is fibromyalgia a form of "affective spectrum disorder?"** *J Rheumatol* 1989, **19(suppl):**15–22.

This article proposes overlaps between FMS and related conditions as well as several psychiatric conditions. All of these syndromes later were proposed to be connected by central sensitization rather than by affective mechanism.

70.• Bennett RM: **Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia.** *Mayo Clin Proc* 1999, **74:**385–398.

A useful review of central sensitization in FMS.

71.• Yunus MB: **Central sensitivity syndromes: a unified concept for fibromyalgia and other similar maladies.** *J Indian Rheumatism Assoc* 2000, **8:**27–33.

An important review of evidence for central sensitization in FMS and other related disorders. It also suggests a new terminology of "central sensitivity syndromes" for these disorders.

72. Yunus MB, Masi AT: **Juvenile fibromyalgia syndrome: a clinical study of 33 patients and matched normal controls.** *Arthritis Rheum* 1985, **28:**138–145.
73.• Yunus MB: **Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation.** *J Rheumatol* 1992, **19:**846–850.

An editorial that proposes a model for FMS pathogenesis with emphasis on aberrant central pain mechanisms interacting with peripheral factors.

74. Wolfe F, Cathey MA, Kleinheksel SM: **Fibrositis (fibromyalgia) in rheumatoid arthritis.** *J Rheumatol* 1984, **11:**814–818.
75. Wolfe F, Ross K, Anderson J, *et al.*: **The prevalence and characteristics of fibromyalgia in the general population.** *Arthritis Rheum* 1995, **38:**19–28.
76. White KP, Speechley M, Harth M, Ostbye T: **The London Fibromyalgia Epidemiology Study: direct health care costs of fibromyalgia syndrome in London, Canada.** *J Rheumatol* 1999, **26:**885–889.
77. Croft P, Rigby AS, Boswell R, *et al.*: **The prevalence of chronic widespread pain in the general population.** *J Rheumatol* 1993, **20:**710–713.
78. Croft P, Schollum J, Silman A: **Population study of tender point counts and pain as evidence of fibromyalgia.** *BMJ* 1994, **309:**696–699.
79. Yunus MB, Ahles TA, Aldag JC, Masi AT: **Relationship of clinical features with psychological status in primary fibromyalgia.** *Arthritis Rheum* 1991, **34:**15–21.
80. Aaron LA, Bradley LA, Alarcon GS, *et al.*: **Psychiatric diagnoses in patients with fibromyalgia are related to health care-seeking behavior rather than to illness.** *Arthritis Rheum* 1996, **39:**436–445.
81. Yunus MB: **Psychological aspects of fibromyalgia syndrome: a component of the dysfunctional spectrum syndrome.** *Baillieres Clin Rheumatol* 1994, **8:**811–837.

82. Hawley DJ, Wolfe F: **Depression is not more common in rheumatoid arthritis: a 10-year longitudinal study of 6153 patients with rheumatic disease.** *J Rheumatol* 1993, **20:**2025–2031.

83. Arnold LM, Iyengar SK, Khan MA, *et al.*: **Genetic linkage of fibromyalgia to the serotonin receptor 2A region on chromosome 13 and the HLA region on chromosome 6 [Abstract].** *Arthritis Rheum* 2003, **48(suppl 9):**S228–S229.

84. Turk DC, Okifuji A, Sinclair JD, Starz TW: **Differential responses by psychosocial subgroups of fibromyalgia syndrome patients to an interdisciplinary treatment.** *Arthritis Care Res* 1998, **11:**397–404.

85. Giesecke T, Williams DA, Harris RE, *et al.*: **Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors.** *Arthritis Rheum* 2003, **48:**2916–2922.

86.•• Burckhardt CS, Clark SR, Bennett RM: **The Fibromyalgia Impact Questionnaire: development and validation.** *J Rheumatol* 1991, **18:**728–733.

An instrument for assessing physical and psychologic functions in FMS that has been widely accepted and used.

87. Granges G, Littlejohn G: **Pressure pain threshold in pain-free subjects, in patients with chronic regional pain syndromes, and in patients with fibromyalgia syndrome.** *Arthritis Rheum* 1993, **36:**642–646.

88. Arroyo JF, Cohen ML: **Abnormal responses to electrocutaneous stimulation in fibromyalgia.** *J Rheumatol* 1993, **20:**1925–1931.

89.• Staud R, Vierck CJ, Cannon RL, *et al.*: **Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome.** *Pain* 2001, **91:**165–175.

This well-designed study demonstrates temporal summation, an important evidence of central sensitization in FMS.

90.• Desmeules JA, Cedraschi C, Rapiti E, *et al.*: **Neurophysiologic evidence for a central sensitization in patients with fibromyalgia.** *Arthritis Rheum* 2003, **48:**1420–1429.

This article demonstrates central sensitization in FMS regardless of patient-reported pain.

91. Mountz JM, Bradley LA, Modell JG, *et al.*: **Fibromyalgia in women: abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels.** *Arthritis Rheum* 1995, **38:**926–938.

92. Gracely RH, Petzke F, Wolf JM, Clauw DJ: **Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.** *Arthritis Rheum* 2002, **46:**1333–1343.

93. Griep EN, Boersma JW, de Kloet ER: **Altered reactivity of the hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome.** *J Rheumatol* 1993, **20:**469–474.

94. Crofford LJ, Pillemer SR, Kalogeras KT, *et al.*: **Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia.** *Arthritis Rheum* 1994, **37:**1583–1592.

95. Bennett RM, Clark SR, Campbell SM, Burckhardt CS: **Low levels of somatomedin C in patients with the fibromyalgia syndrome: a possible link between sleep and muscle pain.** *Arthritis Rheum* 1992, **35:**1113–1116.

96. Martinez-Lavin M, Hermosillo AG: **Autonomic nervous system dysfunction may explain the multi-system features of fibromyalgia.** *Semin Arthritis Rheum* 2000, **29:**197–199.

97. Yunus MB, Khan MA, Rawlings KK, *et al.*: **Genetic linkage analysis of multicase families with fibromyalgia syndrome.** *J Rheumatol* 1999, **26:**408–412.

98. Arnold LM, Hudson JI, Hess EV, *et al.*: **Family study of fibromyalgia.** *Arthritis Rheum* 2004, **50:**944–952.

99.• Vaeroy H, Helle R, Forre O, *et al.*: **Elevated CSF levels of substance P and high incidence of Raynaud's phenomenon in patients with fibromyalgia: new features for diagnosis.** *Pain* 1988, **32:**21–26.

The first report of elevated substance P in the cerebrospinal fluid of patients with fibromyalgia.

100.• Russell IJ, Orr MD, Littman B, *et al.*: **Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome.** *Arthritis Rheum* 1994, **37:**1593–1601.

An important confirmation of elevated substance P in cerebrospinal fluid in patients with FMS.

101. Russell IJ, Michalek JE, Vipraio GA, *et al.*: **Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome.** *J Rheumatol* 1992, **19:**104–109.

102. Bennett RM, Clark SR, Goldberg L, *et al.*: **Aerobic fitness in patients with fibrositis: a controlled study of respiratory gas exchange and 133xenon clearance from exercising muscle.** *Arthritis Rheum* 1989, **32:**454–460.

103. Buskila D, Neuman L, Vaisberg G, *et al.*: **Increased rates of fibromyalgia following cervical spine injury: a controlled study of 161 cases of traumatic injury.** *Arthritis Rheum* 1997, **40:**446–452.

104. Carette S, McCain GA, Bell DA, Fam AG: **Evaluation of amitriptyline in primary fibrositis: a double-blind, placebo-controlled study.** *Arthritis Rheum* 1986, **29:**655–659.

105. Goldenberg DL, Felson DT, Dinerman H: **A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia.** *Arthritis Rheum* 1986, **29:**1371–1377.

106. Bennett RM, Gatter RA, Campbell SM, *et al.*: **A comparison of cyclobenzaprine and placebo in the management of fibrositis: a double-blind, controlled study.** *Arthritis Rheum* 1988, **31:**1535–1542.

107. Bennett RM, Kamin M, Karim R, Rosenthal N: **Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study.** *Am J Med* 2003, **114:**537–545.