ENIGMATIC PAIN AND CENTRAL HYPERLGESIA

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August 22, 1996

THE HYPERALGESIC SYNDROMES

Perplexing and frustrating to patients and physicians alike are the various enigmatic pain syndromes: prominent among them are the primary fibromyalgia syndrome, chronic regional pain and the temporomandibular joint syndrome; headaches, especially chronic daily headache; perhaps most of the common chronic backaches; and what Mayer and others have called visceral hyperalgesia, which includes irritable bowel syndrome, non-ulcer dyspepsia, non-cardiac chest pain, and irritable bladder. Traditionally, patients, physicians, and researchers in the related fields have tended to focus either on the peripheral manifestations of these processes or else on psychological and life situation issues. Thus, migraine has been thought to be a primarily vascular disorder and tension headache related to increased muscle tenseness. The irritable bowel and related syndromes are generally considered to be disorders of mobility and ascribed to events or phenomena involving the peripheral structures, smooth muscle, and peripheral distributions of the autonomic nervous system. Failure to respond to conventional treatment is often attributed to psychological factors, and psychotherapy recommended or attempted.

This traditional focus on either the peripheral manifestations or else the psychology of enigmatic pain syndromes has been notable for its lack of success. Now an emerging body of experimental data and theoretical conjecture is challenging traditional concepts and suggesting new conceptual paradigms. Many, if not most, enigmatic pain syndromes may be actually perpetuated and sometimes caused by mechanisms primarily occurring in the spinal cord, medulla, paleoencephalon and cerebral cortex; the dilated blood vessels in migraine, the muscle tension in chronic daily headaches, the abnormal reactivity patterns of viscera all being peripheral, downstream manifestations or epiphenomena of a more primary disturbance within the central nervous system, the common feature of which is central hyperalgesia.

TABLE I. HYPERALGIA SYNDROMES
Patterns of pain or discomfort occurring over months to years without evident cause or else excessively severe, frequent, or prolonged for such abnormalities as may be present.

TABLE II. DEFINITIONS
HYPERALGIA **Reduced Pain Threshold** **Response to Painful Stimuli Increased and Prolonged** **Primary (Peripheral)** **Secondary (Central)**
ALLODYNIA **Pain Produced by Stimuli that are not Normally Painful**

TABLE III. PUTATIVE EXAMPLES OF HYPERALGESIC SYNDROMES	
SOMATIC	**VISCERAL**
Idiopathic Headache	**Irritable Bowel Syndrome**
Backache	**Irritable Bladder Syndrome**
Fibromyalgia	**Gastroesophageal Reflux**
TMJ Syndrome	**Non-Ulcer Dyspepsia**
Chronic Regional Pain	**Non-Cardiac Chest Pain**

The discussion that follows will review and marshall evidence that abnormal pain regulation underlies a great many of the complaints that beset humankind. We will review basic pain theory, but first, let me give you a sharply truncated history of the life of Mrs. B., chosen out of many similar patients in my practice because she displays virtually the entire spectrum of what we are calling for lack of a better term the hyperalgesic syndromes:

> *Mrs. B. is an 83-year-old woman who complains of fatigue, headaches (both tension-type and migraine with aura), generalized abdominal pain, chronic constipation, heartburn, and chest pain. She is frequently nauseated but rarely vomits. At times, she complains of fibromyalgia-like symptoms. Past history includes a spinal operation forty years ago. There have been bouts of anxiety and depression. She has had many endoscopies and imaging studies and is known to have diverticulosis. She has mild hypertension, though occasionally she has sudden brief marked elevations when anxious. Medications include doxepin 25 mg HS; Ativan 1.0 mg HS; Bentyl 10 mg BID; Tenex 4.0 mg QAM; Premarin 0.625 mg. She eats a high-fiber diet and uses Dulcolax suppositories frequently.*
>
> *Her biography is of interest. Her biological father was an Australian who was killed at sea in WWI when she was a young child. Her marriage was extremely unhappy and ended in divorce after thirty-five years. She has one daughter living. A son born one year after the daughter was killed in the London bombings at age 14 1/2; she is tearful discussing this.*

Thus, in summary, Mrs. B. displays many aspects of somatic and visceral hyperalgesia and has a life story that includes several features said to occur with greater frequency than in the non-suffering population. My goal today is to persuade my audience that this woman has not five or six different disorders, but in reality, only one: a profound and diffuse disturbance in the central processing of pain.

PRINCIPLES OF NOCICEPTION

Pain typically begins with the application of some stimulus that is damaging or potentially damaging to pain receptor terminals and adjacent tissues (in the skin, joints, blood vessels, and the dura mater, for example). In the laboratory, such stimuli are typically physical ones: pressure, heat, chemical. In human study subjects and in patients, pain may originate from externally applied agents, as in the laboratory; and often, as in some enigmatic pain syndromes, for example idiopathic headache, originate endogenously; that is to say, arise somehow within the subject, apparently spontaneously, but presumably in response to some internally generated signal. Activation of the pain terminals of the peripheral afferent nociceptor system results not merely in transduction via depolarization and electrochemical transmission, but importantly in a cascade of physical-chemical events (Fig. 1, Fields 1987). If a noxious substance, (kaolin, carrageenan, or capsaicin are commonly used in these experiments), is injected into the knee of an anesthetized cat, for example, the pain process begins with transduction: the offending stimulus, chemical, mechanical, or thermal, generates a signal that depolarizes the primary afferent nociceptor (PAN), of the C-polymodal, unmyelinated, high-threshold pain fibers and the thinly myelinated fibers.

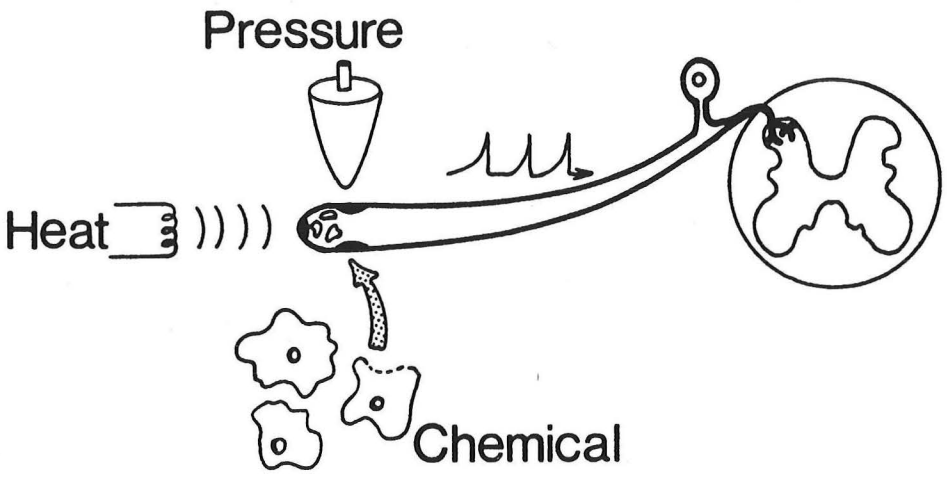

Figure 1. Sensitivity range of the C-polymodal nociceptor. Available evidence suggests that the terminals are sensitive to direct heat or mechanical distortion. Thus transduction can occur at the terminal. The terminals are also sensitive to chemicals released from damaged cells. In this manner, any tissue cell can serve as an intermediate in the transduction process. In a sense, all tissue cells are "receptors" for injury.

Repeated stimuli also recruit the recently discovered "sleeping" nociceptor fibers, small unmyelinated afferent fibers, particularly in deep visceral sites: colon, bladder, and also joints (Ferreira 1993). Many endogenous chemicals can activate and are liberated by PANs, among them hydrogen and potassium, histamine, serotonin (5HT), prostaglandins, and bradykinins (BK). Sensitization--a lower threshold for activation, increase in spontaneous activity and increase in impulse firing frequency and amplitude--occurs with repeated or prolonged stimuli, and is brought about by a variety of locally generated peptides from the primarily activated nerve terminals, from

neighboring nerve terminals through antidromic stimulation, and from adjacent tissue cells. Many algesic peptides act on cells other than PANs, particularly sympathetic postganglionic neurons and white blood cells, which in turn release substances that result in indirect sensitization and in local hyperalgesia: a lower threshold for producing the pain response and the tenderness associated with inflammation. BK, which has been extensively studied, stimulates synthesis of PgE_2 which in turn sensitizes nociceptors to BK, a typical positive feedback loop. BK triggers a cascade of cytokines: production of tumor necrosis factor (TNF) which stimulates production of interleukins 1 & 6, leading to PG production and release of IL8. IL8 stimulates postganglionic sympathetic neurons, contributing importantly to hyperalgesia (Fig. 2, Dray 1993).

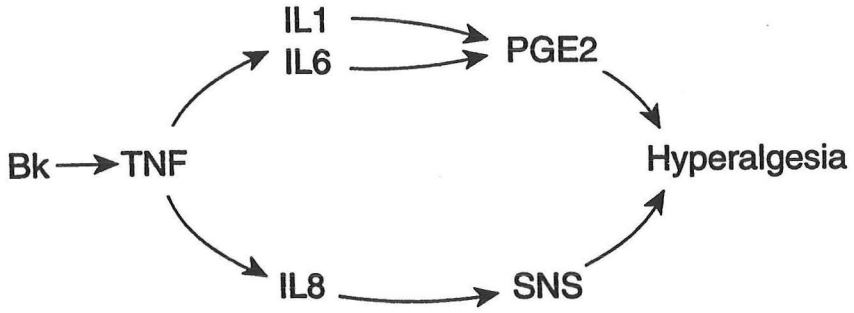

Figure 2

These phenomena are rudimentarily illustrated in three diagrams from Fields' text, *PAIN* 1987, p. 36. In Figure 3a an impulse is generated. In Figure 3b, secondary activation is produced as retrograde antidromic conduction recruits other terminals; substance P is released, among other peptides, and SP causes further accumulation of BK, release of histamine from mast cells and 5HT from platelets. In Figure 3c, H and 5HT levels rise in the extracellular fluid bathing the terminals, secondarily sensitizing nearby nociceptors. This sequence is set in motion by damage to tissue cells as well as nerve terminals.

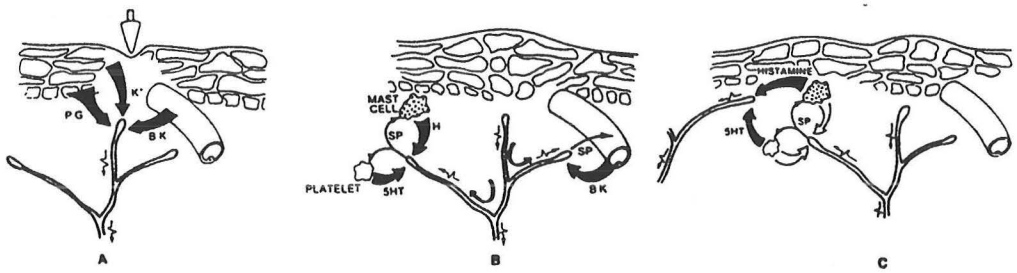

Figure 3

Levine, Fields and Basbaum (1993) have provided a detailed summary of the interactions between PAN's, sympathetic post ganglionic neurons (SPGN), neutrophils, and the several classes of neuroactive substances. (Fig. 4, Levine 1993). Bradykinin (BK) activates the PAN via a protein kinase C (PKC) and calcium-dependent system and sensitizes the PAN via production of PGE_2 from SPGN. Complement (C5a), interleukins, lipoxygenase products potentiate actively. Stimulatory and inhibitory G proteins and cAMP are involved. Opioids of the beta and kappa classes inhibit nociception at SPGN and PAN.

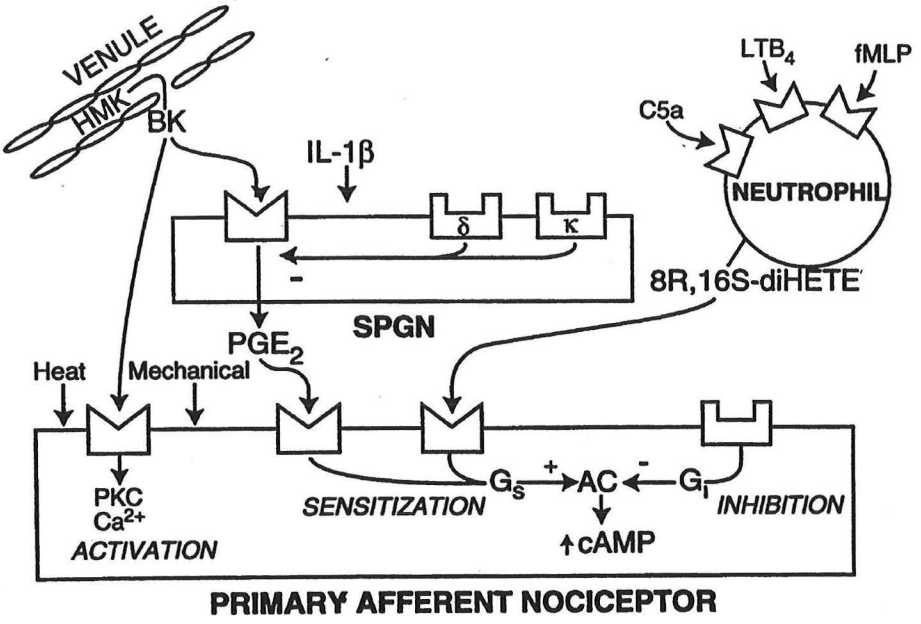

Figure 4. Sites of peptide action in peripheral pathways of pain and hyperalgesia. The inflammatory peptide bradykinin (BK), cleaved from highmolecular-weight kininogen (HMK) circulating in the venules, can activate the primary afferent nociceptor (PAN) in a protein kinase C *(PKC)*- and CA^{2}-dependent mechanism or sensitize the PAN through the production of PGE_2 in sympathetic postganglionic neurons *(SPGN).* Interleukin-lß (IL-1ß) also can sensitize the primary afferent through a similar mechanism. The chemotactic peptides C5a and f MLP activate the neutrophil, as does leukotriene B_4 (LTB_4), and causes the release of the lipoxygenase product *8R, 16S-diHETE,* which sensitizes the primary afferent directly. Primary afferent sensitization probably involves a stimulatory G-protein *(Gs),* and the cAMP second messenger system. Opioid ligands of the δ- and κ-classes can inhibit this sensitization at the level of the SPGN, and the μ-class opioid ligand can do so at the level of the PAN via an inhibitory G-protein (Gi).

The dorsal root ganglion neurons manufacture and transmit to the PAN terminals, as well as presumably centrally, the potent inflammatory and algesic peptides SP and CGRP and their receptors. SP, which coexists in many loci with CGRP, produces vasodilatation, increases vascular permeability, attracts and activates neutrophils and macrophages, increases production and release of prostaglandins and eicosanoids and degranulates mast cells, releasing histamine.

The first synaptic transmissions are widely networked in the dorsal root of the cord, especially laminae 1, 2 and 5, hundreds or thousands of interneuronal connections for entering fibers, connections with autonomic and motor units, before traversing ventrally and contralaterally to form the spinothalamic tracts (Fig. 5, Cervero 1993). The neurochemical processes in the cord become more complex.

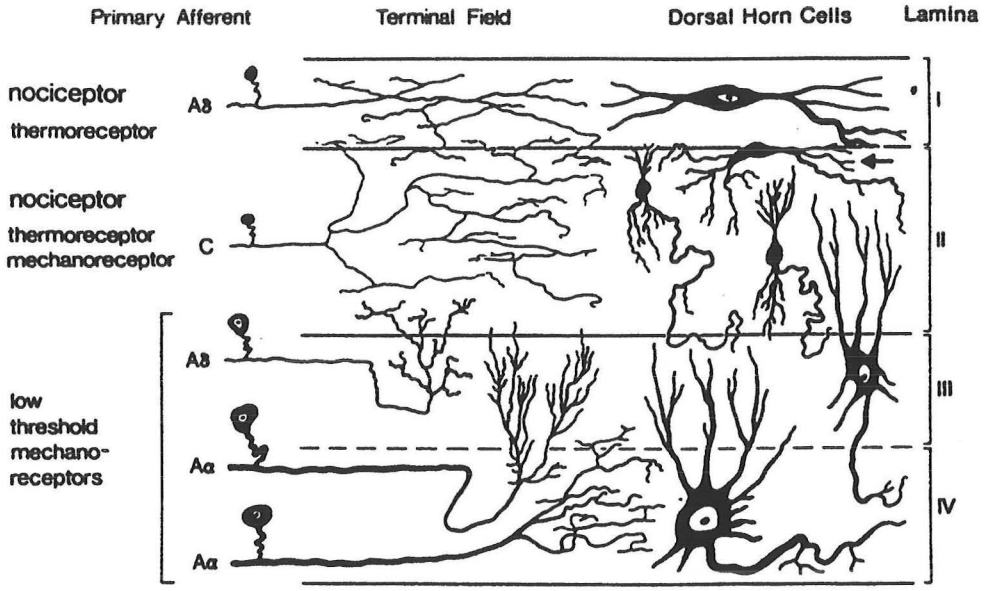

Figure 5. Summary of major components of the upper laminae of the spinal cord dorsal horn. (From Cervero, F., and Iggo, A: The substantia gelatinosa of the spinal cord. *Brain* 103:717-772, 1980.)

The primary afferent nociceptor input is via AB fibers and C fibers. AB nociceptors terminate primarily in lamina I and the outermost part of lamina II. C fiber nociceptors terminate mainly in lamina II. There are some non-nociceptive AB and C primary afferents that also terminate in laminae I and 11.

The deep part of lamina 11 and laminae III and IV receive input only from non-nociceptive myelinated primary afferents.

The second-order cells are of several types; there are larger neurons in laminae 1, 111, and IV, which include nociceptive projection neurons. The cells in lamina 11 are smaller, and, although some project to supraspinal sites, most make local connections.

As illustrated in Fig. 6 (Levine 1993), the PAN discharges neuropeptides and excitatory amino acids (EAA); these bind to receptors in dorsal horn nociresponsive neurons and in some instances at more distant sites. SP and CGRP peptides and receptors modulate both transmitter release and firing of second order neurons. Nitric oxide (NO) functions importantly both in nociception and in linking nerve transmission to metabolic activity. (Goadsby 1992).

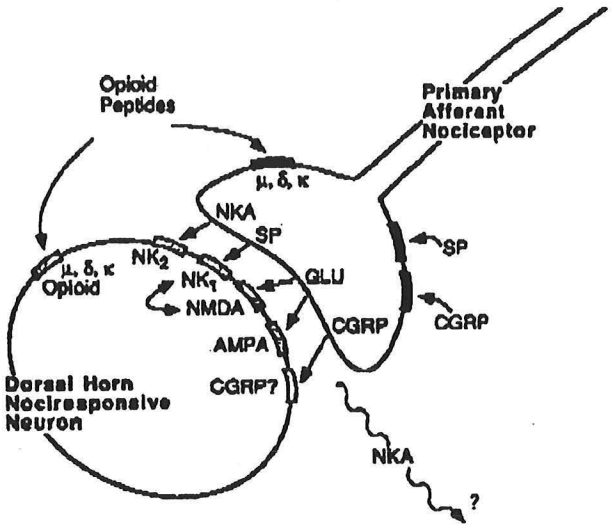

Figure 6. Primary afferents and peptide actions in the CNS. The PAN releases a variety of co-occurring neuropeptides (*NKA, SP, CGRP*) and excitatory amino acids [e.g., glutamate *(GLU).* Thcsc act at several postsynaptic receptors; the *NK,* and NK_2 tachykinin receptors, the *CGRP* receptor, and the *NMDA* and *AMPA* excitatory amino receptors. *NKA* may diffuse to act at a distance from its site of release. There is evidence that *SP* and *CGRP* also act at autoreceptors at neuropeptide-containing primary afferent terminals. In addition, opioid peptides act upon both pre- and postsynaptic μ-, δ-, and κ-opioid receptors to modulate transmitter release and the firing of second-order nociresponsive neurons.

While a major pro-inflammatory, excitatory function is ascribed to SP, it coexists in neurons with other neurokinins, with CGRP, somatostatin (SOM) among others. CGRP powerfully potentiates SP. The slow-acting peptides stimulate release of and prolong activity of EAAs within the dorsal horn. There is good evidence from antibody probe studies (Duggan, 1986) that SP and other neurotransmitter chemicals and their receptors traffic out from their cell bodies to dendrites and terminals.

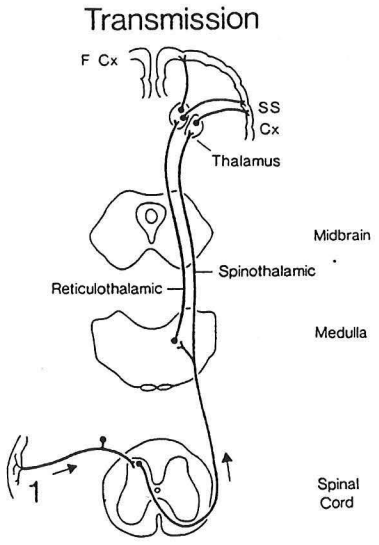

Figure 7

As illustrated in Fig. 7 (Fields 1987, p. 6), the spinothalamic tract (STT) runs up the anterolateral quadrant of the cord to the medulla, where a division occurs, thence through connections to

various nuclei in the midbrain to the thalamic ganglia whence they project laterally to the somatosensory cortex and medially to the frontal cortex.

Figure 8 (Fields 1987, p. 69) is a schematic diagram of this layout. The medial spinothalamic tract pathway projects to the reticular formation, thence to medial thalamus and to the association cortex to eventuate in affect: arousal, excitement, fear, escape: primitive, undifferentiated responses to danger or harm. The phylogenetically more recent neospinothalamic tract projects to centers in the lateral thalamus to arrive at the somatosensory cortex, where the conscious primate experiences pain, assigns to it qualities ("hot", "sharp", etc.) and localizes it precisely.

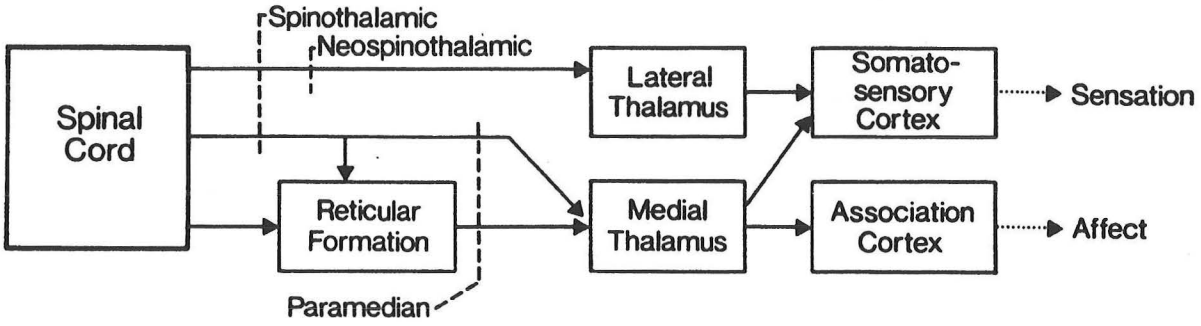

Figure 8. Schematic diagram of the major central nervous pathways that contribute to pain sensation.

The basic principles and agents already discussed, relative to PAN and spinal cord are elaborated in increasing anatomical and biochemical complexity as one proceeds from the brain stem to the midbrain to the higher centers, but the conceptual framework and neurochemical menus appear to remain intact so far as the higher centers have been studied up to now. As a rough estimate, I would offer that programmatic complexity increases by an order of magnitude at each stage, as one proceeds from PAN system to consciousness.

To summarize thus far, we have a vigorous, complex nociceptive system replete with a wonderful array of agents and pathways that act on each other to vastly augment and multiply any incoming stimulus that potentially threatens the organism, and, importantly to produce local activation of major components of the sympathetic, vascular, and immune systems and to produce and to maintain inflammation: all entirely neurogenic in origin.

ANTINOCICEPTION

If this were the whole story, it would seem that we should be in continual pain from "the thousand natural shocks that flesh is heir to". However, this is but half of the nociception story. The other

half is the anti-nociception, or counter nociception story. At every level so far studied (the PAN, spinal cord and brain stem; trigeminal systems and their thalamic and cortical radiations), there are equally complex and potent systems that suppress nociception; that regulate or modulate pain. Figure 9 (Fields 1987, p. 6) diagrams the rostral-caudal pathways from cortex and hypothalamus through the midbrain and medulla periaqueductal grey matter (PAG) and down through the dorsal horn.

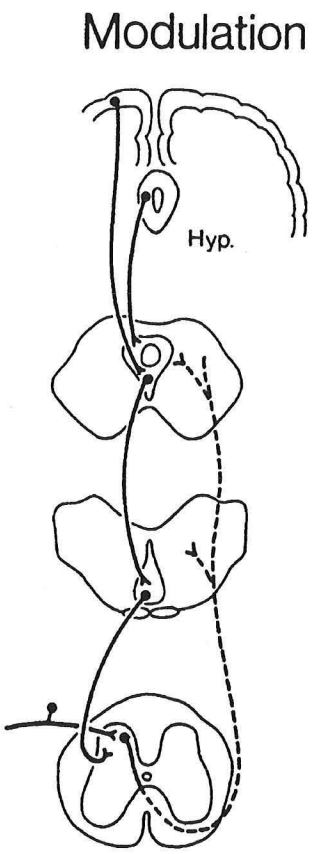

Figure 9. Right: Pain modulation network. Inputs from frontal cortex and hypothalamus (Hyp.) activate cells in the midbrain, which control spinal pain transmission cells via cells in the medulla.

Not illustrated are the recently-demonstrated opioid receptors in peripheral nerve endings: even at its origin, pain encounters opposition (Stein 1995). Centrally, endogenous opioid peptides are found in areas where experimental electrostimulation as well as local application of opiates induce analgesia: the periaqueductal gray matter (PAG), the medullary analgesic centers, and the spinal cord. The brain stem cells that project to the spinal cord to block pain are concentrated in the rostral ventromedial medulla (RVM), rich in serotonin, and the dorsolateral pons which is adrenergic. Studying the RVM and nucleus raphe magnus (NRM), mainly in the rat, Fields and coworkers (Mason 1989, 1992) have discovered and elegantly elaborated an important pain-modulating apparatus. The NRM contains "on" cells and "off" cells which fire reciprocally, the

opioidergic, "off" cells blocking pain transmission; the "on" cells facilitating pain transmission. Thus, central pain modulation is not simply a unidirectional inhibitory process; there is also a mechanism for pain enhancement. This apparatus sits athwart the incoming cord transmission pathways, receives input from noradrenergic and serotonergic as well as opioidergic pathways, has important projections to the trigeminovascular systems through the trigeminal subnucleus caudalis and receives inputs from frontal and somatosensory cortex (Fields 1991). From this conceptual structure, it is but a short jump--requires no great leap of the imagination--to propose that an alteration in the "on-off" system could underlie prolonged or recurrent enigmatic pain syndromes. In fact, Fields et al, have shown that opioid withdrawal, actually one dose of an opioid followed by naloxone in the rat, alters the "on-off" cell set in favor of facilitated pain transmission. By such a means, the RVM centers could drive nociceptive transmission from whatever source, exogenous or endogenous (Kaplan & Fields 1991).

ENDOGENOUS PAIN AND THE NOCEBO RESPONSE

Do painful stimuli in fact arise within the CNS absent exogenous stimuli? Intuitively, we would say, "yes": Every student and clinician is familiar with the patient who develops chest pain following a father's or a business associate's myocardial infarction. Now there is good experimental support for these observations, both the phenomenology and the underlying pathophysiological mechanisms.

Bayer et al (1991) describe a study characteristic of this type of investigation. In their 1991 study, volunteers had their heads connected to a sham pain generator and were asked to report pain according to the settings on a prominently displayed dial as the "generator" increased the pain-simulating inputs. Fifty percent of the subjects reported significant headache; one requested medication for relief. Twenty-five percent of the controls who were told no painful stimulus would be applied reported pain. Gannon et al (1987) by exposing subjects to a stressful cognitive task induced headache in 69% of migraine and tension headache patients and in 25% of control subjects. Similar results have been reported by Schweiger and Parducci (1981) who labeled this the NOCEBO response. These investigators are telling us what we think we already know, that humans are a very suggestible species and that headache and other pain patients may be even more suggestible than the norm. A better question might be, "How does NOCEBO pain come about? What is the mechanism?"

A plausible basis for non-nociceptive excitation of nociceptive neuronal activity has been developed over the past decade or so by Bushnell, Duncan et al (1993) using awake, trained monkeys (Fig. 10). Briefly, a trained, awake monkey, electrodes permanently placed in the major CNS pain pathways, has a heat probe attached to its lip and at certain times receives a stimulus that is painful. The monkey is given various signals (and various distractions that require increased concentration and task discrimination) which signal the monkey to press a button that administers the painful stimulus, which is, of course, followed by a reward, a bit of syrup. The investigators have used this approach to map pain pathways in the trigeminal system, brain stem

and cortex. After a while, the monkey's nociception system becomes activated by the premonitory signal only; the actual physical painful stimulus is no longer required to stimulate brisk pain transmission activity in the nociceptive system, in the trigeminal system and its hypothalamic, thalamic and cortical nociceptive projections. These studies demonstrate how the activation of pain pathways can result from anticipated, remembered, or perhaps imagined pain.

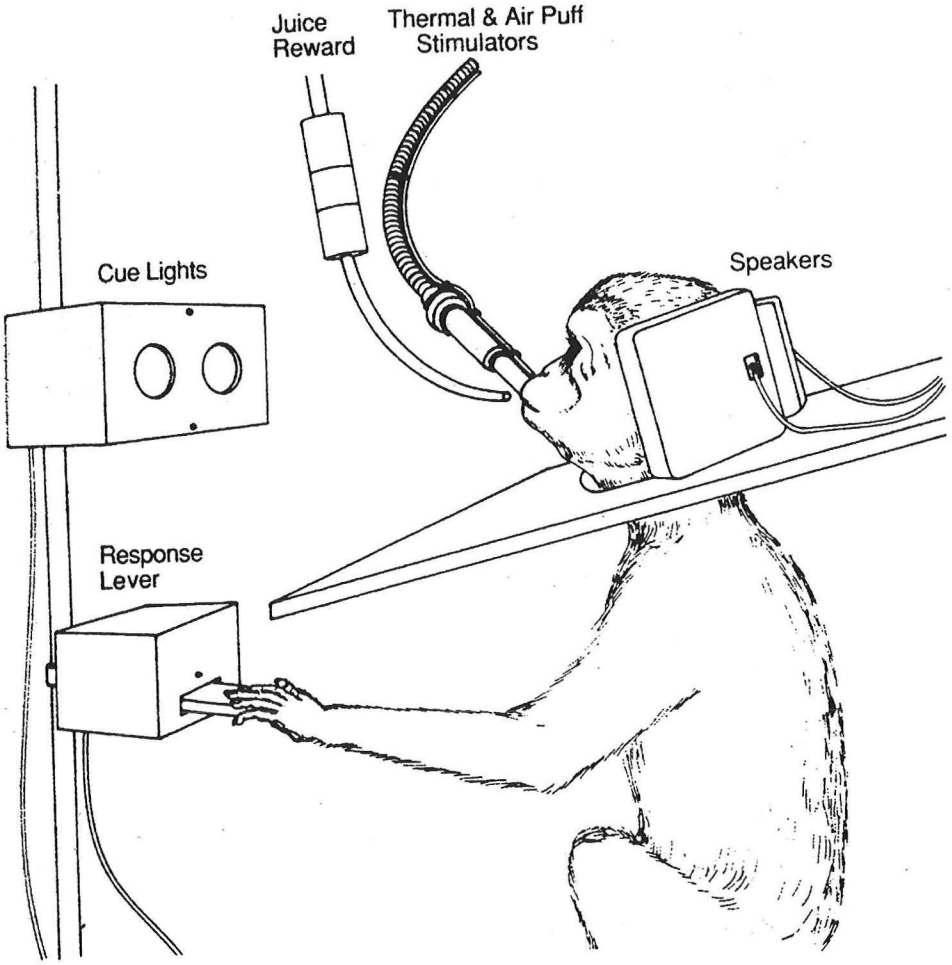

Figure 10

To summarize, pain can originate within the brain as well as peripherally, the perception of severity depending upon stimulus intensity but also upon the balance of excitatory and inhibitory modulating mechanisms at every level.

MECHANISMS IN CHRONIC ENIGMATIC PAIN

How then are we are to apply what we can know about pain regulation to the various chronic enigmatic pain syndromes? The basic thesis argued here is that chronic pain without evident or sufficient cause is usually due to abnormal pain regulation. How might such regulatory malfunction come about? Zimmermann (1991) has listed six possible mechanisms in chronic pain patients:

1) Nociceptor origin: pain from inapparent inflammation or strain involving muscle, tendon, vessel, or viscus.

2) Neurogenic inflammation from neuropeptides liberated from peripheral nerve endings or primary sensory neurons.

3) Neuropathic pain: e.g., from inapparent nerve injury.

4) Central pain: e.g., pain from defective inhibitory control of spinal neurons and/or facilitated pain transmission.

5) Dysregulatory or reactive pain involving persistent efferent-afferent feedback loops.

6) "Psychosomatic" pain enhanced by depression, chronic stress, defective coping, feelings of helplessness.

All of these mechanisms, and doubtless others, play a role in chronic pain. However, in the first three, the source of the pain is discoverable or demonstrable, hence, they are not truly enigmatic; and the fifth, the familiar and often-invoked pain-spasm feedback loop has little experimental evidence to support it and is inconsistently demonstrable in the chronic conditions for which it is blamed, although it may be operative in short-term musculoskeletal pain. Thus, in order to understand chronic enigmatic pain, we must focus on central pain mechanisms, mainly central hyperalgesia, and on supraspinal influences. We have already described peripheral hyperalgesia which lasts for hours. We now need to review central hyperalgesia, which may last for days following stimulation and then offer some plausible explanations for how central hyperalgesia may last for years, or a lifetime.

As illustrated in Fig. 11 (Mayer 1994, *Contemp Int Med*), normally, only a small percentage of the pain-carrying afferent C fibers respond to mechanical stimuli. Following a sensitizing peripheral event, afferent fibers become more sensitive, mechanical fibers transmit pain, and previously unresponsive or "silent" nociceptors become responsive. Central (spinal) sensitization resulting in expanded receptive fields and in increased responsiveness to any given stimulus occurs as a consequence of heightened afferent discharge onto dorsal horn neurons. In central hyperalgesia, dorsal horn excitability outlasts the initiating peripheral event as a result of

molecular events leading to pain memory: for a variable period of hours, perhaps days, subsequent stimuli produce a stronger, more widespread and longer lasting response than before the initiating event.

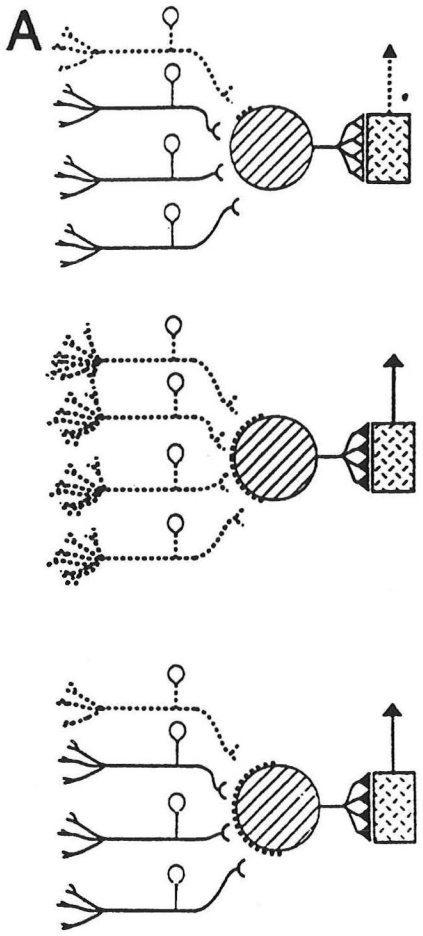

Figure 11

The molecular basis of central hyperalgesia, as yet incompletely understood, is rapidly becoming more clear. The release of excitatory amino acids and the neuropeptides substance P and CGRP from central terminals or primary afferent fibers results in the exhibition of proto oncogenes such as cfos and cjun which turn on genetic machinery to elaborate a variety of neuro chemicals and receptors resulting in long lasting biochemical and neuroplastic (structural or phenotypic) changes. The depolarization of postsynaptic membranes of spinal neurons by glutamate, substance P and CGRP removes the magnesium block or "gate" of the NMDA (n-Methyl d-Asparate) channel,

permitting calcium flux and the activation of nitric oxide (NO) synthetase, involving a calcium-calmodulin-dependent protein kinase (Fig. 12, Mayer 1994, *Gastroenterology*). NO is both an intracellular messenger, increasing cyclic GMP, and a diffusible neurotransmitter feeding back on and facilitating presynaptic neurotransmitter release. Longlasting cellular effects result. The mechanism is similar to that described in long-term synaptic potentiation in the hippocampal gyrus, in the one location subserving conscious memory and in the other, spinal "memory".

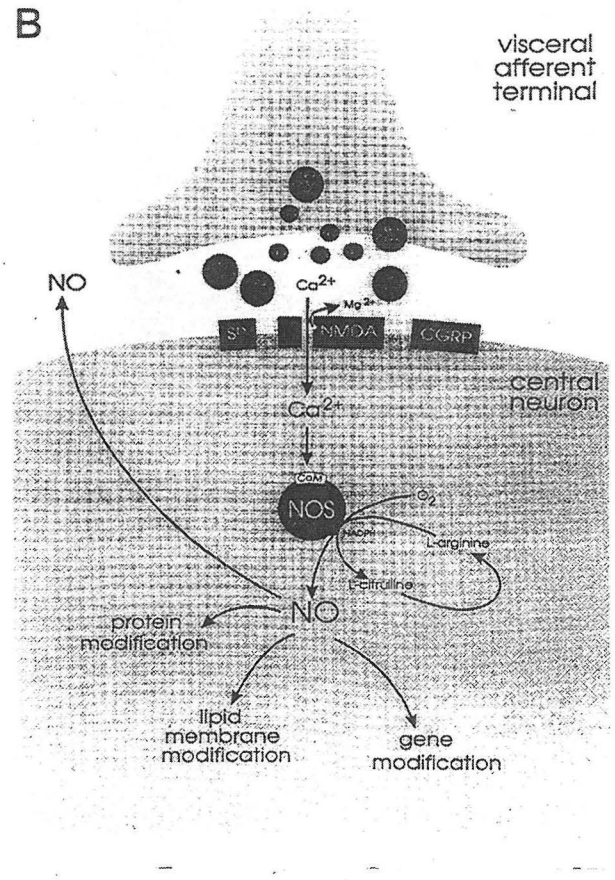

Figure 12

CENTRAL HYPERALGESIA IN HUMAN DISORDERS

The duration of central hyperalgesia depends upon the balance of excitatory and inhibitory inputs and upon the presence or absence of chronic, ongoing stimulation from peripheral afferents, descending spinal and supraspinal pathways, and inhibitory interneurons. If we are to invoke central hyperalgesia as a primary mechanism and unifying concept in chronic enigmatic pain conditions, we must illustrate its occurrence in humans and present some rational hypotheses to explain how such syndromes may be perpetuated for years or a lifetime. Mechanisms involved

in central hyperexcitability, hyperalgesia, and allodynia have been best characterized in models of cutaneous and musculoskeletal nociception, but recent studies emphasize that similar mechanisms operate in the urinary bladder, colon, esophagus, and gallbladder, and in the cardiovascular system. In a study by Dawson (1985) modified by Mayer and Gebhart in their review article of 1994, balloon distention in different parts of the human colon resulted in increased and atypical somatic referral patterns in patients with IBS compared with healthy subjects (Fig. 13). Repetitive noxious distention of the descending colon, ten trials, 60 ml of mercury for 30 seconds every four minutes in seven healthy volunteers, resulted in increasing individual ratings of pain and an increased area of referred sensation, when the tenth distention is compared to the first. In IBS patients by comparison, the initial distentions and the final distentions were both associated with far more extensive somatic referral patterns and higher levels of pain were reported, beginning at lower thresholds. There is no reasonable explanation for these expanded and atypical pain patterns other than expanded central sensitization and central hyperalgesia. While increased peripheral afferent nociception can account for lower thresholds and greater pain intensity, only central sensitization and altered visceral somatic referral patterns can explain the expanded referral areas.

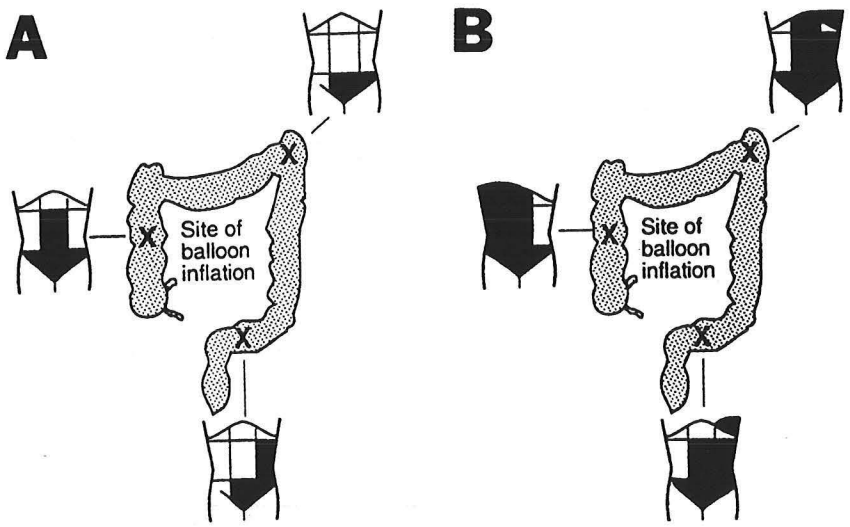

Figure 13

Rao et al (1996) have devised a procedure, impedance planigraphy, to examine esophageal motility and nociception that circumvents confounding biomechanical variables in the esophageal wall, comparing controls to a group of patients with unexplained chest pain in whom cardiac disease had been ruled out and who had normal endoscopy, normal manometry, negative biopsies and no response to empiric omeprazole. As Fig. 14 illustrates, there were sharp differences in pain intensity and pain threshold. There was also decreased esophageal wall compliance and exaggerated esophageal reactivity in the symptomatic subjects. This does not mean that altered

motility causes the pain. On the contrary, as Mayer (1994) has argued, it is more likely that the mechanical dysfunction is the "downstream", or efferent consequence of exaggerated referral patterns and neuronal hyperexcitability in the dorsal horn. Although this experimental protocol was not designed to differentiate central from peripheral mechanisms in nociception, central hyperalgesia best explains the observed phenomena. Furthermore, prolonged, recurrent and easily induced somatic pain of visceral origin requires a central mechanism, whether abnormal afferent stimuli can be elucidated or not. In an editorial comment, Goyal (1996) points out that current studies on the origin of non-cardiac chest pain do not elucidate the relative predominance of peripheral vs. central hyperalgesia, comparing it to "the sounding of a fire alarm in the case of a real fire, or a sensitive alarm activated by smoke without fire, or a defective alarm, "respectively."

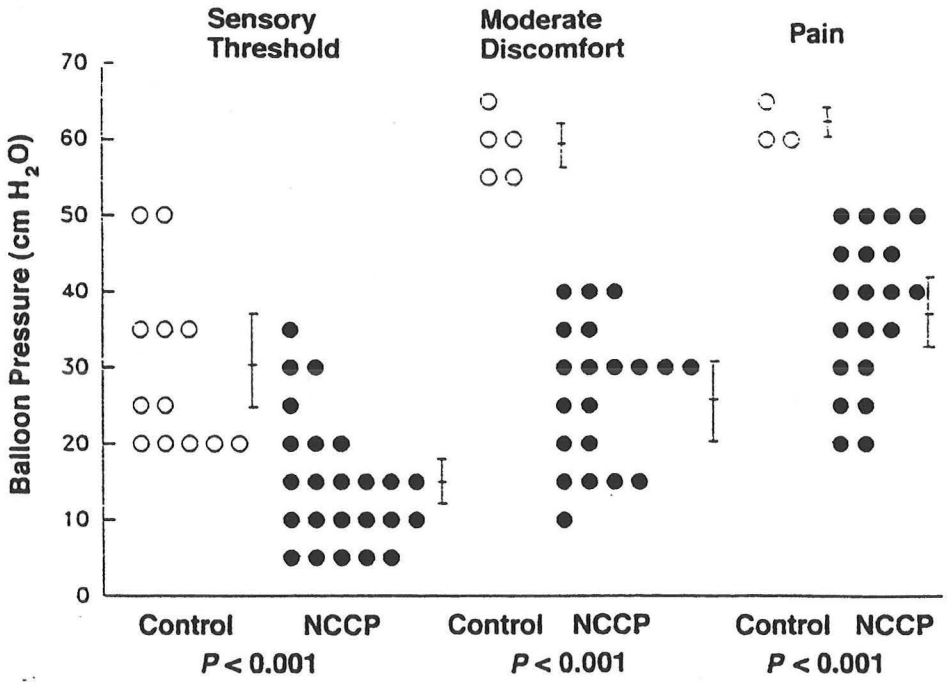

Figure 14

The literature relating to somatic hyperalgesia is older and vaster, and perhaps hence somewhat more difficult to encompass than the more recent literature on visceral hyperalgesia. Only a few representative studies will be cited here, and it should be mentioned that review articles on both somatic and visceral hyperalgesia reference negative studies: chronic pain patients do not report altered pain patterns in every research setting.

ENIGMATIC AND EVIDENT PAIN COMPARED

Granges and Littlejohn (1993, Table 4) compared pain thresholds in primary fibromyalgia syndrome (PFS) patients, chronic regional pain and controls, using an algometer to measure pain at tender points and at nontender control points. Important indices were (1) total myalgia score (the sum of thresholds at tender points and control points); (2) TOTC (sum of thresholds at control points only; (3) mean pain thresholds; and (4) total number of tender points. There were major differences between the three groups in all categories despite some overlap. This was not an observer-blinded study; however, and thus is subject to some observer bias, a problem with some of these studies, not all of which find a role for central hyperalgesia (Yunus 1988, 1991 & Goldenberg 1993).

Table 4. Comparison of the pain threshold variables among the study groups*

	Fibromyalgia syndrome (n =60)	Regional pain syndrome (n=60)	Pain-free controls (n=60)	F statistic	Significance	r^2
TMS, kg/cm2	51.5	79.7	113.0	118.7	0.0001	0.57
(SD)	(9.5)	(18.3)	(31.8)			
TOTC, kg/cm	19.3	26.0	33.9	101.7	0.0001	0.36
(SD)	(6.8)	(7.6)	(9.1)			
Mean pain threshold at 1 tender point site, kg/cm2	1.7	2.9	4.3	102.0	0.0001	0.55
(SD)	(0.5)	(0.8)	(0.3)			
Mean pain threshold at 1 control point site, kg/cm2	4.8	6.5	8.4	50.9	0.0001	0.36
(SD)	(1.7)	(1.9)	(2.0)			
NTEPS, mean number	15.2	7.2	2.7	226.0	0.0001	0.70
(SD)	(2.3)	(3.9))	(3.3)			

*TMS = total myalgia score, which is the sum of pressure pain threshold values at all 18 tender points and at all 4 control points: TOTC = sum of pressure pain threshold values over control points only; NTEPS = total number of tender points. Significance of the F statistic is shown; between-group differences were significant ($P < 0.0001$) for all variables assessed.

A more objective study was reported by Mikkelson et al (1992), from a rheumatology daycare center in Finland. They compared pain thresholds and intensity, testing non-trigger points in muscle and bone in PFS patients and controls. They found highly significant differences. Both these studies, and many others like them, ascribe the differences in PFS and other primary pain disorders to a diffuse disorder of pain perception with an important central component.

If myofascial or fibromyalgia pain were due to spasm and hence peripheral in origin, it should not be difficult to demonstrate increased EMG activity. In fact, the results have been conflicting. Durette et al (1989) reviewed conflicting literature and presented results of standard EMG studies in twenty-one myofascial pain syndrome patients and four PFS patients, finding no evidence of increased neuromuscular activity. Whether or not the time-honored pain-spasm-vicious circle

theory plays a role in chronic somatic pain syndromes is not clear and has received sparse experimental support, and may not be highly relevant because it seems clear that prolonged somatic and visceral pain require prolonged central hyperalgesia as a fundamental mechanism.

HEADACHE

Langemark and colleagues have been studying headache for many years. In a 1993 study, they compared the threshold of the nociceptive flexion reflex in chronic tension-type headache subjects and controls, stimulating the sural nerve and measuring both thresholds and maximum reported pain intensity (Figure 15). They found markedly lower thresholds and lower pain tolerance in tension-type (TTH) patients. The nociceptive flexion reflex is a postsynaptic spinal reflex that correlates strongly with pain perception thresholds. Langemark and colleagues conclude that chronic tension-type headache represents a disorder of endogenous nociception with diminished tone and recruitment of descending inhibitory neurons. Sicuteri et al (Niccolodi, 1994) studied visceral pain thresholds in migraine patients using arm vein distension and arm vein hypertonic saline injections to produce pain of visceral origin, finding marked differences between migraine and normals. The authors explain markedly altered pain processing at sites far distant from the headache to a generalized visceral sensory processing disturbance; whereas, a tension-type headache may be better understood as a disturbance in central somatosensory pain regulation.

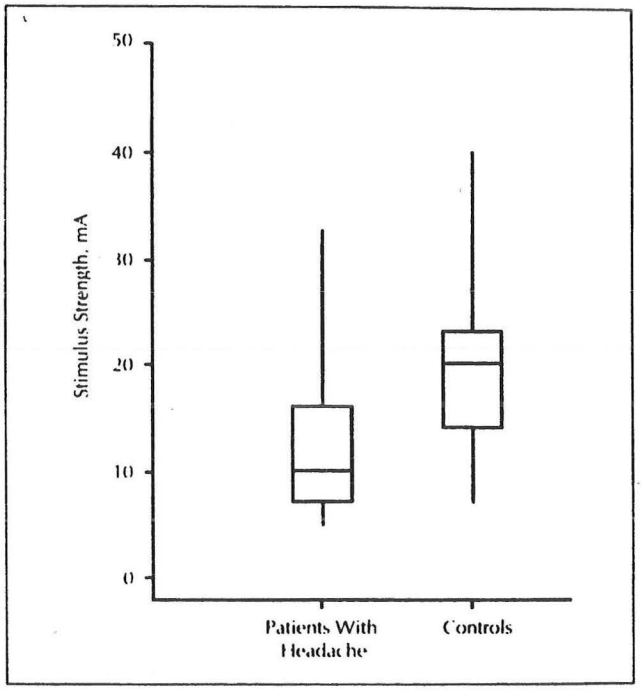

Figure 15. Threshold of the nociceptive flexion reflex in 36 patients suffering from chronic tension-type headache and in 26 healthy controls. Data from an additional four patients and three controls in whom a nociceptive flexion reflex response could not be elicited are omitted. Each box indicates quartiles and median; vertile lines extend out to the extremes. The threshold is decreased in the group of headache sufferers (P <.0001, Mann-Whitney).

OVERLAPPING STATES

If chronic pain syndromes, visceral and somatic, share common underlying mechanisms, we should predict that the syndromes would often overlap, and, such indeed is the case. Several investigators, among them Mayer and Gebhart (1994) and Yunus (1988) comment on extensive overlap between primary fibromyalgia and irritable bowel syndrome. Yunus also mentions frequent overlap between PFS, tension headache, and the premenstrual syndrome. Duckro et al (1994) reported migraine as a not uncommon sequela of chronic low back pain. I have not attempted to encompass it within this review, but a number of authors comment upon the great similarity between PFS and the chronic fatigue syndrome (CFS). A study by Bell et al in 1994 in juvenile chronic fatigue syndrome concluded that they could find no discernible clinical difference between CFS patients and PFS patients.

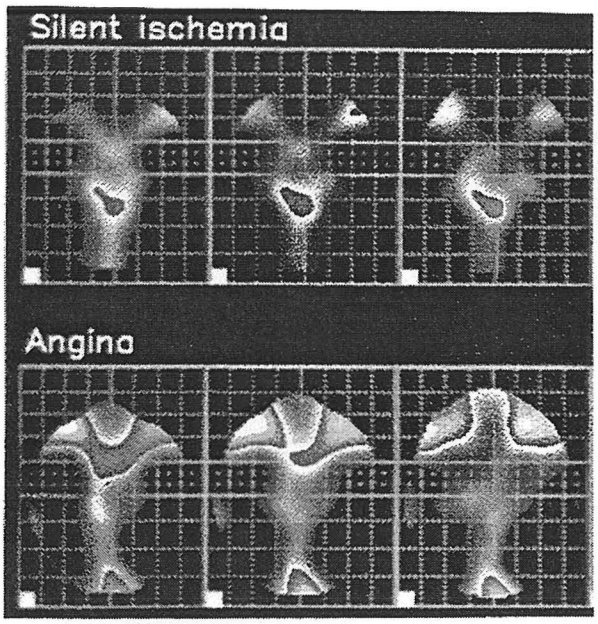

Figure 16

ANTINOCICEPTION OBSERVED

A recent study by Rosen et al (1996) has persuasively illustrated the role of central pain processing in silent and overt myocardial ischemia. In this study, patients with known myocardial ischemia received graded levels of dobutamine-induced ischemia. Position emission tomography (PET) demonstrated the central nervous system responses to myocardial ischemia; specifically, areas of increased blood flow (known to follow the increased glucose metabolism accompanying neuronal activity). In both groups of patients, silent and overt, the thalamus was activated. But only subjects experiencing angina during the protocol demonstrated activation in higher centers,

principally the basal frontal cortex, ventral ungulate cortex and left temporal pole. This is illustrated in Fig. 16 taken from their 1996 paper. The degree of ischemia and the degree of thalamic activation were similar in both groups. The implication is strong that silent ischemia is not merely milder ischemia or altered peripheral nociception, at least in these nondiabetic patients, but rather is due to active inhibition or "gating" of nociception, probably at the thalamic level. The obverse proposition, that subjective pain without ischemia (i.e., non-cardiac chest pain) can be due to augmentation or "inappropriate" activation at the thalamic level was not in the purview of these authors but can easily be inferred.

In summary, it appears that central sensitization and hyperalgesia with widening of somatosensory and visceral somatosensory referral patterns, increased pain intensity, lower pain threshold, and more prolonged pain are common to many, or most, chronic enigmatic pain syndromes.

MECHANISMS OF PROLONGATION: EMOTIONAL FACTORS

Human chronic pain syndromes may last for years or a lifetime. Goldenberg (1989) in one of his reviews notes that after three years of treatment, fewer than 5% of a large group of PFS patients were in remission. It is necessary now to elucidate some plausible mechanisms to explain how central hyperalgesia and altered nociception may become permanent. Let us first consider psychological mechanisms. The psychology of pain has for many years provoked a good deal of controversy and a considerable body of research (Fields 1991; Dworkin 1991; Lautenbacher 1994). Pain is as subjective and difficult to quantitate as mood. Direct measurements of pain transmission pathways and the biochemical and anatomical substrata of pain can be measured only in animals, as in the Bushnell-Duncan experiments. Consequently, what we known about the psychology of pain derives from indirect measurements in humans because direct measurements are rarely possible. Direct measurements are possible on animals, but they cannot describe pain to us. This is one of those subjects that it is better to summarize briefly than at length, and for our purposes, that will perhaps do.

The role of emotional states in pain has recently been reviewed by Fields (1991 and 1987) and by Lautenbacher and Krieg (1994), and excellent discussions can be found in Olesen (*Headache* 1994) and other texts and publications. Interest has focused primarily on depression and anxiety with relatively little investigation or even commentary about the role of anger, which, in some, or in many instances of chronic pain, can underlie anxiety and depression and render the individual more susceptible to pain. The role of anger in pain has recently been reviewed by Fernandez and Turk (1995).

The literature of pain and emotion is complicated by observations that depression, anxiety, and fear may, at times elevate pain thresholds, especially when acute; and at other times, lower pain thresholds, especially when chronic and associated with feelings of hopelessness and loss of control. Pain in humans is also confounded by prior and current drug usage and by issues around employment and liability, compensation, and secondary gain (Littlejohn 1989; McCain 1989).

Fields (1991) divides pain into three components. The sensory component comprises the PAN to CNS pathway; the affective component, the hypothalamus, medial thalamus, frontal cortex, and limbic systems; and the evaluative, i.e., the assessment of pain in the context of current, previous, and anticipated life experiences as modified by the individuals's repertory of techniques for coping with it (Fig. 17).

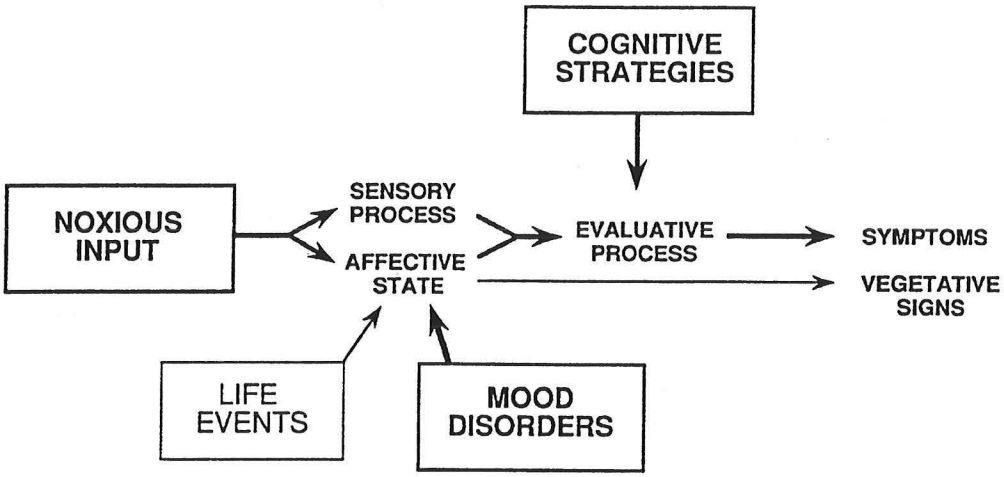

Figure 17

Emotional disorders associated with increased susceptibility and decreased tolerance to pain include: major depression, dysthymic disorder, somatization disorder, and hypochondriasis. Chronic pain patients more commonly complain of depressed mood, sleep disturbance, and somatic preoccupation. A sizable cottage industry has arisen comparing chronic enigmatic pain patients, particularly PFS patients, to rheumatoid arthritis patients; and, chronic headache patients to normal control, and to rheumatoid arthritis patients. Kirkmayer et al (1988) compared 31 PFS and 23 rheumatoid arthritis patients matched for age and socioeconomic class. Many more PFS patients reported a history of somatic symptoms without evident medical explanation, many being "sickly" much of their lives, with more conversion and psychoneurological symptoms, more gastrointestinal symptoms, more psychosexual symptoms and female reproductive pain, as well as headaches and cardiopulmonary symptoms. They suggested PFS is a process of illness behavior resulting from social psychological processes including increased focus on the body, hypochondriacal worry, attribution of emotional distress to somatic causes, leading to more symptom-reporting and help-seeking.

There is no certainty whether the emotional state (typically depression, also anger) comes first or is a consequence of the pain disorder, although the trend towards a commonality of personality traits and family and psychological histories of chronic enigmatic pain patients, in contrast to the normals and to arthritis patients, is suggestive of a pain-prone psychophysiological complex. Heilbruner and Blumer (1982) ascribed four features common to the pain-prone subject: 1) somatic complaint; 2) "silent citizen" (equates with denial); 3) depression; 4) past or present personal and/or family history of spousal abuse, depression, alcoholism, a crippled relative or a relative with chronic illness or pain.

Geisser et al (*Pain* 1994) had emphasized the significance of catastrophizing in chronic pain. Catastrophizing is a state of mind typified or characterized by items in the catastrophizing scale:

"It's terrible, and I'm never going to get better."
"It's awful, and I feel it's overwhelming."
"I feel like my life isn't worth living."
"I worry all the time about whether it will end."
"I feel I can't stand it anymore."
"I feel like I can't go on."

Not surprisingly, this state of mind lowers pain thresholds, even in normal people, and aggravates the affective component of the pain experience. The authors argue that catastrophizing should be amenable to cognitive psychotherapy.

Supraspinal or psychological and emotional influences can perpetuate pain by several mechanisms. Perhaps best understood among these mechanisms are the tonic influences of the descending bulbospinal systems and spinal interneurons: a relative loss of the normal tonic inhibition of nociception and/or chronic activation of pain-facilitating pathways, owing to an ongoing disturbance of mood, emotion, or psychological state (Mayer 1994). The "on-off" pain-modulating centers of Fields et al may play an important role.

ORGANIC MECHANISMS IN CHRONIC HYPERALGESIA

Besides psychological factors, other potential mechanisms may be cited. The neonate possesses immature pathways for pain inhibition, lacking effective descending inhibition of dorsal horn neurons as well as having increased excitability of dorsal horn neurons. With a reported increased vulnerability to nerve injury as well, the neonate may be vulnerable to lasting alteration in pain modulation. In the neonatal rat, section of a single nerve results in irreversible neuronal changes involving dorsal root ganglion cells, dorsal horn neurons, and higher centers. (References 99, 159, 160, 162-165, Mayer 1994.)

Another provocative speculation involves the phenomenon of excitotoxicity. Increased calcium fluxes through NMDA channels may play a role in cell death. Inhibitory interneurons in the dorsal horn are subject to excitotoxicity, resulting in permanent disinhibition of second order sensory neurons (Reference 13, Mayer 1994).

To summarize, although central hyperalgesia has not been directly demonstrated in humans by anatomical and chemical measurements, its manifestations are plentiful and obvious, and no other mechanism satisfactorily explains the observed clinical phenomena. Furthermore, a number of plausible mechanisms can be invoked to explain how long-lasting hyperalgesia may perpetuate vulnerability to pain. Thus, central hyperalgesia may result from nerve injury in a genetically susceptible individual or be brought about by prenatal or postnatal injury, severe or repetitive PAN stimulation, psychological injury and life situation issues eventuating in chronic visceral and somatic pain states, the origin of which may be obvious, obscure, unknown, or repressed.

MANAGEMENT PRINCIPLES AND TECHNIQUES

The management of chronic enigmatic pain syndromes demands strategies to rectify abnormal pain processing. There are two broad avenues of approach: 1) efforts to elevate the pain threshold and/or activate pain inhibition; and 2) efforts to eliminate ongoing provocation.

If many common somatic and visceral pain syndromes share common, underlying pathophysiological mechanisms, we would predict that certain general principles would apply to all chronic enigmatic pain states. Such is indeed the case; and, it is a fact that tricyclic compounds are a mainstay in irritable bowel and bladder syndromes, many types of headache, and most instances of PFS and chronic regional pain. The same may be said of exercise, diet, restorative sleep, and avoiding caffeine. To be sure, within each category, specific treatments and techniques are appropriate: fiber for IBS; serotonin antagonists for migraine.

In almost no other area of medicine is it so important to form a strong therapeutic alliance between physician and patient. These patients are usually distrustful of physicians, and often with good reason. Many have had adverse encounters with health professionals and not a few have suffered some sort of abuse by a parent, husband or other authority figure. Control issues usually arise, particularly about medications. Thus, the eternal verities of the therapeutic relationship are central to the treatment: Listen carefully; offer and provide support; respect the patient and her symptoms (don't minimize); share information and knowledge, and be candid about treatment and prognosis. Patients are usually accepting of the interpretation that their discomfort is largely owing to defective pain processing and not either all psychological or else entirely due to peripheral processes in, for example, muscles and tendons or else the bowel, because traditional therapies have failed or else provided brief respite. Because there are almost invariably control issues, emphasis must be placed on the patient being in charge, not the doctor, the physical therapist, or the itinerant masseuse. Over time, much may be gained through a series of

encounters that leave the patient feeling more in charge of his destiny, more in control of her illness.

Both non-pharmacologic and pharmacologic modalities should be considered, and the first and foremost rule is: avoid addicting medications. Opiates are best interdicted completely, and benzodiazepines must be prescribed with great circumspection. Caffeinated compounds and beverages are candidates for proscription: they play a central role in chronic daily headache and may be largely etiologic in this refractory syndrome. Many chronic daily headache patients are addicted to the popular compounds containing amobarbital, caffeine, and acetaminophen. Add codeine, and there are three addicting medicines in these compounds. Avoiding or discontinuing opiates is particularly important because the drugs themselves may adversely shift, long-term, the pain-anti-pain homeostasis in the central nervous system.

Patients who are taking opiates should be offered detoxification before being accepted into treatment. Failure to insist on this perpetuates the patient's illness and recruits the physician into the patient's drug-providing apparatus.

Most pain patients suffer from nonrestorative sleep. Improving sleep is an important part of the treatment. Tricyclic antidepressant compounds are especially useful because they improve sleep, relax muscles, both somatic and visceral, and elevate pain threshold centrally. Patients who don't tolerate tricyclics may be offered antihistamines or benzodiazepines at bedtime, perhaps adding an NSAID. Clonazepam is especially useful here because of its pronounced muscle relaxing properties, mild sedating properties, and lesser tendency, relative to other benoziazepines, to aggravate depression. More specific pharmacologic approaches to the management of the various syndromes are available from standard texts and recent reviews (Fields 1987 & Olesen 1994).

More fundamental to the long-term management of chronic enigmatic pain states are the non-pharmacologic approaches, psychological, physical, and environmental. "Environmental" doesn't particularly mean avoiding trigger substances, though these may occasionally be a factor in headache and gastrointestinal syndromes; rather, it refers to recognizing and avoiding or else learning to manage aspects of the social environment that aggravate symptoms. Psychological approaches are better accepted by patients if a primary etiologic role is not stated or implied; and efforts at "uncovering" therapy are almost always met with hostility and disengagement. Simple cognitive approaches are helpful, emphasizing and reinforcing positive activities and mental states and recognizing and avoiding catastrophizing and other negative mental states. "Attitude adjustments" are more effective than spinal adjustments.

Perhaps most effective for most patients are the direct physical approaches. Proper exercise, especially stretching and "aerobic-style" exercises are extremely beneficial, probably through activating the pain inhibitory pathways. Pain inhibition is also activated by TENS units and probably by acupuncture and massage, although these provide only temporary relief. Massage is to be undertaken only with specific caveats: almost any kind of subthreshold or mildly painful peripheral afferent stimulation will produce temporary relief, but over-vigorous stimulation, by

pressure, rubbing, or excessive heat may aggravate and perpetuate the illness, in my experience. In fact, Cervero et al (1995) have demonstrated secondary (central) hyperalgesia following repetitive nonpainful stimulation in man.

The prognosis in chronic enigmatic pain syndromes may be better than early published reports suggest (Goldenberg 1989), perhaps because such series are drawn from patients selected by refractory histories and referral to tertiary centers. A more recent report dealing with fibromyalgia in a community practice was much more optimistic (Granges et al 1994). In this study, approximately, half the patients no longer fulfilled criteria for PFS after two years. Interestingly, only regular exercise and self-assessed coping competence correlated strongly with recovery--not drugs, not specific physical therapies, not initial severity.

Finally, Hippocrates' students could have written this paper, absent the bits about molecular biology and pharmacology. Within this century and certainly within the next decade, our understanding of pain will become much more complete and our ability to ameliorate pain and avoid addiction will increase decisively, owing to efforts, such as those I have described, by clinicians and basic scientists. Meanwhile, we may take comfort in the eternal role of the physician as healer. To offer an explanation for distress and a prognosis, to preserve the patient from inappropriate and harmful remedies and diagnostic excesses while supporting and guiding the patient's natural capacity to heal and recover, remain the foundation of our profession.

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