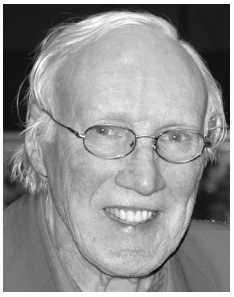
Editorial



Incarnations of Fibromyalgia

Two years ago an original and inoffensive article about fibromyalgia (FM) in the Amish[1] was accompanied and followed by a storm of editorials and correspondence, not addressing the point of the study, but broadly the definition of the condition and its label. In his astonished reply, White describes and discusses FM as "a little understood and poorly treated entity"[2]. Others have stated: "The cause is unknown, as is the cure. Even an effective treatment eludes us."[3]

I will argue that we have long known the cause(s) and that effective treatments have long been available but are unfortunately hidden behind the "Internet horizon." Namely, you need to know about: (1) referred pain, and (2) amplifying factors (and a bit more).

Accompanying this issue of *The Journal* are proceedings of a symposium, "Is Fibromyalgia a Neuropathic Pain Syndrome?", which deals at length with the amplifying factors of FM. Philip Mease suggests: "A unifying hypothesis is that FM results from sensitization of the central nervous system."[4] Further, Crofford concludes that "central nervous system alterations are indeed present in FM, although it is unclear whether these changes cause the syndrome or result from other pathology."[5]

À LA RECHERCHE DU TEMPS PERDU

The topic of pain amplification should include a number of components lost in current literature: the early description of the "central excitatory state" and "central inhibitory state" by Sherrington[6], the mapping of the sensory (and motor) area of the cerebral cortex by Penfield[7], and the phenomena resulting from induction of deep pain by Lewis and Kellgren[8] (confirmed and extended by others, notably Janet Travell[9], and the later articulation of the evolving, changeable "body image" by Kellgren[10]).

In Penfield's sensory homunculus[7] (Figure 1), there is large representation of the lips and tongue (rarely painful in fibromyalgia patients), and a close proximity of the eye and upper face to the large thumb, relevant to the needs of eye–hand coordination. More subtle is the lack of representation of any deep structure, and particularly of spinal structures.

Our body image is plastic. Without looking, a weekend athlete can know the position of a tennis racket or club head, or of other players in team sports. Usually you are minimally aware of your genitalia, but this can change dramatically in appropriate (or other) circumstances. Chronic pain may result in much greater representation of the painful region at several levels of neural representation.

So you can't feel pain in your hip; and you don't know your acetabulum from a hole in the ground. Complaints of pain in the "shoulder" or "hip" must be understood as a regional pain, commonly referred from a remote primary site, resulting in a host of local diagnostic labels that are often wrong.

Referred pain is often accompanied by local skin or deep tenderness, and by such reflex phenomena as reactive hyperemia[11], a visible manifestation of the central excitatory state analogous to the "windup" phenomena. Reactive hyperemia was once suggested as a criterion for diagnosis, but dropped because it lacked sufficient sensitivity and specificity.

Deep tenderness has long been described in close association with regional or widespread pain. Within the painful region, only the absence of tenderness is of value in patient assessment. But according to Kellgren, "the deep tender spot, on the other hand, frequently lies outside the distribution of pain, and the patient is unaware of its existence until it is discovered by the physician. Firm pressure on the deep tender spot produces the steep rise in pain which is characteristic"[12]. Tenderness remote from pain is extremely useful in diagnosis, and signals a referred pain, not a mysterious entity called fibromyalgia.

See Supplement 75: Is Fibromyalgia a Neuropathic Pain Syndrome?

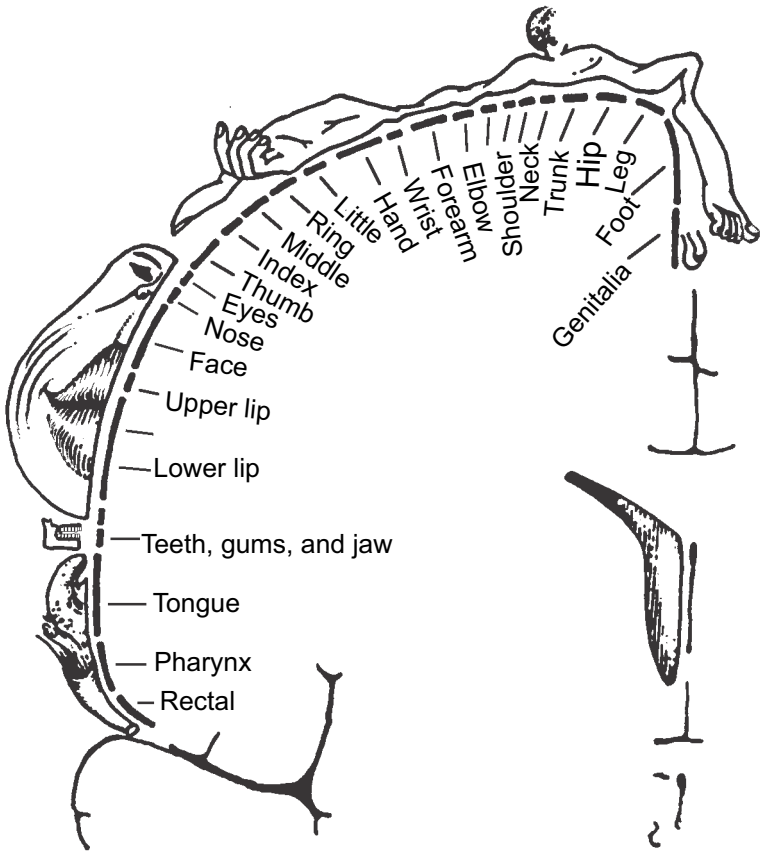


Figure 1. Penfield's sensory homunculus[7]. From *The Cerebral Cortex*, by Penfield W, Rasmussen T. Macmillan 1950. Reprinted by permission of The Gale Group.

PERSONAL HISTORY

I had studied with Kellgren, and the above concepts were useful to me in sports medicine. Wallace Graham had reviewed the confusing literature on "The Fibrositis Syndrome" in *Arthritis and Allied Conditions*[13], respectfully dismissing earlier theories of infection, inflammation, and fatty hernias. Lewis's (and Kellgren's) work was mentioned, but the chapter was sympathetic to psychosomatic features and to "tension rheumatism." After Dr. Graham's sudden death in 1962, Hollander asked me to undertake responsibility for future editions. My first effort appeared in the 7th edition, 1966[14]. I reviewed the work on referred tenderness in detail, including sites such as the mid-portion of the upper fold of the trapezius, upper angle of scapula, coracoid process, second costochondral junction, lateral epicondyle (and others). I also dealt tentatively with muscle spasm, but noted that more severe muscle tension is present in pyramidal tract disease or parkinsonism, without pain. "In addition, other changes may occur in the functional state of the receptor and reflex mechanism at the level of entry of the pain impulse (central excitatory state) and in the peripheral tissue to which pain is referred."

In 1967, Harvey Moldofsky began his studies with us. He was unusual: a psychiatrist who measured physical phenomena. Early, he showed that the painful muscles were electrically silent, when not fighting gravity. That the pain-spasm-pain cycle was a myth was described independently by Kraft[15] and by others. "Tension headache" had become the vague "tension-type headache."

Formal criteria evolved to identify participants for sleep studies and were described in the 8th edition of Hollander's text, in 1972, and summarized in the "Two Contributions" report, published in 1977[16]. Recognition that the deep tender sites were constant in location, and unknown to the patient, allowed rapid objective assessment independent of psychological factors. In asymmetrical regional pain syndromes, multiple asymptomatic tender sites in clumped distributions pointed to the site of origin and defined appropriate therapies.

WIDESPREAD VERSUS GENERALIZED PAIN

Where does the pain come from? "Most fibrositic pains are in the wide areas of reference of the lower cervical and lower lumbar spine...", "attention must be drawn to those sites where pathology steadily accumulates rather than to those sites where pathology is rarely found."[14]

Let me go back to Penfield's homunculus and the "body image." Patients with FM, or with whiplash, or other purely cervical syndromes, rarely or never describe pain in their tongue, lower teeth or lip, or nipple, despite the rich representation of these in the cerebral cortex and their emotional significance. The neurology is complex, involving only parts of the ophthalmic and mandibular divisions of the trigeminal nerve, the apparatus of balance, the spinal accessory nerve, and most cervical nerves. This neurology seems to be organized by the needs of eye-hand coordination, and not by any nerve or spinal segment. Reactive hyperemia is marked in the skin over the upper scapular area, but not between lower scapula and waist. The pain and associated phenomena are widespread, but are not and should not be called "generalized."

ASSOCIATED, CONCOMITANT, AND COMORBID CONDITIONS

The full text of the 1990 American College of Rheumatology (ACR) FM criteria study[17] is unfortunately not available online, so that little is remembered other than widespread pain and 11 of 18 tender points. Studies published in the 1980s and earlier listed many symptoms common in patients with FM: headache, fatigue, depression, irritable bowel syndrome, paresthesias, anxiety, sicca symptoms, urinary urgency, dysmenorrhea history, Raynaud's phenomenon, among others, all more common in subjects with FM than in pain controls; these studies were formally evaluated for sensitivity and specificity. Other symptoms, such as cognitive dysfunction, jaw pain, and abdominal pain, have since been added. Let us accept that these are intrinsic to the condition.

Further, it has been shown that FM, as defined, is more common in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), so that flares of pain in patients with these (and other conditions) may be due to the FM, and are not an indication for more aggressive immunosuppressive or steroid therapy (which may make the pain and tenderness worse[18]). The anxiety, depression, muscle weakness, changed diurnal patterns of secretion of ACTH and cortisol, and of autonomic reactions may be the result rather than cause of FM, and few studies have used controls with similar levels of pain, sleep disturbance, and physical deconditioning. In one series of studies, patients with HIV infection were compared with patients with FM, RA, SLE, and psoriatic arthritis (PsA)[19,20]. Nonarticular tenderness was measured in 152 subjects, 51 with RA, 50 with PsA, and 51 with HIV infection. Twenty-five of 51 RA patients had 11+ tender points, 10 in each of the PsA and HIV groups, the latter despite anxiety, deconditioning, and broken sleep.

DIFFERENT FLAVORS OF FIBROMYAGIA

Two references in Dr. Crofford's article are relevant (if confirmed): the lack of substance P in the cerebral spinal fluid of subjects with chronic fatigue syndrome but no pain[21], and the presence of elevated levels of substance P in the cerebrospinal fluid of subjects with chronic low back pain[22]. While many of the listed symptoms of FM may be attributed directly to referred, amplified pain and associated sleep disruption, and indirectly to the consequences of deconditioning and legitimate anxiety and despair, other paths are of course possible.

Do the abdominal symptoms require a different explanation? Pelvic floor symptoms are common in FM, as is low abdominal and inguinal pain. This pattern of referred pain occurred after injection of lower lumbar discs in a Swedish study of 356 patients with back pain[23]. Levine and Reichling suggest that animal experiments that produced "generalized" hyperalgesia following subdiaphragmatic vagotomy modeled FM. When reminded that this was not seen in humans after similar surgery, they answered, "Through the 1960s, surgical subdiaphragmatic vagotomy was used in attempts to treat severe peptic ulcer disease complicated by recurrent gastrointestinal hemorrhage. While the literature does not mention of an FMS-like syndrome in these patients, this may be related to the fact that diagnostic criteria for FMS were not to be established until decades later"[14]. (This was the time that formal criteria were evolved to define groups of patients for the sleep studies.) How do you do point counts in a quadriped? Or explain neck and low back problems when they don't have clavicles, or locked lumbar hyperextension?

ADDITIONAL PAIN AMPLIFICATION MECHANISMS

Price and Staud have reviewed much of the literature on the anatomy, chemistry, and mechanisms of nociception in chronic pain[25]. One can drown in the soup of chemokines and cytokines. Rowbotham has also considered and argued against the concept that FM is a neuropathic pain syndrome, since there is no evidence of a neural lesion[26]. A newer mechanism has recently been extensively studied, involving microglia and their products, produced in animal models by repair after injury to posterior spinal roots. Microglia seem to be the neurological equivalent of immune effector cells, with products such as interleukin 1ß (IL-1ß) and tumor necrosis factor (TNF)[27,28]. These are not the only nociceptors identified in this model. A role for purinoceptors has been identified[29] and leflunomide, a purine antagonist, could attenuate persistent allodynia in this model[30]. The topic has been extensively reviewed in *Science*[31]. Azathioprine and newer biologic agents may be efficacious in RA because of direct analgesic actions on FM or neuropathic mechanisms, independent of immunosuppressant actions. Sadly, none of the major trials of these agents in patients with RA have included tender point counts.

THERAPIES

The authors of these proceedings say encouraging things about tricyclics, pregabalin and related drugs, opioids, and behavioral management programs. There is evidence of weak short-term benefit from the medications, but no longterm controlled studies have been published. No reference is made to the study of Carette, *et al*[32]. In a 6-month study they found improvement in some measures in early months, but no benefit as compared with placebo at 6 months. Side effects were very common in the treated groups, so that there was little functional benefit. These results are consistent with the 7-year followup study of patients with FM followed in 6 major centers, which found no benefit, at any center, by any measure of outcome[33].

We should not abandon the search for better analgesics, and I would not like to immunosuppress patients with FM. But we would still prefer to identify the presence and mechanisms underlying mechanical problems in the low neck and low back. The affected structures are not known to the patient, and a first step in the treatment process is the discovery of the very marked tenderness in the front of the lowest part of the cervical spine, a region without symptoms. The explanations and demonstrations that follow are time-consuming and incompatible with the economic demands currently facing most rheumatologists or physiotherapists — but they are rewarding. Our experience has made us optimistic. With focused support to the lower neck during sleep, most of our patients with FM lost the tenderness in the upper body sites listed in the ACR criteria. Many remained symptomatic and were found to have a different pattern of referred tenderness, which responded — slowly — to revised, more precise sleeping strategies. With marked or complete relief of signs and symptoms after 2 years[34]. The results of independent studies should be available soon.

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