Sir Victor Horsley, Mr John Marshall, the Nervi Nervorum, and Pain

More Than a Century Ahead of Their Time

Joel A. Vilensky, PhD; Sid Gilman, MD; Kenneth Casey, MD

Sir Victor Horsley (1857-1916) is best known for the many pioneering neurosurgical procedures that he developed during the late 19th century. These advances enabled surgery to be performed on the brain with an acceptable mortality level. Horsley’s research was not limited to neurosurgery; it also extended into basic neurology (eg, motor cortex function) and even general medicine, including many studies on the function of the thyroid gland.

One of Horsley’s first basic research efforts involved the histologic characteristics of peripheral nerves. The effort was probably conducted late in 1883 and was described only in abstract form. It was first published in the British Medical Journal (BMJ) in January 1884 and later that year in similar, but not identical, abstracts in the Proceedings of the Royal Medical and Chirurgical Society of London and the Proceedings of the Physiological Society of London. This research was conducted at the “suggestion” of one of Horsley’s surgical mentors, John Marshall.

Between 1882 and 1884, Horsley was surgical registrar to Marshall, who in 1883 was president of the Royal College of Surgeons. In that year Marshall gave the prestigious Bradshawe Lecture, “Nerve-Stretching for the Relief or Cure of Pain.” Marshall conducted an array of microanatomic and macroanatomic studies for this presentation. Marshall proposed in his lecture that ramifying within the epineurium of the nerve sheath is a “nervi nervorum” that contains branches from the nerve itself. He argued that these tiny nerves are sensitive to pain, particularly when the nerve is subjected to pressure. He thought that this nerve supply of peripheral nerves was comparable with sensory nerves in other body structures, such as joints and teeth.

Marshall referred to particular anatomic locations where pressure-causing pain might be exerted on nerves, including where the sciatic nerve exits the pelvis and where the common fibular (peroneal) nerve wraps around the head of the fibula. Marshall referred to previous research by Philibert Constant Sappey demonstrating the existence of epineural fibers in the optic nerve (as branches from the ciliary nerves) but then said that these fibers had not been demonstrated for ordinary nerves, “but I hope someone will take up the point and succeed in doing so.” Marshall gave the Bradshawe Lecture on December 6, 1883. Horsley’s BMJ abstract verifying the existence of the nervi nervorum (based on a presentation he made to the Royal College of Surgeons) appeared on January 26, 1884, suggesting that Marshall had already asked Horsley to conduct this work by the date of his lecture.

We emphasize the importance of the work of Horsley and Marshall on the nervi nervorum because of recent findings that corroborate their observations and evaluations. Furthermore, although in 1990 Sugar published a tribute to Marshall and Horsley’s investigation into nerve stretching and the nervi nervorum, their work remains typically uncited and unused. Also, Sugar did not present all of the important histologic details reported by Horsley, his functional evaluation of the findings, or Marshall’s speculated changes in the structure associated with inflammation.

Author Affiliations: Department of Anatomy and Cell Biology, Indiana University School of Medicine, Fort Wayne (Dr Vilensky); and Department of Neurology, University of Michigan School of Medicine, Ann Arbor (Drs Gilman and Casey).
The description of encapsulated end bulbs in the epineurium received some recent support. Sauer et al\textsuperscript{13} reported as an unpublished observation that some of the small-caliber nociceptors in rat peripheral nerve sheaths have properties consistent with mechanoreception (ie, fast conduction velocities) (Geoffrey M. Bove, DC, PhD, written communication, July 2004). What is the role of these epineural mechanoreceptors (presumably the pacinian corpuscles, although the Krause end bulbs, which Horsley considered to be tactile receptors, have also been associated with mechanoreception)?\textsuperscript{14}

Horsley believed that the end bulbs enabled pain to be localized along the course of a nerve.\textsuperscript{4,6} He also thought that they might play a role in position sense. Such a role has been hypothesized for joint mechanoreceptors, although this is unproven.\textsuperscript{15} Joint mechanoreceptors have also been hypothesized to participate in reflex responses that protect joints from potentially deleterious actions such as hyperflexion, hyperextension, and overrotation, but again this function is in dispute.\textsuperscript{15} Nevertheless, it is possible that these mechanoreceptors stimulate muscular reflexes to protect nerves from potential damage due to pressure from overlying structures. This is not inconsistent with Marshall’s original hypothesis.

The view that specialized sensory mechanoreceptors exist in nerves is also consistent with a recent study\textsuperscript{16} demonstrating that free nerve ending is probably a misnomer. Under serial electron microscopic analysis, these endings (in dog testes) appear to have features specialized for nociception that perhaps vary by region and structure.

In 1883, Marshall presciently suggested that in inflamed states the nervi nervorum may become an especially significant pain generator (Figure). He speculated that inflammation results in the release of irritating “plastic materials” (ie, cells capable of reproducing) and fluids that excite the nervi nervorum, causing the sensation of pain.\textsuperscript{8} This speculation is remarkably consistent with a study\textsuperscript{13} demonstrating that inflammatory mediators (specifically a mixture of bradykinin, histamine, and
serotonin) cause the presumptive nociceptors in the nervi nervorum of the rat sciatic nerve to release calcitonin gene–related peptide and prostaglandin E2. Such a release would, as Marshall speculated, contribute to chronic neuropathic pain.12 Similarly, joint mechanoreceptors are believed to become nociceptive under inflammatory conditions.15

The ideas that Horsley and Marshall generated on the importance of the nervi nervorum in neuropathic pain were ahead of their time, and both men should be recognized for their remarkable insight into this putative pain-generating structure. In addition, Horsley’s description of the existence of pressure receptors in nerve sheaths, especially in light of the new view of “free nerve endings,” should be reinvestigated for its possible contribution to current understanding of reflex responses and neuralgia.

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Correspondence: Joel A. Vilensky, PhD, Indiana University School of Medicine, 2101 Coliseum Blvd E, Fort Wayne, IN 46805 (vilensk@ipfw.edu).

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REFERENCES