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Mechanisms of neuropathic pain: nerve, brain, and psyche: perhaps the dorsal horn but not the sympathetic system

Jose Ochoa, M.D., Ph.D., D.Sc.,[1] and Renato J. Verdugo, M.D., M.Sc.[2]

[1]Oregon Nerve Center, Good Samaritan Hospital and Medical Center, and Department of Neurology and Neurosurgery, Oregon Health Sciences University, Portland, Oregon, USA; [2]Department of Neurology, Faculty of Medicine, Universidad de Chile, Santiago, Chile

Address correspondence and reprint requests to Jose Ochoa, M.D., Oregon Nerve Center, Good Samaritan Hospital and Medical Center, 1040 N.W. 22nd Ave., Suite NSC-600, Department of Neurology and Neurosurgery, Oregon Health Sciences University, Portland, Oregon 97210, U.S.A.
Tel: 503-226-6699
E-Mail: hhassann@lhs.org

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Hierarchy

Neuropathic pain was a theme given priority during the World Congress of Neurology recently held in London. Why so much interest in neuropathic pain? Because so many patients are suffering from it, and so many doctors are investigating and treating it. Why so many patients? Because most do not respond to therapies that researchers tell physicians to apply, and the more patients fail to respond, the more doctors puzzle about neuropathic pain. Why don't patients respond? Because, while some patients' illnesses are truly incurable, most receive the wrong therapy. Why the wrong therapy? It is because the assumptions about their pathophysiology are often flawed.

Hypothetical mechanisms of neuropathic pain: a brief history

Early concepts of neuropathic pain invoked specific pain receptors and pain fibers. The argument took into account the existence of primary sensory units that respond to natural stimuli that evoked pain. Therefore acute nerve injury causes pain because the irritated axons of those nociceptors generate afferent impulses that the brain decodes as pain. Intraneural microstimulation studies strongly endorsed this concept [1,2]. The pain is felt precisely in the territory of the nerve because the brain function of *locognosia* is somatotopic, even at the single-unit level [3]. It seemed that in chronic neuropathy pain would also be explainable by nociceptor activation. The alternative "fiber dissociation" theory of Noordenbos [4], preceding the "gate control" theory of pain, was short-lived. It proposed that in the central nervous system, primary input from large-caliber tactile afferents inhibited the input from small-caliber pain afferents. Noordenbos retracted his original theory when, together, we showed that the theory was incompatible with quantitative histopathology [5].

In the last two decades ideas have changed. Nociceptors are now thought to have a restricted role in neuropathic pain. They are believed to cause the pain in acute nerve injury, but chronic pain could largely emanate from hypothetical secondary central neuronal sensitization. Several reasons prompted this paradigm shift.

1. A "rejection of specificity" theory by Melzack and Wall [6], with revival of a modified Weddell's pattern theory of sensation, in the shape of the "gate control" theory. In other words, the subjective quality of somatic sensations would not be determined by activation of anatomophysiologically distinct afferent systems; it would be determined by the particular way in which the brain would abstract information from the complex input conveyed by afferent units of different modalities. As recently as

the 1980s, Patrick Wall, an inspired theorist, restated the concept that primary central nervous system mechanisms naturally determine the subjective quality of sensations and advocated that, in the "hyperpathic syndrome," acquired abnormal central mechanisms are responsible for neuropathic hyperalgesia. In his "challenge to specify" theory, Wall listed several clinical/neurophysiologic observations, which in his view precluded a peripheral mechanism for the "syndrome" [7]. The argument was robustly countered, on the basis of direct microrecordings from patients' nerves, by Cline *et al.* [8].

a. Wall [7]: "No recordings from normal or damaged nociceptors have shown the expected signs of summation or long latency and prolonged after-discharge, which would be required to explain the sensory experience." Cline *et al.* [8]: "Pain which outlasts the stimulus has a peripheral explanation in our patient, in light of the observed prolonged after-discharges from sensitized nociceptors."
b. Wall [7]: "The rapidity with which the syndrome occurs following trauma has no peripheral correlate." Cline *et al.* [8]: "It is no surprise that the onset of symptoms following injury may be quite rapid because C nociceptors are capable of becoming sensitized within minutes following noxious stimulation."
c. Wall [7]: "The failure of nerve grafts to cure the symptoms once the graft has reinnervated its target tissue..." Cline *et al.* [8]: "The idea that delayed failure of nerve graft therapy indicates a central dysfunction ignores a reasonable peripheral explanation: nociceptors whose sensitized state cannot be expressed symptomatically when the skin is denervated, might recreate the painful symptoms when reinnervating the target."

Incidentally, it is not generally appreciated that Graham Weddell himself rejected his "pattern" theory:

> "In the early days, from my work in the cornea, I really believed there was a pattern theory, and that meant that the way the impulses came from the cornea determined what the perceptive response was. We put electrodes in the back of the cornea and some in the front of the cornea and we said, All right, if cold is this and is a pattern, and warmth is that and it is a pattern, there should be a quite clear-cut pattern front to back. There was not! This worried us terribly. After that we watched and looked and we were not happy that we could prove...mind you, I got physicists to show me that the electrodes were in the wrong place, the temperature probes were in the wrong place. It is an awfully long time ago and our apparatus was not very sophisticated. But, I was pretty worried about this because if the pattern theory had won, it would have been in the cornea: it didn't. I have the feeling that the pattern theory, broadly speaking: out." (Authorized audiotaped personal communication, 1981).

2. The abundance of atypical cases of chronic, seemingly neuropathic, pain that defy the laws of anatomy, physiology and pathology of nerves. (We will come back to these cases.)
3. The frequent failure of neurectomy to relieve chronic pain from physical trauma [9].
4. The most persuasive reason behind the shifted paradigm has been the clear demonstration that experimental irritation of primary nociceptors, or experimental nerve damage in animals, regularly induces temporary hyperexcitability of spinal cord neurons, which are assumed to mediate pain.

The hypothetical concept of "sympathetically maintained pain" (SMP) has coexisted with these basic hypotheses that invoke primary nociceptor dysfunction or secondary central sensitization to explain chronic neuropathic pain. The intellectual roots of this concept were empirical [10]. Indeed, at its inception the concept arose on the basis of nonvasogenic, presumed neurogenic (autonomic) circulatory signs and has been aberrantly nurtured by "diagnostic" sympathetic blocks. In the 1990s the concept of SMP was uprooted using an evidence-based approach. We showed that sympathetic blocks relieve pain through unchecked placebo effect. Moreover, sympathectomy does not cure chronic "neuropathic" pains. Finally, the objective signs in those patients, typically labeled "RSD" (reflex sympathetic dystrophy), are nonspecific and explainable otherwise. When the concept of SMP collapsed, it carried with it the concept of "RSD" [11,12].

Validated neuropathic pain mechanisms

A variety of primary somatosensory mechanisms may be abnormal in patients with chronic neuropathic pains. Different mechanisms may coexist in an individual. Examples, as detected in real patients, are well documented and comprehensive overviews are available [13,14]. Primary mechanisms include: sensitization of peripheral nociceptor endings, ectopic nerve impulse generation in pathological axons, central release of unbalanced blends of primary afferent input, and brain-mediated psychogenic pseudoneuropathy [15]. Chronic pain caused by primary pathology of the central nervous system is a reality of intriguing pathogenesis, whose investigation meets the prohibitive logistical hurdle of cellular neurophysiology of human central neurons. Chronic pain caused by presumed pathology of the central nervous system, secondary to primary peripheral dysfunction, meets the same hurdle, and yet it is taken for granted.

Today's vox populi

The reigning diagnostic paradigm subclassifies chronic neuropathic pain patients into two major descriptive groups that imply pathophysiologic contexts: those carrying sufficient primary nerve pathology (the old "causalgia," today's complex regional pain syndrome [CRPS] II); and those carrying not sufficient current peripheral pathology, but, instead, untestable secondary consequences within the spinal cord, of past, resolved, peripheral injury (CRPS I).

The attribution of secondary spinal neuronal sensitization was initially by default. The atypical subgroup of "neuropathic" pain patients was not explainable by the stringent and testable laws of nerve function and dysfunction. There was nonanatomical expansion of sensory (and motor) symptoms, and touch now caused pain:

> "In the painful states associated with hyperesthesia and hyperpathia, the lesion in the periphery induced abnormal functioning in the central nervous system, presumably at spinal level. This statement is based on the fact, that tactile stimulation causes pain, and on the fact of spread of pain and hypersensitivity beyond the territory of the lesion" [16].

The secondary central attribution for atypical clinical pain was considered proven when covered by the patina of science. Cellular "wind up" and sensitization of dorsal horn neurons are unquestionable, as shown in transient animal experiments, and continue to be invoked as key abnormalities:

> "Continual input to the dorsal horn as a result of spontaneous firing in C fiber sensory neurons causes sensitization of dorsal horn neurons, which increases their excitability such that they respond to normal (a β fiber) inputs in an exaggerated and extended way. Thus, stimuli that would normally be innocuous are now painful" [17].

The theoretical requirement to perpetuate the transient hyperexcitable central state in order to match chronic symptoms has been addressed through highly indirect arguments, emanating from behavioral observations in patients with ill-differentiated chronic "neuropathic" pains.

> "An altered central processing can be dynamically maintained for long periods of time by ongoing input from nociceptive primary afferents from the periphery" [18].

Two major flaws remove evidential power from all secondary central attributions hypothesized to explain atypical chronic CRPS I patients: (1) these patients show absence of cellular neurophysiological data; and (2) unlike the animal models that develop testable secondary central changes, these patients do not have sizable nerve injury or peripheral inflammation. Equally significantly, animals and patients with sizable nerve injury do not develop the atypical clinical profiles theoretically attributed to result from secondary central changes.

Current standards also ignore the reality that, clinically, these "neuropathic," "RSD–CRPS" patients make a broader heterogeneous population, generated through a variety of potentially testable primary mechanisms. Nevertheless, the non-neurologists who largely treat these patients do not recognize gross differences. When testable diagnostic hypotheses are ruled out, and the attending doctor does not understand the case, a mythical diagnosis is entertained. Such cult bypasses the refutability principle: since the hypothesis cannot be tested, it cannot be validated, but it cannot be ruled out either. Therefore, the "diagnosis" becomes permanent and may condemn the patient to chronic illness behavior [19].

The characteristically atypical "CRPS" patients that puzzle doctors

The abundant atypical cases of chronic neuropathic pain deserve a closer look, because their mere existence has been a cardinal reason for clinical extrapolation of the experimental concept of secondary central neuronal sensitization. These patients characteristically display:

- nondermatomal sensory dysfunction,
- nonmyotomal motor dysfunction,
- a nonspecific physiological modality shift: now touch causes pain (allodynia),
- normal reflexes,
- paradoxical expansion and worsening of symptoms with time,
- normality of neurophysiological tests (both peripheral and central motor and sensory conduction).

It was fashionable to explain these atypical patients as reflecting SMP, until Verdugo [11] showed in the early 90s that SMP is a placebo artifact. When SMP and RSD disappeared as concepts, CRPS emerged.

What is CRPS I? It is good old "RSD." What does the official definition from the IASP say about it? It clearly specifies: in CRPS I there is no nerve injury. Concerning the system affected, it states, "Peripheral nervous system, possibly central nervous system." Concerning the usual course: "variable." Concerning pathology: "unknown." And diagnostic criterion 4 reads, "This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction" [20]. In other words, CRPS I holds for as long as the physician is perplexed and unaccountable. Bruehl *et al.* [21] regard the current criteria for CRPS as "having inadequate specificity and likely to lead to over-diagnosis." As we all know, lack of specificity disables exclusion of patients who do not have a presumed condition [22].

The psyche

A strong case can be made for the concept that these atypical CRPS I patients are pseudo-neurologic in nature. For Shorter [23], pseudo-neurologic profiles reflect psychoneurologic, psychogenic disease (like pseudo-seizures):

> "Much illness of an apparently neurologic nature consists of conversion reactions, otherwise known—to mention just a few of the more recent labels—as nondisease, psychosomatic illness, persistent somatization, or functional illness. Although hysteria has been downplayed in official nosology, it remains a robust analytic category. In the present context pseudo-neurologic illness seems most appropriate for those patients who have the symptoms but not the pathology of an organic lesion of the nervous system. All of these labels designate some breakdown in the mind and body relationship; they all presuppose a high degree of suggestibility on the part of sufferers and they all have a historical dimension."

In somatization, the overwhelmed, miserable, or panicky brain creates, automatically and secretly, a set of physical

symptoms. The brain can only generate neurologic symptoms. But the brain is an amateur neurologist, so it creates a caricature of true neurologic deficits. Neurologists recognize the cartoon readily. Psychiatrists depend on our prior recognition. Pain management doctors simply ignore it. Criteria for pseudo-neurologic conversion-somatization are not just the absence of organic signs, nor just normality of physiologic tests, nor abolition of pain by placebo. Criteria rest on explicit evidence that the profile emanates from brain and not from nerve and include: muscle weakness with interrupted effort because of an impoverished willful cortical drive, in the presence of normal reflexes; nonanatomical anesthesia or paralysis that might be reversed by placebo, in the presence of normal reflexes; and possible cure by cognitive psychotherapy.

Positron emission tomography scans of patients with psychogenic pain show a remarkable anomaly of cortical activation [24]. The emotional limbic brain lights up and likely modulates sensory decoding. Analogous dysfunction of motor programming is reported in psychogenic paralysis [25]. Further, "we would suggest that hysterical paralysis... involves selective inhibition of action through the modulation of specific basal ganglia and thalamocortical systems, with such inhibition being possibly triggered outside conscious will by various emotional stressors, through limbic inputs..." [26].

Neglect and witch hunt of the psyche

Why do psychologists so often miss the psychopathology of pseudo-neurologic patients?

In part, it is because of the impressive but nonspecific objective signs, which include atrophy and circulatory changes. These misleading signs are simply explained by disuse or may be self-inflicted [27]. But, again, to a major extent psychopathology is missed because it has been replaced by a cartoon of neurologic dysfunction. Why is there such reluctance to accept the concept that a disorder of brain function, such as conversion-somatization, may cause chronic pains and other symptoms? The prevailing cultural stigma against psychologic dysfunction and mental illness is primarily responsible. Patients prefer physical diagnoses, such as RSD–CRPS or chronic fatigue, to psychiatric diagnoses. This phenomenon is not new. In the 18th century patients preferred to be diagnosed with the "English Malady" rather than hysteria, "vapors," or hypochondriasis. In the book *The English Malady, or Nervous Distempers of All Kinds,* George Cheyne [28] articulated masterfully the doctor's despair when misjudged by patients and colleagues:

> "Nervous distempers are under some kind of disgrace and imputation in the opinion of the Vulgar and Unlearned. They pass among the multitude for a lower degree of Lunacy. Often when I have been consulted in a case, and found it to be what is commonly called 'nervous,' I have been in the utmost difficulty when desired to define or name the distemper. If I called the case glandular, with nervous symptoms, they concluded I thought them pox'd or had the King's Evil. If I said it was vapors, hysteric or hypochondriacal disorders, they thought I called them mad or fantastical and was thought as rude, a fool, a weak and ignorant coxcomb, and perhaps dismissed in scorn for seeming to impeach their courage."

Iatrogenesis

There is much iatrogenesis in the realm of misdiagnosed chronic "neuropathic pain patients" [19,29]. Patients who get labeled with neuropathic pains—RSD, SMP, or CRPS, for example—are always harmed through two avenues: (1) omission of an appropriate differential diagnosis for a condition that might be treatable; and (2) commission of direct iatrogenesis, largely inspired in the belief that the spinal cord was injured by prior nociceptor input. Awerbuch [30] has defined iatrogenesis as "abnormal diagnostic behavior, which leads to abnormal illness behavior in the patients and is invariably compounded by abnormal treatment behavior." There is something genial about Awerbuch's definition: iatrogenesis starts with the wrong diagnosis. It is no surprise that treatment doesn't work. Bell [31] denounces such "abnormal treatment behavior," stating, "The newfound experts developed therapeutic empires with a vigorous entrepreneurial spirit that was undeterred by the ineffectiveness of their treatment methods."

Practical implications and recommendations for the future

If the biopsychosocial reality of "neuropathic pain patients" is as it seems to be, then there are multiple clinical implications. Patient evaluation should include rigorous neurological input. Patient management should include expert psychiatric evaluation of atypical (CRPS I) patients and should resist the inbred concept that these patients "are depressed because they have chronic pain." Ron's [32] wisdom fully applies here:

> "The contact with the medical profession at this stage may serve to consolidate the symptoms by paying undue attention to them or by providing a quasi-scientific explanation. In this way, a symptom that initially may have a doubtful significance in the patient's mind becomes legitimized and the presence of anxiety or depression is explained away as an appropriate reaction to a disturbing physical symptom."

Patient management should exclude invasive procedures addressed against the sympathetic nervous system or the spinal cord, and both the inert and active placebo effects should be stringently monitored to avoid common misinterpreted attributions. We must protect pseudo-neuropathy patients from iatrogenesis. The pejorative connotation that neuropsychiatric illness means faking or madness should be eradicated through education. We are often misquoted as

supporting the wrong concept that all CRPS is psychiatric (and therefore shameful) in origin [33].

Animal research should prioritize development of genuine animal models of the enigmatic CRPS I, rather than of the understood CRPS II patients. We must develop improved methods to assess nociceptors and sensory C-fiber function, improve their assessment via microneurography supplemented by tracking latency threshold *a la* Hugh Bostock FRS [34].

The forensic issues must be addressed. We must decide who is to be held responsible for the pseudo-neurologic illness behavior and disability. Among the patients, malingerers should be held responsible. The extent to which third-party payers and society as a whole might be accountable calls for thoughtful revision of the law.

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