PATHOGENESIS

Most investigators in this field believe that the primary abnormality leading to expression of symptoms in fibromyalgia and related conditions is aberrant central nervous system function.[1, 9, 12] Furthermore, there is a general belief that the central components of the "stress response" are playing a major role in symptom expression, in that these systems are capable of being activated by a variety of stressors, and disturbances in this system can have effects on sensory processing and autonomic and neuroendocrine function. The principal components of the human stress response are the corticotropin-releasing hormone and the locus caeruleus-norepinephrine/autonomic (sympathetic/locus coeruleus-norepinephrine) nervous systems.[13] The corticotropin-releasing hormone system is primarily centered in the hypothalamus, and the sympathetic/locus coeruleus-norepinephrine system in the brain stem. Activation of these systems by a variety of stimuli propagates a series of physiologic changes known as the *stress response*.

There is a substantial body of literature regarding this system that cannot be reviewed in detail, but several relatively recent advances in this area may be germaine to illnesses such as fibromyalgia. For example, several investigators have noted that although this system is adaptive in animals and early human species, it may be maladaptive in the 20th century. In everyday life, this "stress" system is much more likely to be activated by daily events that have no threat to survival (e.g., sitting in traffic) than for the intended purposes of this system (e.g., to protect against predators, starvation).

Different types of stress lead to markedly different biologic responses, in both animals and humans. The environment within which stress occurs may be the most important determinant of the physiologic consequences. Stressors perceived as inescapable or unavoidable, or that are accompanied by lack of predictability or support, evoke the strongest adverse biologic consequences. This could conceivably explain why victims of trauma, such as motor vehicle accidents, appear to have a much higher rate of the development of fibromyalgia and myofascial pain than do those who are responsible for the accident.

Finally, within any species, there are genetic differences in the activity of the biologic stress response as well as in systems that process sensory information such as pain. The aggregate data collected from such studies suggest that individuals may be born with a certain "setpoint" for the functioning of such systems and that subsequent environmental exposures may change that setpoint during the life of that organism. For example, early life stressors can have a permanent and profound impact on the subsequent biologic response to stress in animals because of the plasticity of the nervous system. Studies in rodents have demonstrated that exposure to endotoxin, trauma, and separation in the neonatal period all lead to permanent changes in the subsequent biologic response to stress, extending throughout the life of the animal.[14] This plasticity may be due to changes in the numbers of neurons or number of circuits and increases or decreases in gene expression, leading to permanent changes in molecules that define the function of the system. This permanent effect of early stressors could explain why individuals who have fibromyalgia, CFS, somatoform disorders, irritable bowel syndrome, and other disorders in this spectrum report a higher than expected incidence of childhood physical and sexual abuse.

The areas of nervous system function that may be playing some role in the pathogenesis of fibromyalgia include sensory processing, autonomic and neuroendocrine systems, and psychobehavioral influences.

Abnormalities in Sensory Processing

Several investigators have moved beyond determinations of tender point counts and dolorimeter values in fibromyalgia to more extensively examine the basis for widespread pain and tenderness in this condition. Such studies have demonstrated that fibromyalgia patients cannot *detect* electrical, pressure, or thermal stimuli at lower levels than normal individuals do, but the point at which these stimuli cause pain or unpleasantness is lower.[15, 16] Other studies have examined regional differences in pain sensitivity and have demonstrated that although tender points are anatomic locations that are more sensitive to *pressure*, these regions are actually less responsive to both electrical and thermal stimuli than "control points." [15] In studies examining the precise location of the hyperalgesia in fibromyalgia, it appears as though the largest difference is deep to skin, but not exclusively muscle.[17]

Some data on pharmacologic treatment of fibromyalgia patients may offer insight into the mechanism involved in pain transmission. Sorensen and colleagues[18] examined the responsiveness of fibromyalgia patients to morphine, lidocaine, and subanesthetic doses of ketamine. They found that most subjects responded to one or more of these substances with decreased pain, although to different combinations of these medications, and the rate of placebo response was low. They suggested that this demonstrates that spinal or supraspinal mechanisms are involved in pain maintenance in this condition and that this may be due to heterogeneous processes.

Other modulating influences have been examined to elucidate the precise mechanism involved in pain transmission. One possible link between the systemic symptoms that these individuals experience and the diffuse pain is the sympathetic nervous system. There is emerging evidence that fibromyalgia may be characterized by a decrease in the activity of descending, anti-nociceptive pathways that begin in subcortical structures, including the locus caeruleus, and descend into the spinal cord. Under normal conditions, these pathways are tonically active and inhibit the upward transmission of pain. Kosek and colleagues[19] demonstrated that isometric contraction of muscle exerted the expected analgesic effect on pressure pain threshold in normal subjects, whereas fibromyalgia patients responded to this maneuver with a paradoxically lowered pain threshold. Other investigators studied the effect of a tonic painful stimulus on pain threshold in fibromyalgia patients and found that in contrast to control subjects, there was no increase in pain threshold.[20] They suggested that this indicated a lack of descending noxious inhibitory control mechanisms in the fibromyalgia patients.

Other investigators have used "functional" brain imaging in persons with fibromyalgia to substantiate the notion that there may be a disturbance in pain processing in this condition. Mountz and colleagues[21] collected data on women with fibromyalgia by single-photon emission computed tomography and found regional differences in blood flow in areas involved in pain transmission, such as the caudate nucleus. In contrast, Yunus performed baseline positron emission tomography on 10 subjects with fibromyalgia and found these scans to be normal.

Although nearly all of the research on sensory processing in fibromyalgia has focused on the processing of pain, some data suggest a more generalized disturbance in sensory processing. For example, many persons with fibromyalgia experience sensitivity to loud noises, bright lights, odors, drugs, and chemicals. These symptoms of generalized sensitivity to multiple stimuli account for the significant number of persons with fibromyalgia who also could be classified with "multiple chemical sensitivity" (an acknowledged misnomer for these symptoms).[22]

Other investigations have attempted to identify specific neurochemical abnormalities that may be associated with abnormal pain transmission. Several groups

have demonstrated that patients with fibromyalgia have approximately threefold higher concentrations of substance P in cerebrospinal fluid (CSF) than those of normal control subjects. [12, 23, 24, 25] Substance P is a pro-nociceptive peptide stored in the secretory granules of sensory nerves and released on axonal stimulation. There is remarkable consistency between the findings of these groups of investigators, and in all cases there is little overlap in substance P levels between the fibromyalgia patients and normal control subjects.

The meaning of these elevated CSF substance P levels is not entirely clear. The substance P could theoretically be derived from overactive peripheral nociceptive fibers or from central neurons. An elevated CSF level of substance P is not specific for fibromyalgia; this finding has also been noted in patients with osteoarthritis of the hip and chronic low back pain. It is likely that these findings are related to the presence of pain, because persons with CFS do not display this finding.[26] Russell has demonstrated that these substance P levels in fibromyalgia are stable or rise over time and do not change in response to an acute painful stimulus.[26A] The same magnitude of elevation of CSF substance P is found in fibromyalgia patients with and without psychiatric co-morbidities.[23] Animal models suggest that substance P and excitatory amino acids act synergistically at the level of the dorsal column of the spinal cord to contribute to the development of allodynia (a diffuse state of heightened sensitivity to normally nonpainful stimuli as seen in fibromyalgia). In these models, excitatory amino acids act rapidly to acutely change pain threshold, whereas substance P acts more slowly and is likely to be more operative in chronic pain states.

Several other substances are known to have prominent effects on nociception that may be abnormal in fibromyalgia. For example, norepinephrine has an anti-nociceptive function centrally, and the level of its principal metabolite, 3-methoxy-4-hydroxyphenethylene, is low in the CSF of fibromyalgia patients.[27] This finding again supports the possibility that descending anti-nociceptive influences from the autonomic nervous system could be a potential mechanism for the allodynia and hyperalgesia in fibromyalgia. It is also of note that some of the most effective drugs in treating central pain syndromes like fibromyalgia act by augmenting central adrenergic activity.

Finally, there is some evidence to justify a role for low central levels of serotonin in several disorders within this spectrum. There are data suggesting a generalized defect in serotonin synthesis or metabolism in fibromyalgia indicated by low levels of serotonin and its precursor, L-tryptophan, in the serum as well as by low levels of the principal metabolite, 5-hydroxyindoleacetic acid, in the CSF (serotonin is undetectable in the CSF of humans).[27, 28]

Although most evidence suggests that fibromyalgia is a disorder characterized by a *dysregulation* of the central nervous system, recent evidence from Rosner and coworkers[29] suggests that a subset of patients with this symptom complex may be suffering from unrecognized cervical spinal stenosis, or the Chiari malformation. In this setting, compression of the cervical cord, or restriction of vertebral blood flow, could conceivably be responsible for diffuse pain, fatigue, and autonomic dysfunction. In several case series, patients with symptoms of fibromyalgia and CFS have markedly improved with decompressive surgery. Controlled studies under way should help delineate whether this is a common or rare cause of fibromyalgia symptoms.

Hypothalamic-Pituitary Axis Dysfunction

Substantial data indicate that the hypothalamic-pituitary axes function abnormally in subsets of persons with fibromyalgia and related disorders.[30] Each of these disorders differs somewhat with respect to the precise perturbations, and hypothalamic function is "abnormal" in only a small subset of subjects in all instances. In fibromyalgia, most studies have revealed low 24-hour free urinary cortisol, exaggerated corticotropin release in

response to corticotropin-releasing hormone challenge, and abnormal diurnal rhythmicity of secretion of cortisol and other hormones. Adrenal insufficiency also occurs in response to exercise in fibromyalgia, because cortisol levels paradoxically fall rather than rise in response to physical exertion.[31] This post-exercise adrenal insufficiency, as well as the decreased sympathetic response to exercise noted later, might in some way contribute to the severe post-exertional pain fatigue that both fibromyalgia and CFS patients experience. These changes in the hypothalamic-pituitary axis are opposite to those seen in melancholic depression, which is characterized by chronically increased stress system activity.

Changes have also been noted in the growth hormone (GH) axis that suggest abnormal hypothalamic function. Insulin-like growth factor 1 (IGF-1) is produced in the liver, primarily in response to GH, and is responsible for many of the biologic activities of GH. Bennett and associates[32] have demonstrated that IGF-1 is low in about a quarter of fibromyalgia patients. The defect in GH secretion that leads to the low IGF-1 appears to be hypothalamic in origin, because these individuals fail to secrete GH in response to a variety of types of stimulations.[32] Although administration of recombinant GH to this subset of fibromyalgia patients has been demonstrated to be of clinical benefit, the expense of this treatment and the likelihood that other less expensive treatments may be of similar efficacy have limited the use of this modality.

Autonomic Nervous System

There are also identifiable abnormalities in autonomic nervous system function in many of the disorders in this spectrum. Just as with studies of neuroendocrine function, though, only a subset of fibromyalgia patients have "abnormal" autonomic function, depending on how this is defined. Various studies have demonstrated that subsets of persons with fibromyalgia as well as other similar disorders, such as CFS, display low baseline sympathetic tone and an inability to respond to stressors.[7, 31, 33] The clinical manifestations that are related to autonomic dysfunction are not entirely clear but may include orthostatic intolerance (e.g., as in neurally mediated hypotension), vasomotor instability, and visceral dysfunction.

Psychiatric, Psychologic, and Behavioral Factors

There has been a long-standing debate about the role of psychiatric, psychologic, and behavioral factors in fibromyalgia. Some contend that *all* of these symptoms are "supratentorial" in origin, or that fibromyalgia represents a state of distress or vulnerability, whereas others counter that the rate of psychiatric co-morbidities in these conditions is similar to any chronic disease.[34, 35] A review of the accumulated data in these conditions supports a few consistent observations.

Approximately 20 to 40 percent of individuals with fibromyalgia seen in tertiary care centers have an identifiable current mood disorder, such as depression or anxiety disorder.[36] The lifetime incidence of psychiatric co-morbidities in tertiary care patients may be as high as 40 to 70 percent over several studies.[36] These data are among those used by Hudson and colleagues[8] to posit that there is a spectrum of disorders including fibromyalgia, migraines, irritable bowel, and affective disorders that may share a common genetic predisposition and underlying pathogenic mechanisms. However, some of these differences in the current and lifetime history of mood disorders are probably due to health care-seeking behaviors, because lower lifetime incidences of affective disorders are typically noted in individuals with fibromyalgia who are identified in the general population.[37] This same relationship between the setting of care and the rate of co-morbid psychiatric conditions has been consistently noted in irritable bowel syndrome.

Myriad complex psychosocial factors play a significant role in some individuals with

fibromyalgia, as with nearly any chronic medical illness. These include behavioral pathways, such as sick role behavior and maladaptive coping mechanisms; cognitive pathways, such as victimization and loss of control; and social pathways, such as interference with role functioning and deterioration of social or other support networks. Psychosocial factors are known to play a particularly prominent role in the transition from acute pain to chronic pain and disability. As pain progresses from the acute phase into chronicity, problems emerge for the individual, such as job loss, financial constraints, and distancing of friends. If patients' responses to these problems are maladaptive, such as avoidance of work, friends, financial responsibilities, and physical activity, the patient may become distressed and overwhelmed by the pain and its negative impact on life. Increased stress, learned helplessness, depression, increased anxiety, anger, distrust, entitlement, and somatization can all emerge and worsen symptoms, probably by interrelated physiologic and psychologic mechanisms. All of these factors can be important in dictating how individuals report symptoms, how and when they seek health care, and how they respond to therapy. This may also explain why cognitive behavioral therapy (CBT), which addresses many of these issues, has generally been effective in the treatment of individuals with fibromyalgia as well as nearly any other chronic medical condition.

Other Hypotheses

A series of hypotheses regarding the cause of fibromyalgia have generally been abandoned in favor of the central nervous system theories. For example, although there may be some nonspecific abnormalities in skeletal muscle in this entity (perhaps related to deconditioning), it is unlikely that these play a major role in symptom expression. The primary reason for discarding the skeletal muscle hypothesis is the overwhelming data demonstrating that there is a generalized disturbance in pain threshold in this condition that extends well beyond skeletal muscle. Another early hypothesis, proposed by Moldolfsky and colleagues,[38] was that the symptoms of fibromyalgia may be primarily due to an underlying deficiency of stage II/IV sleep. Poor sleep is a frequent complaint in this condition, and some patients with fibromyalgia have objective abnormalities noted in sleep studies. Even though disturbed sleep is likely to play a significant role in symptom expression in some patients and may contribute to some of the physiologic abnormalities (e.g., low IGF-1), the aggregate data do not support the notion that disturbed sleep alone is causing this illness.