Placing pain on the sensory map: Classic papers by Ed Perl and colleagues

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This essay looks at two papers published by Ed Perl and co-workers that identified specifically nociceptive neurons in the periphery and superficial dorsal horn.


AFTER CENTURIES OF BEING DENIED sensory status on a par with vision, audition, gustation, olfaction and taction, pain was finally recognized as a discrete sensory modality due to the pioneering and classic work of Ed Perl (Fig. 1) and his co-workers. Over the course of <5 yr, Perl and three colleagues discovered and described the primary afferents dedicated to the detection and representation of noxious cutaneous events and the central neurons that reliably integrate information from subsets of these nociceptive afferents. While the findings of Perl and colleagues revolutionized the neurobiology of pain, the nonbiased survey approach taken also gave rise to insight into tactile and thermal somatosensation. The findings, published in one Journal of Physiology article and two Journal of Neurophysiology articles, are “of the first rank and of acknowledged excellence”, the Oxford English Dictionary’s definition of classic.

It is important to understand the historical context in which Perl and his colleagues did the work described below. At the end of the 19th century, Von Frey modified Müller’s list of specific energies to include warm, cold and pain as well as touch, assigned known anatomical receptors to each of these cutaneous sensations (shockingly, he correctly assigned pain to free nerve endings) and, most importantly, postulated that receptors excited by particular stimuli accessed a distinct path within the CNS to evoke a corresponding percept (unless you are well versed in 19th century, scholarly German, I recommend the accounts of these works in Melzack and Wall 1962; Norrsell et al. 1999). On the recognition that peripheral nerves contain elements that co-vary in diameter and conduction velocity (Erlanger and Gasser 1924), Bishop, Zotterman and others used multiunit recordings and a population form of the collision test (between natural stimuli distally and electrical stimulation proximally) to demonstrate that touch traveled in the Aβ and Aδ fiber populations, temperature in the Aδ and possibly C fiber populations and pain in the Aδ and C fiber populations (Douglas and Ritchie 1957; Heinbecker et al. 1933; Zotterman 1939). Melzack and Wall took exception to the anatomical, physiological and psychological specificity inherent in Von Frey’s schemes, aptly pointing out that a single stimulus can give rise to pain or touch, depending on the circumstances (Melzack and Wall 1962). They further argued against a correspondence between fiber diameter populations

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FIG. 1. E. R. Perl.
and percepts. In this fray entered Perl and his colleagues with two critical innovations of approach. First, they did not come into the studies below with a specific hypothesis or bias but rather collected data, lots of data, until a coherent picture emerged. Second, they studied single units rather than fiber populations or field potentials.

In the earliest paper, Burgess and Perl described a population of lightly myelinated primary afferents, with conduction velocities in the Aβ range, that respond only to noxious mechanical stimulation (Burgess and Perl 1967). They built on Sherrington’s term “noci-ceptor” to inaugurate “nociceptor” as the moniker for such afferents. A subsequent paper published in the *Journal of Neurophysiology* describes two populations of unmyelinated primary afferents that respond to noxious stimulation: polymodal nociceptors and high-threshold mechanoreceptors (Bessou and Perl 1969). The polymodal nociceptors were named such because they respond to mechanical, thermal (both hot and cold) and chemical (weak acids) stimuli, but only in the noxious range. Bessou and Perl further showed that polymodal nociceptors are sensitized by heat applied to the receptive field. Nociceptors differ in their receptive field structures and sizes but share the common property of having a paucity of unprovoked activity. Finally, Bessou and Perl noted that no adequate stimulus was found for roughly 10% of the cutaneous afferents identified by electrical stimulation; it is possible that these are the fore-runners to the currently-recognized class of “silent nociceptors”, afferents that only code for peripheral events after severe injury or inflammation (Schaible and Schmidt 1985; Schmelz et al. 2000).

Perl’s work also clearly demonstrates that unmyelinated and lightly myelinated primary afferents are not the exclusive purview of pain or even of pain and temperature. The majority of Aδ fibers studied responded to hair movement and collision tests demonstrated that these hair receptive afferents account for the Aδ peak in the compound action potential. While not in the majority, the low-threshold mechanoreceptor, unresponsive to noxious or thermal stimuli, was the most frequently recorded unmyelinated afferent. In the late 1970s and early 1980s, Perl worked with Alan Light, and then with Lee and Sugiura to demonstrate that small diameter fibers terminate in the superficial dorsal horn but with an anatomical bias according to function rather than diameter. Nociceptors and thermoreceptors terminate dorsally in laminae I and II outer whereas low-threshold afferents enter the inner substantia gelatinosa and dorsal nucleus proprius (Light and Perl 1979; Sugiura et al. 1986). This work should serve to caution those hoping to study nociception by recording from small diameter dorsal root ganglion cells or superficial dorsal horn cells in vitro.

Perl recognized that specificity in the periphery would all be for naught unless at least some degree of specificity obtained centrally. Therefore Christensen and Perl (1970) examined dorsal horn units receiving input from slowly-conducting afferents. In their paper published in the *Journal of Neurophysiology*, they demonstrate that cells in the superficial dorsal horn, principally in lamina I, respond to unmyelinated and lightly myelinated primary afferents. They described cells that respond only to noxious mechanical stimulation, those that respond to noxious mechanical and thermal stimuli and those that respond to innocuous thermal changes, principally in the cooling direction. These three cell types align remarkably well with those described both morphologically and physiologically by Craig and colleagues nearly three decades later (Craig et al. 2001; Han et al. 1998).

On re-reading the body of work produced by Perl and his co-workers, I was struck by how many enduring truths were reported in these three papers. Today, classification schemes come and go, rarely extending beyond a single laboratory and its descendants or past a single decade. Yet, nearly four decades after their discoveries, Aδ fiber nociceptors excited by noxious mechanical stimulation as well as C fiber polymodal nociceptors and high-threshold mechanoreceptors remain the principal afferent players in cutaneous pain and are studied by dozens of laboratories. Perl was the first to recognize the critical importance of primary afferent neurons exclusively activated by noxious stimuli (Perl 1971). In the 1980s, stimulation of individual Aδ and C fibers in human provided dramatic confirmation that excitation of nociceptors typically gives rise to a pain percept (Torebjork 1985). Despite the work of Perl and Christensen demonstrating the critical contribution of dorsal horn cells exclusively activated by noxious stimulation, many continued to focus attention on convergent cell populations located in the ventral dorsal horn and intermediate horn rather than on neurons in the marginal layer and substantia gelatinosa. The predominant influence of nociceptors and superficial dorsal horn cells on pain processing and behavior has been recently re-discovered and confirmed by those using genetic manipulations to alter pain processing (Hu et al. 2006; Malmberg et al. 1997; Naveilhan et al. 2001). Thus pain behavior, including allodynia, depend on molecules present in nociceptors of the dorsal root ganglion and cells of laminae I and II (Coull et al. 2005; Malmberg et al. 1997).

The papers highlighted here prove the fundamental idea that there exist a distinct set of neural units that code for painful stimuli in the periphery and in the dorsal horn. Yet, operationally these studies were exploratory missions rather than the hypothesis-driven experiments currently in neurobiological fashion (Akil 2003). Perl deliberately recorded and characterized every afferent with a conduction velocity under 51 m/s (Burgess and Perl 1967) or 2.2 m/s (Bessou and Perl 1969). He and Christensen carefully mapped field potentials elicited by activity in slowly-conducting afferents, concluded that the superficial marginal zone was the main target of these afferents, and then characterized every single unit isolated in that region. Thus Perl approached the question of “what do slowly-conducting afferents do?” with a nonbiased physiological survey using carefully chosen stimuli for potential somatosensory modalities – light touch, pressure, pinch, cut and puncture, warm and hot, cool and cold, and acid. Further, recognizing that an accurate portrait of any population requires a large sample size, Perl and his colleagues characterized 513 lightly myelinated and 131 unmyelinated primary afferents and 110 dorsal horn cells, totals that have since only rarely been approached or surpassed (Craig et al. 2001). Given the open-minded methodology and large dataset, no one should be surprised that the findings of Perl and colleagues have withstood the test of time, being as relevant today as when first reported, the sign of a true classic.

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REFERENCES


