

# Proposed pathogenesis of fibrositis<sup>1</sup>

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While the pathogenesis of fibrositis is not clearly understood, it is useful to consider it as a disorder of pain modulation which is due at least in part to deficient concentrations of certain amines in the central nervous system. Any clinical entity which interferes with stage IV sleep (as indicated by disturbed delta wave patterns), whether "psychogenic" or "organic," can cause fibrositis. Thus it is not appropriate to speak of "primary" and "secondary" forms of the disease. The large number of persons who suffer from the pain, fatigue, depression, and anxiety associated with fibrositis mandate further investigations into its causes and treatment.

Index term: Fibrositis

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Two separate sets of criteria are presently used to define fibrositis<sup>1,2</sup> (*Tables 1 and 2*). However, neither set of criteria has been sanctioned by the American Rheumatism Association and thus further study of appropriate patient populations is necessary. Typically, the patient complains of pain "all over," often characterized as deep aching or burning pain located between the shoulder blades and radiating to the posterior neck, occiput, shoulder, and distally along the posterior aspect of the arms. Most patients also describe midline chest pain radiating to the anterior chest wall and lumbosacral pain radiating to the posterior aspect of the legs. While the pain may last for many years, the severity tends to fluctuate, usually being exacerbated by periods of immobilization, exposure to cold, and tension. Other symptoms which often accompany general myalgia include occipitofrontal headaches, dizziness or lightheadedness, per-

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**Table 1.** Criteria for the diagnosis of fibrositis according to Moldofsky et al<sup>7</sup>

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1. Widespread aching lasting more than three months
  2. Local tenderness at 12 of the following 14 sites:
    - a. Midpoint of the upper fold of the trapezius (bilateral)
    - b. Second interspace just lateral to the costochondral junction (bilateral)
    - c. "Tennis elbow" sites 1 to 2 cm distal to the lateral epicondyles, affecting the muscle that tenses when the long finger is extended (bilateral)
    - d. At the origin of the supraspinatus muscle, above the scapular spine and near the medial border (bilateral)
    - e. Anterior aspect of the inter-transverse spaces of the low cervical spine (C3-7) (unilateral)
    - f. Interspinous ligaments of the low lumbar spine (L4-S1) (unilateral)
    - g. Upper outer quadrants of the buttock, in the anterior fold of the gluteus medius muscle (bilateral)
    - h. Medial fat pad overlying the medial collateral ligament of the knee, proximal to the joint line (bilateral)
  3. Skin roll tenderness over the upper scapular region
  4. Disturbed sleep, morning fatigue and stiffness
  5. Normal erythrocyte sedimentation rate, SGOT, rheumatoid factor, antinuclear factor, muscle enzymes, and sacroiliac radiographs
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vative fatigue, globus hystericus, palpitations, a "nervous" stomach, sleeplessness, and alternating constipation and diarrhea. On physical examination, a great many tender points (including those outlined in the *Figure*) are found on palpation; other tender areas may include the rhomboids, longissimus dorsi, belly of the pectoralis major, erector spinae, hamstrings, the vertebra prominens spinous process, and the episacral fat pad. Deep tendon reflexes tend to be symmetrically brisk. Neck and low back motion may be reduced

by muscle spasm. The joint examination should show no evidence of synovitis or decreased range of motion. Subjective tenderness of the joints may occur in a few patients.<sup>2</sup> Otherwise, the physical examination should be normal, as should be laboratory tests. One minor "abnormality" is straightening of the normal lordotic curve of the cervical spine on lateral radiographs, which merely suggests muscle spasm and is entirely non-specific.

Because of the generalized nature of fibrositis,

**Table 2.** Criteria for the diagnosis of fibrositis according to Yunus et al<sup>2</sup>

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1. Obligatory criteria
    - a. Aches, pains, or stiffness lasting at least three months and involving three or more anatomic sites
    - b. Absence of secondary causes
  2. Major criterion
 

Five tender points (usually the same points as in *Table 1*, but less rigidly defined)
  3. Minor criteria
    - a. Modulation of symptoms by physical activity
    - b. Modulation of symptoms by weather
    - c. Aggravation of symptoms by anxiety and stress
    - d. Poor sleep
    - e. General fatigue
    - f. Anxiety
    - g. Chronic headache
    - h. Irritable bowel syndrome
    - i. Subjective swelling
    - j. Numbness

For a diagnosis of fibrositis, both obligatory criteria must be positive, coupled with either (a) the positive major criterion and three minor criteria or (b) five minor criteria

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the differential diagnosis is extensive. Symptoms may be indistinguishable from early or mild hypothyroidism,<sup>3</sup> though the sluggish deep tendon reflexes seen in the latter condition may help in differentiation. Metabolic disorders which affect calcium homeostasis and produce bone pain can also be confused with fibrositis, and care should be taken to differentiate muscular from bony tenderness. Early or mild connective tissue disease may mimic fibrositis: this includes ankylosing spondylitis, rheumatoid arthritis, and systemic lupus erythematosus in young persons and polymyalgia rheumatica in the elderly. However, abnormal radiographs, autoantibodies, and elevated acute-phase reactants are helpful. Infectious diseases, including subacute bacterial endocarditis and post-viral myalgia, must not be overlooked. The stiffness, paucity of movement, and expressionless face seen in extrapyramidal neurological diseases can often be mistaken for fibrositis.

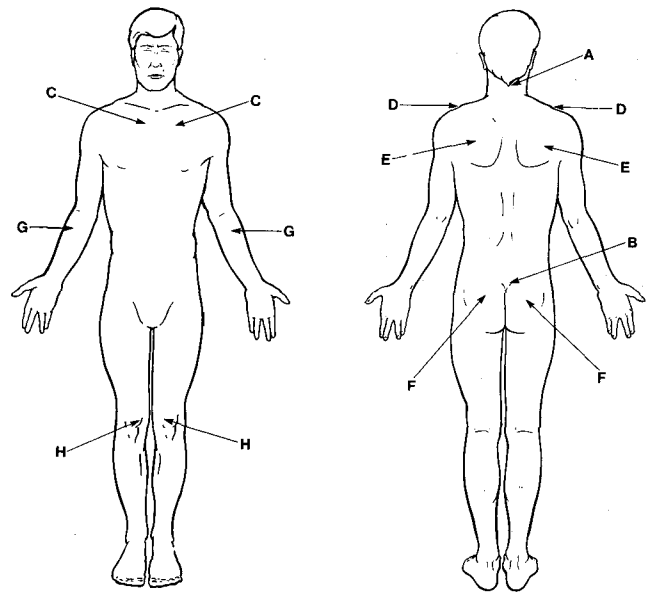
**Theories of pathogenesis**

The term *fibrositis* was proposed by Gowers in 1904,<sup>4</sup> although the syndrome had been reported in the medical literature many years before. Simons published an excellent review in 1975 and 1976.<sup>5,6</sup> The important historical theories may be roughly divided into three categories:

1. *Nodular*: the muscle itself is abnormal, or extraneous material has been deposited at the painful site.
2. *Neurovascular*: trauma or some other factor gives rise to a lesion which then activates the regional reflex pathways which mediate distal vasodilatation and hyperalgesia.
3. *Psychogenic*: the overriding cause of the symptoms is psychopathological.

The clinical observations and laboratory studies which resulted in these theories help explain some of the signs and symptoms of fibrositis. Taken together, they imply that there is a relationship between fibrositis, local phenomena with referred hyperalgesia, and depression. Two recent studies by Moldofsky et al help to relate these factors.

In 1975, Moldofsky et al<sup>7</sup> reported their findings regarding fibrositis and non-rapid eye movement (non-REM) sleep disturbance. They first studied the electrophysiological patterns of sleep in 10 patients with fibrositis (mean age, 51.9) for two or three nights using standard electroencephalographic (EEG) techniques. In 7 patients, stage



**Fig.** Areas of point tenderness in fibrositis. A = interspinous ligaments (C4-6), B = interspinous ligaments (L4-S1), C = second intercostal junction, D = trapezius (upper fold), E = supraspinatus origin, F = gluteus medius, G = forearm (extensor muscle), and H = knees (medial fat pads).

IV sleep was contaminated with alpha rhythm; in 3, delta waves (considered the hallmark of stage IV sleep) were entirely absent. The authors concluded that stage IV sleep is deficient in patients with fibrositis. In the second part of the study, 6 paid volunteers 19 to 24 years of age were studied. During the first two nights, sleep was undisturbed. For the next three nights, they were deprived of stage IV sleep by application of an auditory stimulus whenever more than four delta waves appeared on EEG. Thereafter, they spent two more undisturbed nights in the sleep laboratory. All subjects were evaluated with a dolorimeter and questionnaire. Dolorimetry was performed twice during each 24-hour period and demonstrated increased muscular tenderness on the mornings following stage IV sleep deprivation. The subjects also complained of fatigue, anorexia, and heaviness of the limbs. Symptoms were alleviated when the subjects were allowed to sleep normally for two or three nights. In a second paper,<sup>8</sup> subjects were deprived of rapid eye movement (REM) sleep and stage IV sleep; however, only the latter-group experienced fibrositis-like symptoms.

In order to fully appreciate the implications of these clinical studies, it is necessary to review

sleep physiology and the role of indoleamines. Sleep may be divided into two phases, REM and non-REM. REM sleep occupies approximately 25% of total sleeping time and recurs approximately every 90 minutes; it is associated with rapid conjugate eye movements and decreased striated muscle tone in the trunk and extremities. Non-REM sleep may be subdivided into stages I, II, III, and IV. The proportion of high-amplitude (delta) waves increases as the subject progresses from stage I through stage IV. Uncontaminated stage IV sleep is comprised almost entirely of delta waves. A normal person spends a mean of 9%–12% of sleeping time in stage IV. The neurotransmitter serotonin, produced in the median raphe cells of the brainstem, is important in non-REM sleep.<sup>9–13</sup> Norepinephrine, produced in the locus ceruleus of the pons, seems to be necessary for REM sleep. Chemicals such as L-tryptophan, tricyclic antidepressant drugs, chlorpromazine, and fenfluramine have all been shown to increase stage IV sleep, presumably because of their ability to increase the relative concentrations of serotonin in the central nervous system (CNS).<sup>9,12,13</sup> On the other hand, L-dopa, benzodiazepines, reserpine, and barbiturates decrease the percentage of stage IV sleep, presumably because they lower CNS concentrations of serotonin.<sup>9,12</sup>

In human beings, sleep is an active process with regard to endocrine function. Growth hormone and prolactin attain their highest concentrations during stage IV sleep.<sup>11</sup> Thyroid-stimulating hormone and luteinizing hormone are also preferentially released into the circulation during sleep,<sup>11</sup> though peak release and synthesis do not appear to be stage-specific. Kovačević and Radulovački<sup>14</sup> have demonstrated high levels of serotonin and its breakdown products in the hippocampus of cats during stage IV sleep, suggesting that synthesis is increased; however, their studies required killing the animals and can not be duplicated in humans.

Concentrations of serotonin in the CNS have also been linked to perception of pain. In animal studies, decreased concentrations of CNS serotonin have been associated with increased sensitivity to pain.<sup>15,16</sup> Sicuteri<sup>17</sup> produced symptoms of hyperalgesia and myalgia in 4 patients using parachlorophenylalanine, a selective enzyme inhibitor of serotonin synthesis. Other animal studies have shown that synthesis of brain serotonin is dependent upon the disposition of plasma-free tryptophan.<sup>18</sup> Moldofsky and Warsh<sup>19</sup> have dem-

onstrated an inverse relationship between plasma-free tryptophan and subjective perception of pain in 8 patients with fibrositis. Further animal studies have shown that serotonin potentiates the analgesic effects of beta-endorphin and enkephalin.<sup>20,21</sup> Finally, a recent study involving 11 women with fibrositis showed increased serum levels of beta-endorphin compared to controls or to a third group of patients with rheumatoid arthritis.<sup>22</sup>

Affective disorders have also been linked to fibrositis. The early work of Schildkraut et al<sup>23</sup> in the mid-1960s demonstrated relationships among norepinephrine, serotonin, and depression. Both low and normal concentrations of serotonin and 5-hydroxyindoleacetic acid have been found in patients with depression.<sup>24,25</sup> Asberg et al<sup>25</sup> feel that at least one form of endogenous depression is characterized by low serotonin concentrations in the CNS as measured in the cerebrospinal fluid. In addition, laboratory studies of sleep have documented a decrease in stage IV sleep in patients with primary and secondary depression.<sup>26,27</sup> Payne et al<sup>28</sup> compared the Minnesota Multiphasic Personality Inventory (MMPI) profiles of 30 patients with fibrositis to those of controls and patients with rheumatoid arthritis. The profiles in fibrositis patients showed higher levels of abnormality and were more variable than those in the other two groups, "indicating that they were more psychologically disturbed. . . ."

Thus, it is clear that neurotransmitter balance is disturbed in depression and may be important in the pathogenesis of fibrositis. This information allows us to postulate some relationships between depression, the concentrations of serotonin in the CNS, stage IV sleep, and enhanced pain sensitivity with referred hyperalgesia:

1. Depression or other factors deprive the individual of stage IV sleep.
2. Decreased stage IV sleep results in concentrations of serotonin in the CNS.
3. Deficient CNS serotonin interferes with the normal physiological function of endorphins and enkephalins.
4. These chemical abnormalities result in increased sensitivity to pain in normally tender areas such as the belly of the trapezius, the extensor muscles at the forearm (distal to the lateral epicondyle), the second costochondral junction, the medial aspect of the knee, and various intervertebral ligaments.

5. These constantly painful areas produce referred dysesthesia resulting in distal pain and paresthesias, the "pain all over" described by so many patients with fibrositis.

Unfortunately there are some major difficulties which must be resolved before we can accept this hypothesis without reservation:

1. Increased serotonin production during stage IV sleep has not been demonstrated in man to our knowledge. In order to measure the concentration of serotonin in the hippocampus and other areas of the brain, it is necessary to section the brain during stage IV sleep. Until other methods of quantitating the concentration of these amines are devised, this problem will remain unresolved.

2. It is known that the serotonin precursor L-tryptophan can increase the relative time spent in stage IV sleep when given in 5- to 7.5-g doses prior to sleep.<sup>29</sup> Moldofsky et al<sup>30</sup> were unable to reduce the symptoms of fibrositis in a small group of patients who were given 5 g of L-tryptophan before sleep. However, in the same study, symptoms of myalgia were controlled by a small dose of chlorpromazine, another agent which has been shown to increase the relative quantity of stage IV sleep. There are several possible explanations for these findings. The authors may not have given the patient sufficient L-tryptophan to appreciably raise serotonin levels. It is equally likely that the disturbance of pain modulation experienced by patients with fibrositis may not be explained on the simple basis of decreased concentrations of serotonin in the CNS, and that the ratios of various amines may be more important than the absolute concentration of any one of them.

3. Tricyclic antidepressant drugs have been suggested for the treatment of fibrositis because they increase the relative percentage of stage IV sleep.<sup>31</sup> It is known that some of these drugs, including imipramine, increase the relative concentrations of serotonin in the CNS by blocking the re-uptake of this amine.<sup>12</sup> It is tempting to suggest that tricyclic antidepressant drugs control the symptoms of fibrositis by their effects on sleep and CNS serotonin. However, they have been used in a variety of seemingly unrelated chronic pain syndromes, including tension vascular headaches, post-herpetic neuralgia, diabetic neuropathy, trauma, malignancy, and degenerative joint disease,<sup>32-35</sup> and in these papers, the authors postulated a central action by which the drug alters

perception and sensation of pain, as well as a less-well-defined peripheral analgesic action. It may be that patients with fibrositis who respond to tricyclic antidepressant drugs are simply receiving the benefits of these nonspecific analgesic effects, and that any changes in CNS serotonin concentration or stage of sleep are unimportant.

4. Although interest in a histopathological lesion in the muscles or connective tissue in patients with fibrositis has been unpopular since the 1920s, this theory has not been entirely ruled out. In 1957, Brendstrup et al<sup>36</sup> were able to demonstrate a metachromatic staining substance in the interfibrillar connective tissues in 9 out of 12 patients who had biopsy of the sacrospinalis muscles prior to disk surgery for lumbosacral pain. Other abnormalities included microscopic findings of widened interstices, an increased number of infiltrating mast cells as well as muscle cell nuclei, and a slight accumulation of lymphocytes. Chemical analysis of the muscle tissue from these 12 patients showed an increased intercellular potassium and a 50% increase in hexosamine and chloride compared to the controls. These authors believed that such changes could be explained by muscle injury due to edema. Nearly 20 years later, Fassbender and Wegner<sup>37</sup> studied samples of the trapezius muscle taken from 11 patients with fibrositis. Electron microscopy showed progressive stages of destruction, including degeneration of the mitochondria, glycogen deposits in the muscle cells, and swollen endothelial cells occluding the capillaries. These same changes can be seen in hypoxia.

5. The CNS amine theory of the pathogenesis of fibrositis is based on the finding by Moldofsky et al that deficient stage IV sleep results in lowered pain thresholds.<sup>30</sup> However, Golden et al<sup>31</sup> were unable to demonstrate decreased delta sleep in the majority of their patients with fibrositis. Campbell et al<sup>38</sup> have observed increased sensitivity to pain at certain tender points in patients with fibrositis but were not able to demonstrate decreased pain thresholds in other muscles.

### "Secondary fibrositis"

Recently fibrositis has been classified as either "primary" or "secondary" by some authors.<sup>1,2</sup> "Primary fibrositis" is not accompanied by any other pathological musculoskeletal condition, whereas "secondary fibrositis" occurs in association with osteoarthritis, a connective tissue dis-

order, or some other condition which can cause musculoskeletal symptoms. The definition of "secondary fibrositis" does not provide a clear role for the associated condition as either the sole cause of "secondary fibrositis" or simply a contributing factor.<sup>1</sup> If we accept the previously stated hypothesis of pathophysiology for fibrositis, we can dispense with these definitions and the problems inherent in them.

Payne et al<sup>28</sup> and Ahles et al<sup>39</sup> have demonstrated that patients with fibrositis are more psychologically disturbed than controls. Wolfe et al<sup>40</sup> have shown that patients with "secondary fibrositis" share this psychological disturbance compared to controls or to patients with rheumatoid arthritis alone. Our report of hypothyroidism presenting as fibrositis<sup>3</sup> suggested that the underlying cause was reduced delta sleep as described by Kales et al.<sup>41</sup> Wittig et al<sup>42</sup> have demonstrated that patients with chronic pain "experienced alpha-intrusion into delta sleep," the very abnormality described in patients with "primary fibrositis."

We recognize that fibrositis can accompany other painful musculoskeletal conditions such as rheumatoid arthritis,<sup>43</sup> making diagnosis and treatment of the underlying condition more challenging. However, if we accept the hypothesis that fibrositis is caused by any clinical entity which interferes with delta sleep, whether "psychogenic" or "organic," then the resulting symptoms will be the same regardless of the cause. *Sensory input fibrositis* may accompany sensory neuropathy, painful arthritis, or intervertebral disk disease. *Psychological input fibrositis* may accompany anxious obsessive-compulsive states, depressive reactions, and conversion neurosis. *Pharmacological input fibrositis* may accompany caffeine abuse, anorexigenic stimulant use, narcotic withdrawal, and asthma drug therapy. *Metabolic imbalance fibrositis* is exemplified by myxedema. In this sense, all fibrositis is secondary, so that the terms "primary" and "secondary" are not appropriate.

### Treatment

The treatment of patients with fibrositis can be a challenge. These people are often difficult to deal with. Frequently they have been "doctor shopping," either by choice or necessity. They are plagued by chronic, deep, poorly localized, aching pain which is often accompanied by fatigue, depression, and anxiety. If you are the

second, third, or fourth doctor they have consulted, they may exhibit hostility and distrust, having been told previously that "there is nothing wrong with you" or "it's all in your head." Understandably, these people are desperate for help. In such cases, it is first necessary to reassure the patient that there is no evidence of cancer or any inflammatory connective tissue disease. We believe it is important to use the words "cancer," "rheumatoid arthritis," and "systemic lupus erythematosus." Next, the patient must understand that fibrositis will not lead to progressive joint deformity, muscle weakness, or paralysis. Finally, it is necessary to make it clear to the patient that although the condition can be treated, when life again becomes stressful and poor sleep returns, the symptoms are likely to return as well.

Many patients will benefit if the physiology of the disorder is explained. They must be helped to understand that the pain of fibrositis is not imaginary. We find it useful to explain that cumulative fatigue, emotional strain, poor sleep, and poor exercise habits are all related to their problem and must be dealt with. If poor sleep is a major complaint, a low-dose tricyclic antidepressant drug which affects primarily serotonin, such as doxepin hydrochloride (10–25 mg taken one or two hours before bed) is often helpful. A recent double-blind controlled study has demonstrated that the tricyclic derivative cyclobenzaprine helps relieve pain and stiffness,<sup>44</sup> thus helping to legitimize the use of tricyclic drugs in the treatment of this disorder. For analgesia, we recommend aspirin or acetaminophen. In our experience, muscle relaxants, anti-anxiety agents, and anti-inflammatory medicines are not very helpful. In a recent double-blind crossover study, prednisone (15 mg/day given for two weeks) failed to improve the symptoms of fibrositis,<sup>45</sup> demonstrating that treating inflammation does not treat fibrositis. Active exercise also seems to be helpful. Patients should be referred to a physiatrist or physical therapist to learn maneuvers which can increase the range of motion of the neck, shoulders, lumbosacral spine, and hips, and to be instructed in the proper use of dry or moist heat. Cervical traction can be beneficial. Penny et al<sup>46</sup> have demonstrated that improved cardiovascular conditioning may improve the symptoms of fibrositis, and for this reason, we suggest that young, vigorous patients engage in strenuous exercise.

## Conclusions

Our understanding of the pathogenesis of fibrositis is incomplete. The hypothesis that fibrositis is a disorder of pain modulation, due at least in part to deficient concentrations of CNS amines, helps explain some of the phenomena which have been observed in this syndrome and allows us to treat patients with relatively innocuous drugs on a "scientific" basis. This is important because fibrositis affects such a large portion of the population. In 1971, the British rheumatologist John Glyn estimated that patients which "defy accurate anatomical or pathological diagnosis" make up one third "of all those problems with which we are daily faced."<sup>47</sup> In a more recent study, Wolfe and Cathey<sup>48</sup> reported finding fibrositis in 14.6% among 1,473 consecutive patients evaluated in a rheumatology clinic.<sup>48</sup> The large number of patients affected has social and economic implications, and further investigations into the causes and treatment of fibrositis are necessary.

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