Stim - Nerve

Direct effect of electrical stimulation on peripheral nerve evoked activity: implications in pain relief

RONALD J. IGNELZI, M.D., AND JUDITH K. NYQUIST, PH.D.

Division of Neurological Surgery, Veterans Administration Hospital and University of California School of Medicine, San Diego, California

Experiments were performed with a peripheral neurostimulator, used clinically for pain relief, on isolated cat cutaneous peripheral nerve to determine the effect of electrical stimulation on components of the compound action potential. The results show that neurostimulation alters the conduction velocity and the amplitude of both the A-alpha and beta and the A-delta waves with the more slowly-conducting A-delta component showing the greatest changes. This direct alteration of peripheral nerve activity distal to the first synapse in the spinal cord might contribute to the mechanism of pain relief.

KEY WORDS · electroanalgesia · nerve stimulation · peripheral nerve compound action potential · gate-control hypothesis

PERIPHERAL electroanalgesia has become an effective clinical method of controlling pain in recent years. The gate-control hypothesis of Melzack and Wall[11] has been invoked to explain the mechanism of such relief. Inherent in this hypothesis is that inhibition of small-fiber pain input by large-fiber activity occurs through interactions at the spinal cord level. The authors studied the effects of percutaneous neurostimulators used clinically on isolated peripheral nerve evoked activity in the cat and found that stimulation alters peripheral nerve activity before the first synapse in the spinal cord. These alterations could be the mechanism of pain relief obtained with these devices.

Materials and Methods

Ten cats weighing 2.5 to 3.5 kg were anesthetized with intraperitoneally injected chloralose-urethane. Lengths of the sural or superficial radial nerves measuring 50 to 130 mm were exposed and dissected from surrounding tissue. Bipolar hook stimulating electrodes were placed at one end of the exposed nerve, recording electrodes at the other end, and a peripheral nerve stimulator cuff,* of the same type implanted in humans for pain relief in an intermediate position. Neurostimulator parameters were set in the range reported for pain relief in human patients. With the electrodes in place, the entire nerve and electrode assembly was covered with mineral oil warmed to 35° C. The central end of the exposed nerve was severed, leaving the nerve isolated from the central nervous system.

*Stimulating electrode cuff made by Avery Laboratories, Incorporated, 145 Rome Street, Farmingdale, New York 11735.

A

F

J Neurosurg 45: 159-165, 1976

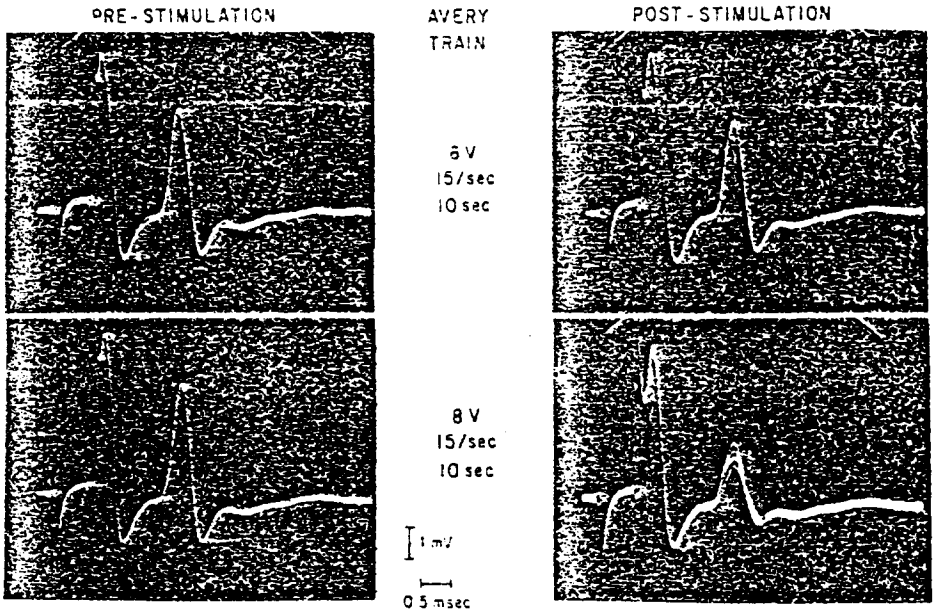

FIG. 1. *Upper:* Sural nerve compound action potentials evoked by a 100 V, 0.6 msec pulse stimulus show an A-alpha and beta peak corresponding to a 62.4 m/sec conduction velocity and an A-delta peak with a 25.8 m/sec conduction velocity. Following a 10 sec train of 15 pulses/sec at an intensity of 6 V applied through the neurostimulator cuff, the A-delta wave shows a slight reduction in amplitude and decrease in conduction velocity (to 24.6 m/sec). No change in the A-alpha and beta wave was observed. *Lower:* When the neurostimulator stimulus intensity was increased to 8 V, both waves showed a reduction in amplitude and a decrease in conduction velocity. Records in this and subsequent figures represent three to five superimposed traces and, in this figure, show the beginning of amplitude recovery. Negativity is signaled by an upward deflection. Conduction distance = 53 mm.

Stimulus pulses were applied to one end of the nerve with a Grass S88 stimulator.† Intensities of 60 to 150 V and pulse widths of 0.5 to 0.9 msec were sufficient to evoke nerve compound action potentials. The A-alpha and beta, A-delta, and C wave components were differentiated by conduction velocity. To facilitate comparison among experiments, all latency measurements have been converted to conduction velocity by dividing the latency-to-wave peak by the conduction distance between stimulating and recording electrodes. The compound evoked potentials were amplified with an AC-coupled amplifier, displayed on a Tektronix 565 oscilloscope‡ and directly photographed from the oscilloscope screen. Long latency and small amplitude C waves were summed using a Nicolet 1072 averaging computer. The nerve compound action potential was recorded before and after neurostimulator pulse trains of varying stimulus intensity, repetitive frequency, and duration to determine the effect of the pulse train on the A-alpha and beta, A-delta, and C fiber components.

Results

The lowest stimulus intensity for evoking nerve activity was 2.4 to 2.7 V in most experiments. Conduction velocities for the largest, most rapidly conducting A-alpha and beta fibers ranged from 40 to 100 m/sec; for A-delta fibers they ranged from 15 to 30 m/sec. The C wave consisted of activity in small, unmyelinated fibers conducting less than 1 m/sec. The results presented and discussed will be confined to neurostimulation effects on the A-alpha and beta and the A-delta waves, as the C wave proved difficult to monitor consistently. At the long conduction distances used, it is possible that temporal dispersion precluded sufficient simul-

†Grass S88 stimulator manufactured by Grass Instrument Company, 101 Old Colony Avenue, Quincy, Massachusetts 02169.

‡Tektronix 565 oscilloscope manufactured by Tektronix, Incorporated, PO Box 500, Beaverton, Oregon 97005.

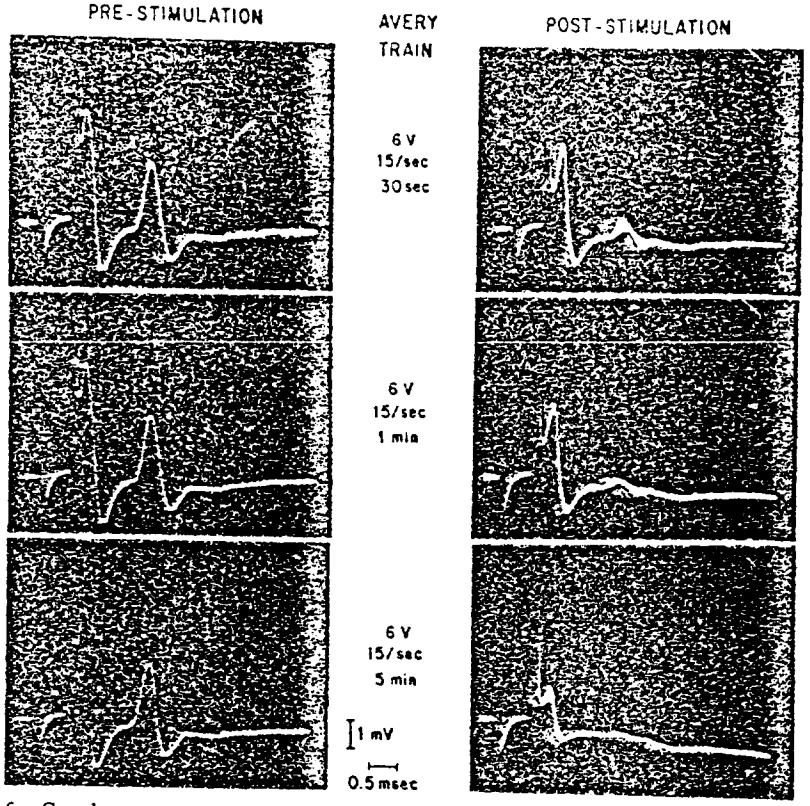

FIG. 2. *Left:* Sural nerve compound action potentials evoked by a 100 V, 0.6 msec pulse stimulus. *Right:* Following a 6 V, 15/sec pulse train applied through the neurostimulator cuff for durations of 30 sec *(upper)*, 1 min *(center)*, and 5 min *(lower)*, both the A-alpha and beta and A-delta waves show a reduction in amplitude at all durations and a slowing of conduction velocity at the 1 min duration. Negativity is signaled by an upward deflection. Conduction distance = 35 mm.

taneous activity to produce a recordable C wave. Interpretation was uncertain because often, even when a C wave was recorded and a neurostimulator influence noted, the effect was not reversible and the C wave did not recover to prestimulation values. It is possible that the slight mechanical pressure exerted on the nerve by the cuff to ensure adequate electrode contact could have produced changes in individual fibers, but such a mechanical effect alters large fibers before small fibers are affected.[14]

Pulse trains applied through the cuff neurostimulator for 1 sec to 30 min subsequently altered all components of the compound action potential for varying periods of time following termination of the neurostimulation. In all experiments, the A-delta wave showed greater changes following neurostimulation than did the A-alpha and beta wave. In seven of 10 experiments, the effect of the neurostimulator train was to reduce the amplitude or to increase the latency to the peak of the A-alpha and beta and the A-delta components of the compound action potential, or both. Figure 1 shows the effects of 6 V and 8 V neurostimulator trains applied for 10 sec on the A-alpha and beta and the A-delta waves of the sural nerve. An 8-V stimulus reduced the amplitude of both components, but the A-delta wave showed the greatest reduction, to less than one third. Both waves also showed reduction in conduction velocity. The rapid recovery of the A-delta wave amplitude toward prestimulation values began before the recovery of conduction velocity (Fig. 1 *lower right*). Figure 2 shows the effect of a 6 V, 15/sec neurostimulator pulse train applied for 30 sec, 1 min, and 5 min. Note the greater influence on the A-delta wave at all pulse train durations. Figure 3 shows the gradual recovery of the A-alpha and beta wave over the course of the 12 minutes following termination of the neuro-

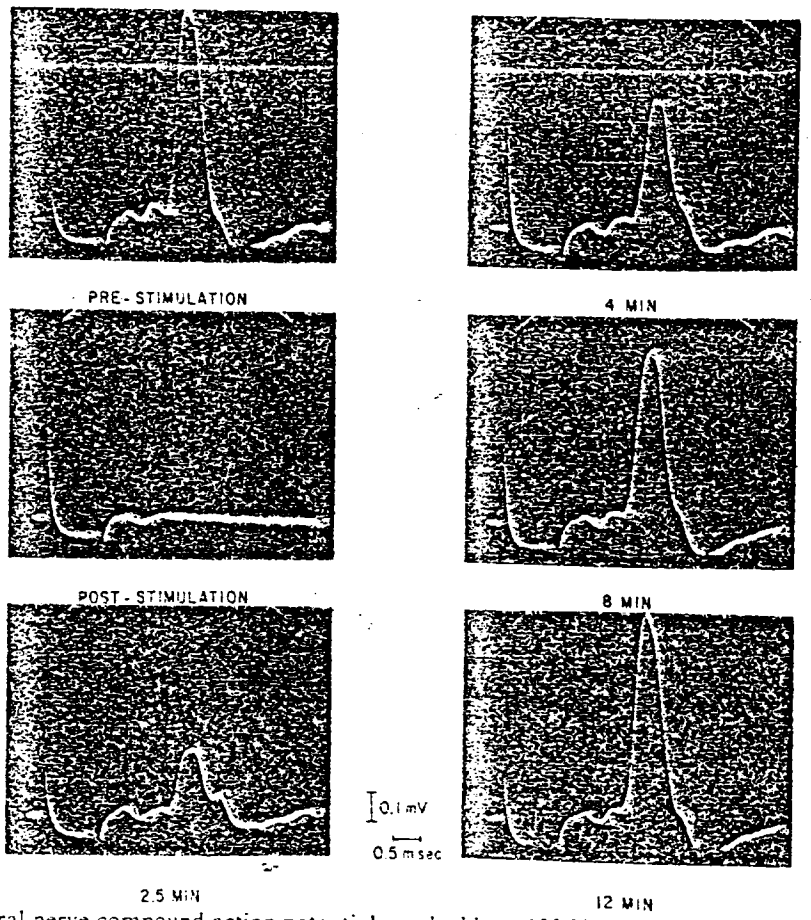

FIG. 3. Sural nerve compound action potentials evoked by a 100 V, 0.9 msec pulse stimulus. Following a 6 V, 15/sec pulse train applied through the neurostimulator cuff for 5 min, the A-alpha and beta wave is initially completely abolished and shows a gradual recovery within 12 min. Conduction distance = 89 mm.

stimulator pulse train. The A-delta wave initially present was not recorded at this point in the experiment. The A-alpha and beta wave was completely abolished initially, but recovered to 29% of prestimulation amplitude in 2½ min, 57% by 4 min, 86% by 8 min, and to prestimulation amplitude in 12 min. Concomitant conduction velocity changes were slight; an initial peak value of 33.6 m/sec was slowed to 31.8 m/sec at 2½ min and recovered to 32.3 m/sec in 12 min.

An unexpected finding in three experiments was the poststimulation enhancement of both amplitude and conduction velocity of the A-alpha and beta and the A-delta components following their initial poststimulation reduction. Figure 4 shows that the A-alpha and beta wave was initially shifted later in time, and by 11 min had recovered initial peak conduction velocity without significant alteration in amplitude. The A-delta wave, after an immediate and dramatic reduction in amplitude, at 3 minutes showed greater amplitude and peak conduction velocity compared with prestimulation values. By 11 min post stimulation, the A-delta peak had increased 2.6-fold and was shifted 0.65 msec earlier in time.

Discussion

Electroanalgesia for chronic intractable pain states has become an attractive alternative to ablative procedures of pain pathways. Clinical pain relief that often lasts many

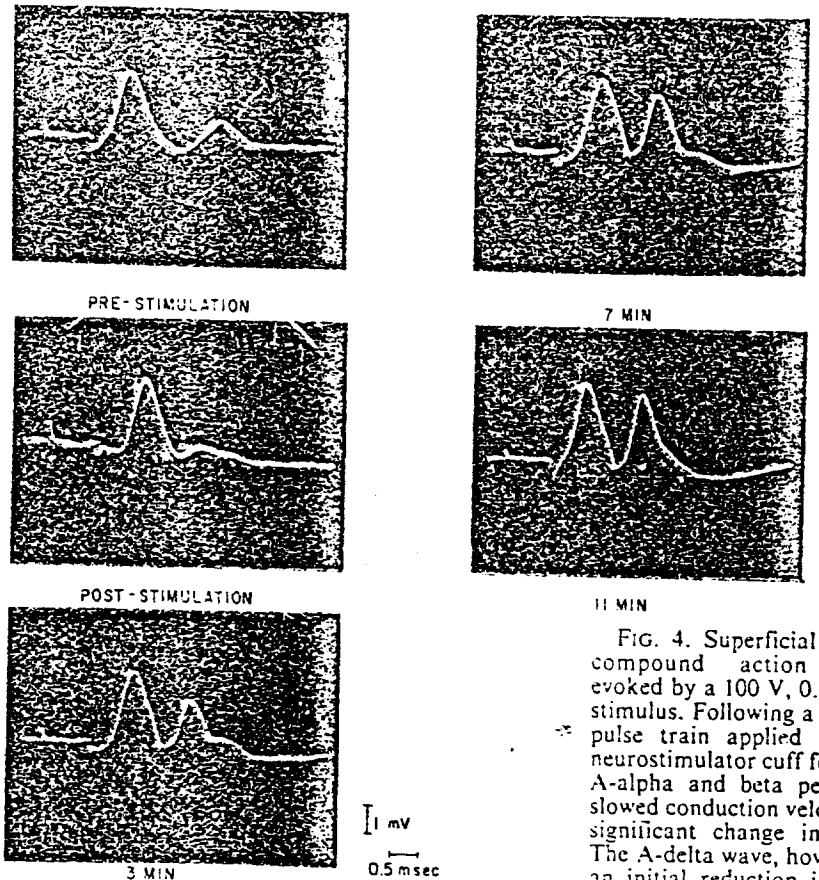

FIG. 4. Superficial radial nerve compound action potentials evoked by a 100 V, 0.9 msec pulse stimulus. Following a 14 V, 15/sec pulse train applied through the neurostimulator cuff for 5 min, the A-alpha and beta peak shows a slowed conduction velocity with no significant change in amplitude. The A-delta wave, however, shows an initial reduction in amplitude followed at 3 min by an increase in amplitude and faster peak conduction velocity compared to prestimulation values. By 11 min the A-delta wave is 2.6 times prestimulation amplitude with a concomitant increase in peak conduction velocity from 24.4 m/sec to 36.7 m/sec. Conduction distance = 77 mm.

hours beyond the period of stimulation has been achieved in cases of traumatic peripheral neuropathies with either implanted cuff stimulators[10] or transcutaneous devices.[9,12,20] In addition to the reports of clinical pain relief, a number of psychophysical studies in normal subjects have shown that non-nociceptive peripheral stimulation (either natural or cutaneous electrical shock) elevates pain threshold and tolerance to high-intensity, painful, electric shock or to natural painful stimuli.[5,13,15]

The gate hypothesis of Melzack and Wall,[11] which states that large-fiber stimulation results in suppression of small-fiber nociceptive input at spinal cord levels, has been widely accepted as the mechanism of clinical pain relief and the elevation of pain threshold and tolerance. However, others have suggested that more peripheral events might be involved. Campbell and Taub[2,16] reported that the A-delta component of the median nerve compound action potential was suppressed by neurostimulation in human subjects and proposed that the concomitant analgesia resulted from peripheral blockade of these fibers, not from central spinal cord suppression. They reported that C fibers were not blocked at the intensities of stimulation used. Torebjörk and Hallin[17] reported similar findings and suggested that an A-delta fiber "fatigue" distal to the spinal cord contributes in part to the mechanism of pain relief. Our observations on cat nerve isolated from the spinal cord support this concept.

Animal studies on the effect of electrical stimulation on individual component fibers of peripheral nerve may be relevant to the inter-

pretation of our compound action potential data. Casey and Blick[3] reported changes in peripheral nerve fibers subjected to a constant current stimulus, a method useful for selectively blocking large diameter fibers by anodal polarization while leaving the smaller diameter fibers conducting. They found, however, that the polarizing current caused changes in conduction velocity prior to block with no concomitant changes in action potential amplitude. Furthermore, the temporal order of blocking was not strictly a function of initial conduction velocity, although the magnitude of velocity decrease is related to fiber diameter. As anodal polarization was applied, the large A-alpha and beta wave showed the first changes (a transient increase in amplitude), but the A-delta wave was usually the first to be blocked. In our experiments, the A-delta wave underwent the first changes in amplitude or conduction velocity or both, and was also the first to be blocked. Differences in results may be due in part to different forms of blocking stimulation in the two studies.

Our results suggest that repetitive stimulation through a neurostimulator causes similar selective conduction velocity changes and ultimate fiber block. It is not known whether these altered or blocked fibers are activated by nociceptive or non-nociceptive natural stimuli. Reports that A-delta and C fibers also mediate non-painful, low-threshold mechanical input as well as non-painful temperature changes[1,7,8] emphasize that it is difficult to categorically assign a role in mediation of pain to these fibers.

Using single-fiber recordings, we plan to determine individual changes in conduction velocity and complete fiber block, or both, caused by neurostimulation. Such recordings will allow precise determination of the relationships between fiber size, susceptibility to neurostimulation, and natural stimulus modality.

In a chronic study by Wall and Gutnick,[18] rat sciatic nerves were sectioned and a terminal neuroma allowed to form at the central cut end for 9 to 40 days. It was subsequently shown that if the neuroma was driven to a high level of activity by direct electrical stimulation, the ongoing activity, which presumably was painful, ceased after the stimulation. High-frequency tetanic stimulation is known to hyperpolarize central terminals[19,21] and may also be the mechanism by which high-frequency antidromic invasion of a neuroma inactivates neuroma discharge. These two studies[3,18] indicate that repetitive electrical stimulation of the nerve can alter the peripheral nerve fibers directly and the peripheral site of generation of painful inputs. It should be pointed out that the low-frequency (15/sec), alternating polarity pulse stimulation in our study is not directly comparable to the constant current stimulation of Casey and Blick or to the high-frequency (100/sec) pulse trains used by Wall and Gutnick. The findings suggest, however, that similar mechanisms may be involved.

With the available data, it is not possible to assess the relative importance of observed alterations in the conduction velocity and the amplitude of the compound action potential components. Changes in the conduction velocity of individual fibers would be recorded as changes in the amplitude and the latency of individual wave components of the compound action potential. This could explain the records in Fig. 4. If the most rapidly conducting fibers in the A-alpha and beta range underwent a reduction in conduction velocity, the arrival of action potentials at the recording electrode would be shifted later in time, resulting in an A-alpha and beta wave of longer peak latency and larger amplitude. Furthermore, if the more slowly conducting fibers in the A-alpha and beta range were reduced in conduction velocity, the arrival of activity would also be shifted later in time and sum with the fibers in the A-delta range, resulting in an A-delta wave with shorter peak latency and larger amplitude. Precise interpretation of changes in conduction velocity and amplitude of compound action potential components depends on recording the changes in single peripheral nerve fiber activity caused by neurostimulation.

Since activity in A-delta fibers has been correlated with perception of pain in man,[4] our findings support the idea that suppression of A-delta fiber activity results in suppression of painful input to the central nervous system. Since alterations were also observed in the A-alpha and beta wave, we propose that changes in non-nociceptive cutaneous sensibility (touch, pressure, hair movement, vibration) might also be a concomitant of therapeutic neurostimulation. This hypothesis is supported by the clinical findings of

Goodman[5] who reported that both touch and vibration sensibilities were altered by dorsal column stimulation at the intensity levels providing pain relief.

Summary

Our results show that repetitive stimulation of isolated peripheral nerve causes changes in both the A-alpha and beta and the A-delta waves of the compound action potential. Similar stimulus parameters provide clinical pain relief, suggesting that A-delta wave suppression and pain relief are correlated. Whereas the Melzack-Wall gate-control theory emphasizes that small-fiber pain input suppression by large-fiber stimulation occurs at the spinal cord, our data lend support to the idea that peripheral changes occur before the first spinal cord synapse.

References

1. Bessou P, Perl ER: Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. J Neurophysiol 32:1025–1043, 1969
2. Campbell JN, Taub A: Local analgesia from percutaneous electrical stimulation. A peripheral mechanism. Arch Neurol 28: 347–350, 1973
3. Casey KL, Blick M: Observations on anodal polarization of cutaneous nerve. Brain Res 13:155–167, 1969
4. Collins WF Jr, Nulsen FE, Randt CT: Relation of peripheral nerve fiber size and sensation in man. Arch Neurol 3:381–385, 1960
5. Goodman SJ: The effect of dorsal column stimulation on cutaneous sensation. Presented at the 43rd Annual Meeting of the American Association of Neurological Surgeons, Miami, Florida, April 6–10, 1975
6. Higgins JD, Tursky B, Schwartz GE: Shock-elicited pain and its reduction by concurrent tactile stimulation. Science 172:866–867, 1971
7. Iggo A: Cutaneous thermoreceptors in primates and sub-primates. J Physiol 200:403–430, 1969
8. Kenton B, Kruger L, Woo M: Two classes of slowly adapting mechanoreceptor fibres in reptile cutaneous nerve. J Physiol 212:21–44, 1971
9. Loeser JD, Black RG, Christman A: Relief of pain by transcutaneous stimulation. J Neurosurg 42:308–314, 1975
10. Long DM: Electrical stimulation for relief of pain from chronic nerve injury. J Neurosurg 39:718–722, 1973
11. Melzack R, Wall PD: Pain mechanisms: a new theory. Science 150:971–979, 1965
12. Meyer GA, Fields HL: Causalgia treated by selective large fibre stimulation of peripheral nerve. Brain 95:163–168, 1972
13. Satran R, Goldstein MN: Pain perception: modification of threshold of intolerance and cortical potentials by cutaneous stimulation. Science 180:1201–1202, 1973
14. Strain RE Jr, Olson WH: Selective damage of large diameter peripheral nerve fibers by compression: an application of Laplace's law. Exp Neurol 47:68–80, 1975
15. Sullivan R: Effect of different frequencies of vibration on pain-threshold detection. Exp Neurol 20:135–142, 1968
16. Taub A, Campbell JN: Percutaneous local electrical analgesia; peripheral mechanisms, in Boninca JJ (ed): **Advances in Neurology, Volume 4: International Symposium on Pain.** New York: Raven Press, 1974, pp 727–732
17. Torebjörk HE, Hallin RG: Excitation failure in thin nerve fiber structures and accompanying hypalgesia during repetitive electric skin stimulation, in Bonica JJ (ed): **Advances in Neurology, Volume 4: International Pain Symposium.** New York: Raven Press, 1974, pp 733–735
18. Wall PD, Gutnick M: Properties of afferent nerve impulses originating from a neuroma. Nature 248:740–743, 1974
19. Wall PD, Johnson AP: Changes associated with post-tetanic potentiation of a monosynaptic reflex. J Neurophysiol 21:148–158, 1958
20. Wall PD, Sweet WH: Temporary abolition of pain in man. Science 155:108–109, 1967
21. Wall PD, Wickelgren B: Afferent hyperpolarization and post-tetanic potentiation of a monosynaptic reflex. J Physiol 196:135P, 1968

This work was supported by Veterans Administration Research Grant No. 0323-01.

Address reprint requests to: Ronald J. Ignelzi, M.D., Neurosurgery (112A) Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, California 92161.