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LOCAL ANALGESIA FROM PERCUTANEOUS ELECTRICAL STIMULATION AND A PERIPHERAL MECHANISM

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Pain is in itself an evil; and, indeed, without exception, the only evil.

Jeremy Bentham

ABSTRACT

Pain and touch thresholds to a needle stimulus were measured on a finger of each of 11 subjects as a function of the presence or absence of continuous, 100 Hz, 1 msec, electrical stimulation delivered proximally to the digital nerves of the finger tested at intensities of either 10-12v, 22v, or 50v. At 10-12v touch threshold alone was elevated; at 22v both touch and pain thresholds were elevated, and at 50v, anesthesia and analgesia resulted. The averaged median nerve compound action potential resulting from either periodic bursts or continuous 50v, 100 Hz, 0.5 msec duration, electrical stimulation to the digital nerves of a finger was studied in each of 5 subjects. An A delta wave was recorded with periodic bursts of stimuli, but was absent with continuous stimulation. These results indicate that analgesia from electrical stimulation results from peripheral blockade of A delta fibers. A critique of the specificity, and pattern theories, and gate control hypothesis of pain is provided.

As[1] with other sensory modalities the analysis of neural mechanisms giving rise to the experience of pain has met with two approaches. In one, the so called "specificity theory," the conscious experience of pain is said to be the direct result of stimulation of nociceptors--i.e. receptors which fire only with noxious stimulation (Sinclair, 1955). The alternative "pattern theory" maintains that pain results from the number of impulses in the peripheral nerve, the pattern of nerve fibers stimulated, and their spatial and temporal interrelationships. Any given fiber may contribute to a variety of sensory experiences depending on activity within neighboring fibers (Sinclair, 1955; Weddell, 1955).

The specificity theory dates back to 1838 when Johannes Müller advanced the doctrine of specific irritability (also specific energy), which maintains that different nerve fibers are specialized to respond to different modes of stimulation. Blix, in 1884, described tiny spots on the skin which seemed to be specialized to transmit different sensory modalities. Then von Frey (1894, 1895, 1896) advanced the belief that skin spots which appeared to respond preferentially to a specific mode of stimulation had their own histologically distinct

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[1] For a shorter version of this paper see: Campbell, J.N., Taub, A. (1973). Local analgesia from percutaneous electrical stimulation and a peripheral mechanism. <u>Archiv. Neurol</u>. In press.

end-organs. It follows that each sense must have its own cutaneous receptor, stimulation of which gives rise to that sensation. Subsequent attempts to demonstrate a definite relationship between sensory spots and types of cutaneous receptors have been unrewarding (Hagen et. al. 1953). Though there was some speculation as early as 1916 (Ranson, and Billingsly, 1916) that C fibers might mediate pain sensation, this hypothesis was not formally put forward until the 1930s. In 1927 Gasser and Erlanger made recordings of sensory nerve compound action potentials, and identified what are now known as the A, B, and C elevations. Evidence was presented to show that the fastest conducting fibers were the large myelinated A fibers, and that the slowest conducting fibers were the small unmyelinated C fibers (Young, 1942). It became popular then, as it is now, to attempt to correlate activity within various portions of the fiber size spectrum with various sensation. Adrian (1931) joined others in suggesting that pain sensation may be mediated by small myelinated and C fibers. This idea arose in part because of the evidence put forth by Bishop and Heinbecker (1930), that the C fiber elevation had an electrical threshold twenty times that of the fastest conducting A fibers. Clark, Hughes, and Gasser (1935) gave support to Adrian's notion by demonstrating respiratory and cardiovascular reflexes, such as those seen with noxious stimuli, when C fibers were electrically stimulated. The problem arose however, that no one had directly associated

small fiber activity with the experience of pain in a conscious human being. To overcome this problem techniques were divised to differentially block small and large fibers, to see if in so doing dissociation of pain from other cataneous senses might be achieved. Fabritus and Berman observed in 1913 that pain sensation was the last sense modality to be lost with nerve compression. Since Gasser and Erlanger (1927, 1929) showed that nerve velocity is directly proportional to fiber diameter, and that pressure caused abolition of faster conducting fibers first, they concluded that pain must be mediated by the small myelinated and C fibers. Asphyxia was shown to have a similar effect as compression. These early experiments have been repeated many times, and similar results have been obtained (Sinclair, 1948; Weddell et. al. 1948; Heinbecker el. al. 1934; Bishop, and Heibecker, 1935; Gasser, 1943).

While this work was going on it was also noted that cocaine (and later procaine) had a reverse effect on sensory modalities with pain being one of the first sensations to disappear. Several studies have demonstrated that slow conducting fibers tend to be blocked first by these local analgesics, thus supporting the notion that pain sensation is subserved by activity in small fibers (Gasser, and Erlanger, 1929; Heinbecker et. al. 1934; Bishop, and Heinbecker, 1935; Gasser, 1943). Many experimenters have found local analgesics to have variable effects on sensation and nerve potential recordings, thus making much of these data difficult to

interpret (see Sinclair and Hinshaw, 1950 for a summary of these criticisms, and also for a discussion of nerve compression experiments).

The idea that small fibers play an important role in pain sensation was buttressed by work reported in 1960 by Collins, Nulsen, and Randt. The sural nerves of awake patients scheduled to receive cordotomies for various intractable pain problems were isolated, and electrically stimulated at various intensities, while at the same time the compound action potential was recorded. Patients did not report pain until the stimulus intensity was high enough to cause an A delta elevation (corresponding to the smallest group of myelinated fibers) in the compound action potential recording. Single shocks at these intensities resulted in sensations ranging from mildly unpleasant stinging to a burning sensation. Repetitive firing resulted in stinging, sticking, burning, or aching sensations, which in most patients was too uncomfortable for repetition. When stimulus intensities were increased to the point where the C elevation appeared, patients described a much more severe type of pain. A single stimulus resulted in unbearable pain, and with repetitive stimulation subjects refused to continue the experiment. At the time the C wave appeared there was always multifiring among the A fibers, and the question arose, is it the multifiring in the A fiber range, or the firing of C fibers, or is it the combination of these two events which gives rise to unbearable pain? To help clarify

this problem Collins, Nulsen, and Shealy (1966) reported that they were able to block A fibers by depolarizing them with a rapid series of make and break shocks, and then maintain depolarization by cooling the nerves to 10 to 12 degress C. This procedure allowed C fibers to be stimulated to the exclusion of A fibers. When a single electrical stimulus of C fibers was applied no sensations were reported by subjects. A summated stimulus (3 or more per second) was always appreciated as painful, and again the pain was so severe many subjects refused to continue the experiment. Unlike the previous experiment, when A fiber function was left intact, the pain was poorly localized, and there was a delay of 2 to 4 seconds before pain was reported.

The conclusion is inescapble that small fibers play a crucial role in eliciting the sensation of pain. Perhaps no other cutaneous sensory modality has been so closely linked to activity within fibers of a given diameter. One might be tempted to go further and maintain that nociceptor stimulation has a one to one relationship with the sensation of pain. Though this is a notion widely reported in general textbooks, it is by no means a clear cut issue. Weddell and Miller (1962) summarize a wide variety of techniques designed to elicit pain to the exclusion of other sensations, but have been uncusscessful.

It is now firmly established that C fibers have a wide range of sensitivities, and only a minority of these fibers actually serve as nociceptors. Suspicion that this might be

the case arose, when Lele and Weddell (1959) showed that sensations such as touch could be perceived on the cornea, which is innervated only by C fibers. Zotterman (1939) stood alone in advancing the possibility that C fibers have multiple functions until 1957, when Douglas and Ritchie, using a very clever indirect technique (antidromic occlusion), demonstrated that C fibers react to a wide range of cutaneous stimuli. These results have since been substantiated by more direct techniques (see Douglas, and Ritchie, 1962 for a review of this subject). It is now clear that a large proportion of mamallian C fibers respond to gentle mechanical stimuli (Douglas, and Ritchie, 1957; Iggo, 1960), with others responding best to small temperature changes (Hensel, Iggo, and Witt, 1960; Iriuchijima, and Zotterman, 1960; Brown, and Iggo, 1967; Burgess, and Perl, 1967). It was also shown that A delta fibers are responsive to hair movement (Brown and Iggo, 1967; Burgess et. al. 1967). The problem for a time, as noted by Iggo (1966), was that it was very difficult to find nociceptors among the small fibers. This in part prompted Melzack and Wall (1965) to advance the "gate control" hypothesis, which maintains that the proportion of small fibers firing in relation to the number of large fibers firing determines in part whether the subject feels pain. More recent evidence however (Bessou, and Perl, 1969), indicates that nociceptors occupy a large proportion of the small fibers. For those who wish to detract from the

specificity theory, it must finally be conceded that no one has ever demonstrated that stimulation of nociceptors by themselves leads to the experience of pain.

As indicated earlier the pattern theory argues that it is the spatio-temporal pattern among peripheral sensory nerves that gives rise to the sensation of pain. Pattern theories in general have been used to explain a wide range of neurological function, and typically they gain in popularity where there is frustration in finding specialization within the nervous system. With relation to pain physiology the pattern theory has only been advanced as a concept, and no one has defined the spatio-temporal relationships necessary for there to be pain (a possible exception is the gate control model, which is seen by its authors as a union of the specificity and pattern theories). Though admitting that peripheral nerves may have some specialization, and that small fibers may have an important role in the production of pain, this specialization is seen only as means by which a spatio-temporal relationship is established among the nerve fibers which are firing (Sinclair, 1955; Weddell, 1955). Because of the vagueness (i.e. non-specificity) intrinsic to the pattern theory it is very difficult to design an experiment to refute this notion. The fact that isolated volleys in the C fiber range are sufficient to induce pain, and reflexes known to occur with pain (Franz, and Iggo, 1968) argues that large fiber input plays a supplementary, but not

a necessary role in pain sensation. Further evidence to support this contention will be presented in the discussion.

It is within the central nervous system (CNS) that the specificity theory of pain falls subject to criticism. Dorsal horn cells and cells of the trigeminal nucleus respond to a wide range of stimuli (Wall, 1960; Wall, and Cronly-Dillon, 1963; Wall, and Taub, 1962; Kruger, and Michel, 1962). Though central cells have been reported that respond exclusively to noxious stimulation (Gordon, and Landgren, 1961; Lolmodin, and Skoglund, 1960; Eisenman et. al. 1963). these cells are not as plentiful as one might expect (Melzack, and Wall, 1965). Also care must be taken in interpreting data on alledged nociceptors. Though Poggio and Mountcastle (1960) found nociceptors in the posterior nuclear area of the thalamus in anesthetized animals, Casey (1964) found that such cells respond to a wide range of stimuli in the awake animal.

Though some might interpret the success of anterolateral cordotomy in the spinal cord as implying a specific pain pathway, the fact that pain often recurs (White, and Sweet, 1970), implies that other ascending systems may play a role in the production of pain. In addition proponents of the pattern theory may argue that interruption of the anterolateral system in the cord interferes with many other fiber systems beside the spinothalamic tract, and that such an interruption also interferes with spatio-temporal relationships among ascending systems. On the other hand proponents of the specificity

theory may argue that the failure of posterolateral and posterior column section to interfere with pain sensation (Kenard, 1954; Norton, 1969) indicates at least some specialization of spinal cord pathways in producing pain.

With regards to the relative paucity of established central nociceptors, it should be pointed out that most spinal neuron studies have been done in lamina I-V, while recent evidence indicates that the origin of the spinothalamic tract is in lamina VI through VIII (Trevino, Maunz, Bryan, and Willis, 1972; Dilly, Wall, Webster, 1968; Fetz; 1968; Price and Wagman, 1969 ; Szenthagothai, 1964). It would therefore be of interest to have more careful searches in these areas for nociceptors. It should also be noted that unit recording studies are intrinsically biased toward studying large cells because of the difficulty in finding, holding, and recording from smaller cells. It may well be that the nociceptors are to be found predominantly among the smaller cells of the CNS.

In an attempt to combine certain aspects of the pattern and specificity theories, Melzack and Wall (1965) put forward the "gate control" hypothesis of pain. This hypothesis postulates that: (1)Both large and small fibers (A delta and C fibers) have an excitatory effect on central transmission cells,which in turn project to higher areas in the CNS, thus leading to the sensation of pain. (2) Large fiber input also causes excitation within cells of the substantia gelatinosa (SG), which in turn causes primary afferent depolar-

ization (PAD), thus resulting in pre-synaptic inhibition of excitatory influence of afferent fibers on the central transmission cells. (3) Small fibers have a negative influence on activity within the SG which leads to primanry afferent hyperpolarization (PAH), which in turn causes pre-synaptic facilitation of the overall affects of large and small fibers on the central transmission cells. The gate is therefore the SG, whose open or shut position depends on the proportion of large vs. small fiber input.

The gate control hypothesis has many inadequacies, and these will be summarized later in the paper. One of the positive features of this work is that it has provided impetus for the development of new therapeutic approaches to the problem of clinical pain. In 1967 Wall and Sweet delivered 100 Hz, 0.1 msec electrical stimulation to the infra-orbital nerve of normal subjects (themselves) via subcutaneous needle electrodes, and observed decreased appreciation of pinprick on the face in the region of the infra-orbital nerve distribution. Patients with a variety of chronic pain syndromes then received similar electrical stimulation to the peripheral nerves innervating the region to which pain was referred, and temporary relief from pain was obtained. Since none of the subjects found the electrical stimulation itself painful, it was inferred that only large fibers had been stimulated, though no compound action potential data had been obtained. Others have reported similar results in the treatment of clinical pain (Meyer, Fields, 1972; and Wilson, 1972).

Relief from clinical pain has been reported to accompany electrical stimulation of electrodes placed on the dorsal columns in man (Nashold, and Friedman, 1972; Shealy et. al. 1970; Shealy, 1969). Such stimulation was reported to be effective only when paresthesias were produced in the regions of pain referral. It has been postulated that dorsal column stimulation works by causing antidromic stimulation of the dorsal column fibers, leading to stimulation of collaterals to the dorsal horn thus "closing the gate", and inhibiting activation of the central transmission cells (as proposed in the gate control model). It has for example been shown, that dorsal column stimulation in cats can inhibit activity in certain lamina V cells (Hillman, and Wall, 1969).

In this paper the results of two experiments are reported. In the first it is shown that percutaneous electrical stimulation of digital nerves in the median nerve distribution of man can produce analgesia and anesthesia in the distal portion of the finger stimulated. In the second experiment it is shown that these effects result at least in part from blockade of peripheral sensory fibers. These results will later be discussed in terms of the theorectical understanding of pain mechanisms.

EXPERIMENT 1

Effects of Digital Nerve Electrical Stimulation on Touch and Pain Thresholds to a Distal Needle Stimulus

Subjects. The subjects of this study were eight male and three female volunteers ranging in age from 20-27 years. They were informed of the general nature of the experiment, but did not know what specific results were to be expected.

Procedure and apparatus. Steel disc electrodes (1.5 cm in diameter) with electrode paste on the surface were taped firmly to the medial and lateral aspects of either the index or middle finger of either hand. Both digital nerves were stimulated by two separate synchronous sources. The cathode was placed proximally and the anode distally along the finger. A stimulating system consisting of a Devices Digitimer(type 3290), a Devices Counter-Time (type 3251), and two Devices Isolated Stimulators (Mk. IV) produced a square wave stimulus at 100 Hz, 1 msec.

The subjects were divided randomly into two groups. One group received a 10-12 v stimulus (3 times threshold for sensation) to each digital nerve, and the other received a stimulus of 22 v. The 22 v stimulus could not be applied suddenly without protest of pain or discomfort. To reach this value, the stimulus voltage was increased gradually over a 5-20 minute period, depending on individual tolerance.

Using a servo-controlled tactile probe developed in this laboratory, the point of a 22 gauge needle was delivered to the skin at varying time intervals, with precise (within 10 microns) control of the cutaneous deformation. The needle, moving vertically and continuously at a frequency of 1 Hz, was applied to the skin just proximal to the nailbed of the immobilized finger in 0.1 mm increments of deformation. The point of application was visualized by a stereomicroscope. Subjects were blindfolded. Touch thresholds were determined by the method of limits (Osgood, 1953). Pain thresholds were determined by lowering the needle to the point where pain was reported. The subjects were instructed not to report a "pricking" sensation as painful. The needle was then raised quickly to avoid the production of a lasting indentation of the skin, which was found to alter later threshold determinations. Each pain threshold determination was repeated three times.

Touch and pain thresholds were determined, for each subject, with, and without, electrical stimulation. In each group half of the subjects received electrical stimulation first, and in the other half the order was reversed.

A minimum of five minutes between trials was taken to minimize any effects electrical stimulation might have on subsequent determination of touch and pain thresholds. A problem encountered was that when the 22 v repetitive electrical stimulus to the digital nerves was delivered, the testing needle would sometimes pierce the skin before

pain was reported. This was thought to alter further threshold determination, and data from these particular studies were discarded.

Results

The sensation associated with low levels of electrical stimulation of the digital nerves was reported as being that of a paresthetic numbness. Paresthesia increased with electrical stimulus intensity to the point where pain was reported. The intensity of paresthesia decreased with time, despite constancy of parameters of the electrical stimulus. When voltage was increased to a level reported as painful, that pain also decreased within seconds to minutes. When the electrical stimulation was discontinued for approximately one minute, and then reapplied, pain was again reported.

The finger stimulated was no different in temperature from the other fingers on the hand, although at times the stimulated hand was somewhat cooler than the non-stimulated hand. Cyanosis of the stimulated finger was never noted.

Mean touch and pain thresholds with and without electrical stimulation are presented in Table I. Threshold values are given in mm of cutaneous deformation. The threshold for touch without electrical stimulation was assigned the value 0. Paired statistical analysis of the effects of electrical stimulation on touch and pain thresholds was performed, using Student's t test (Fisher, 1967). In group I (10-12 v) elec-

TABLE I

Thresholds for pain and touch measured by millimeters of skin deformation by a needle as a function of the presence or absence of proximal electrical stimulation at 10-12 volts (Group I) and 22 volts (Group II).

GROUP I (10-12 v)

	TOUCH THRESHOLD		PAIN THRESHOLD	
SUBJECT	WITHOUT	WITH STIMULATION	WITHOUT	WITH STIMULATIO
1	0	0.03	0.20	0.38
2	0	0.18	1.08	1.10
3	0	0.30	2.10	2.10
4	0	0.20	1.55	1.55

GROUP II (22 v)

	TOUCH THRESHOLD		PAIN THRESHOLD	
SUBJECT	WITHOUT	WITH STIMULATION	WITHOUT	WITH STIMULATION
1	0	2.62	2.57	3.12
2	0	3.45	2.33	3.45
3	0	1.30	1.57	2.00
4	0	0.63	0.70	1.06
5	0	0.53	0.90	1.40
6	0	2.86	2.39	2.86
7	0	1.05	0.63	1.05

trical stimulation raised the touch threshold alone ($t=3.19$, $df=3$, $p<.05$). In group II (22 v) electrical stimulation raised touch ($t=4.00$, $df=6$, $p<.01$), and pain ($t=5.75$, $df=6$, $p<.001$) thresholds. The high intensity stimulus produced a greater increase in touch threshold ($t=2.65$, $df=9$, $p<.05$) than did the low intensity stimulus.

Table II shows the distance in mm between touch and pain thresholds in group II with and without electrical stimulation. The distance between the thresholds for touch and pain was greater ($t=3.22$, $df=6$, $p<.01$) with the electrical stimulus off than with it on.

Examination for other effects of electrical stimulation revealed none, except occasionally in adjacent fingers. These effects consisted of decreased appreciation of pinprick, and an elevation of the pain threshold. With higher voltages (greater than 22 v) the effect on adjacent fingers was more noticeable. In one study the index and ring fingers were stimulated, and a marked increase of touch and pain thresholds was observed in the middle finger.

During threshold testing with the 22 v electrical stimulus on, the testing needle would sometimes puncture the skin, and bleeding would result. At these times subjects often reported a vaguely located pain, unlike that initially caused by the vertical movements of the needle. This pain was continuous, and was described as a feeling of "soreness" or "ache."

TABLE II

Distance in millimeters between pain and touch thresholds in Group II (22 volts) as a function of the presence or absence of electrical stimulation.

SUBJECT	WITHOUT	WITH STIMULATION
1	2.57	0.50
2	2.33	0
3	1.57	0.70
4	0.70	0.43
5	0.90	0.87
6	2.39	0
7	0.63	0

EXPERIMENT 2

A Peripheral Mechanism for Analgesia Produced by Electrical Stimulation

Methods. With a Biomac-1000 special purpose digital computer, it was possible to record the averaged compound action potential of the median nerve transcutaneously at the wrist. A stimulus of 50 v, 100 Hz, 0.5 msec was delivered to both digital nerves of one finger, first in periodic bursts (every 30 sec for 0.5 sec), and then continuously.

Six subjects were tested. Steel disc electrodes were taped in place over the digital nerves of either the index or the middle finger. Identical electrodes were used for median nerve recording. The recording electrode was placed directly over the median nerve on the flexor side of the wrist. The ground electrode was a pliable metal strip wrapped around the palm. Electrode paste was used on the ground and electrode discs. It was found necessary to insulate the ground strip from the stimulating electrode with petroleum jelly since perspiration short-circuited the stimulating electrodes to ground. The compound action potential was amplified (5000 x) via a Grass P511 pre-amplifier. An average of five hundred signals was taken. The periodic bursts of electrical stimuli were interrupted three times during the recording, for two minutes at a time, to minimize discomfort to the subject. Following the series of stimuli in periodic bursts, continuous electrical stimulation was

delivered, but its intensity was gradually raised to a level of 50 v over a 5-20 minute period. Pain was reported with each increment of voltage, subsiding within seconds to minutes. When the stimulus level of 50 volts had been reached, signal averaging commenced.

Results

With periodic bursts of stimuli at 50v, the subjects were uncomfortable, perspired, and complained of pain. The bursts were perceived as painful during each burst, and as most painful at the beginning of a burst series, and immediately upon resuming burst stimulstion following each rest period. With continuous electrical stimulation at 50v, five subjects did not feel pain once the final stimulus intensity had been reached. One subject noticed intermittent pain which was associated with involuntary movement of the finger. At the conclusion of the experiment, paresthesias were noted in the stimulated finger for approximately 1/2 hour. Effects lasting longer than 1/2 hour were not described by the subjects. During continuous stimulation at 50v, a needle stimulus produced no sensation whatever at the finger tip except for a brief "jab" sensation if the needle was thrust through the skin.

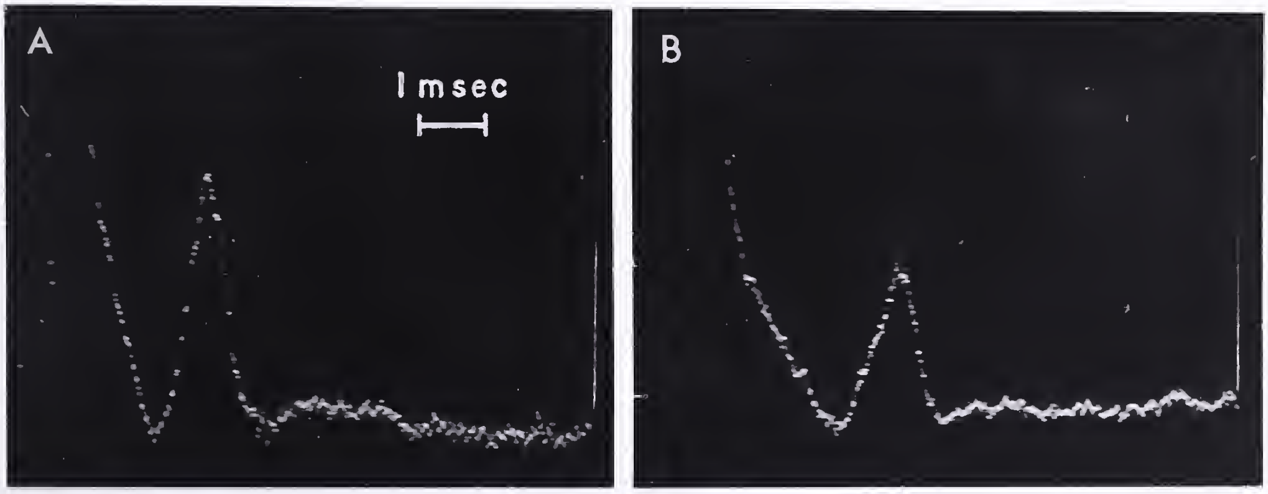
An A delta wave was always present in the averaged compound action potential record obtained during the series of

periodic bursts, but was either diminished in amplitude or was entirely absent with continuous stimulation. The A delta wave varied in configuration and latency to some extent from subject to subject. Fig. 1 shows a representative example from a single subject.

The compound action potential in Fig. 1A was recorded during the series of periodic bursts of electrical stimuli, and that in Fig. 1B during continuous electrical stimulation. An A delta wave was present with periodic bursts of stimulation, and was absent with continuous stimulation. The A alpha wave evoked by continuous stimulation was longer in latency and lower in amplitude (Fig. 1B) than the A-alpha wave evoked by the periodic stimulus in bursts (Fig. 1A).

The A alpha wave in Fig. 1A begins at a latency corresponding to a velocity of 33.4 m/sec. In Fig. 1B the A alpha wave begins at a latency corresponding to a velocity of 29.3m/sec. The A delta wave in Fig 1A occurs at a latency corresponding to a velocity ranging from 16-23 m/sec.

Fig 1 -- Median nerve averaged compound action potential (500 signals) recorded transcutaneously at the wrist as a function of 50 v, 100 Hz, 0.5 msec, stimulation of both digital nerves of the index finger. Conduction distance 12 cm. Fig. 1A: Electrical stimulus delivered in bursts for 0.5 sec every 30 sec. A-alpha latency 3.6 msec (33.4 m/sec); A-delta latency 5.2 msec (16 m/sec). Fig. 1B: Continuous electrical stimulation, 50 v level reached over 10 minute period. A-alpha latency 4.1 msec (29.3 m/sec). No clearly defined A-delta wave.



DISCUSSION

These experiments indicate that a 10-12 v, 100 Hz, 1 msec continuous electrical stimulation to the digital nerves raised the threshold to touch but not that to pain in the tip of the finger stimulated. A 22 v stimulus, however, raised the threholds both to touch and to pain, as tested by a distal needle stimulus. Further, the more intense electrical stimulus itself was painful if introduced suddenly; the pain caused by sudden introduction of the intense electrical stimulus diminished over á period of seconds.

When a 50 v electrical stimulus was delivered to the digital nerves in periodic bursts (100 Hz,0.5msec, for 0.5 sec, every 30 sec), an A delta wave appeared in the averaged compound action potential of the median nerve, and subjects complained of pain. When the same stimulus was given continuously, the A alpha elevation decreased in amplitude and increased in latency, and the A delta wave disappeared, along with the sensation of pain.

As indicated earlier A delta fiber stimulation has been associated with a report of pain sensation in man (Collins et. al. 1960). The rise in threshold for pain, as tested by a needle stimulus, when electrical stimulatiion was applied proximally, associated with a marked decrease in the amplitude of the A delta portion of the fiber spectrum, suggests that that portion of the A delta fiber

spectrum responsible for conduction of input from nociceptors (Perl, 1968) has been functionally blocked by high frequency and high intensity electrical stimulation. (It is not possible, however, to conclude, from the observation of the disappearance of the A delta elevation, that all A delta fibers in the volley have been blocked, as a portion of this decrement in size of the volley may be produced by decrease in size of individual action potentials, or by asynchrony in conduction of individual action potentials.)

This type of peripheral blockade was first used by Bishop (1932), and later Bishop, and Heinbecker (1935), who administered a brief series of strong make and break shocks from an induction coil to isolate C fiber input. After the tetanus it was found that large myelinated fibers were unable to conduct for periods of a few seconds to a few minutes, depending on the strength of the shocks. Recovery occured first in slow conducting fibers. With stronger currents C fiber input could also be blocked. This method has been used to study isolated C evoked pressor response (Laporte, and Montastruc, 1957), C evoked muscular reflexes (Laporte, and Bessou, 1958), and C evoked responses in the midbrain, and medulla oblongata (Collins, and Randt, 1958, 1960). This technique has more recently fallen into disuse as a means of isolating C fiber input, because it has been found that there is often residual spontaneous firing of the large fibers (Mendell, and Wall, 1964), and because the block is not as rapidly reversible as other forms of block (Manfredi,

1970a;Zimmerman, 1968).

The observation that the sensation of pain produced by the electrical stimulus itself decreased in intensity with time, was most intense at the onset of stimulation, and was always present when stimulation was delivered in short bursts, is consistent with the assumption that a short period of time, measured in seconds, is required for the functional blockade of A delta fibers to occur, and that recovery from such blockade is rapid. This assumption is confirmed by the continued presence of the A delta elevation in the compound action potential when the electrical stimulus to the digital nerves is delivered in short bursts.

With respect to touch sensation it was noted that both low and high intensities of continuous electrical stimulation to the digital nerves produced a rise in the touch threshold as tested by a needle, but that the rise in threshold was significantly greater during high intensity electrical simulation. It was also noted that the intensity of tactile sensation produced at any given level of electrical stimulation decreased with time. These observations suggest that a similar blockade of A alpha fibers (stimulation of which has been associated with a report of the sensation of touch in man, Collins et. al. 1960) had occured. The A alpha elevation of the median nerve compound action potential decreased in amplitude during continuous stimulation, more so than during periodic bursts of stimuli, an observa-

tion compatible with this hypothesis.

During continuous electrical stimulation with the 50 v stimulus the latency of the A alpha fiber group was seen to decrease. This suggests that the larger fibers within the A alpha volley were preferentially blocked. In Table II, derived from measurements of touch and pain thresholds to a needle stimulus during continuous electrical stimulation at 22 v, it is seen that while both touch and pain are appreciated and their thresholds elevated, such elevation does not occur uniformly, the touch threshold approaching that of pain. This again suggests a nonuniform blockade of larger and smaller myelinated fibers, the larger fibers being preferentially blocked.

The observation that during continuous electrical stimulation with the 50 v stimulus, tactile sensation was absent despite the presence of a definite A alpha elevation in the median nerve compound action potential, suggests the necessity for the activation of a large number of A alpha fibers as a requisite for the touch experience.

It was noted that high intensity electrical stimulation often caused a decreased appreciation of pinprick in adjacent fingers. An elevation of pain threshold was especially seen when the finger between two electrically stimulated fingers was tested. This particular effect may result from antidromic stimulation and blockade of digital nerves in the palm, although central nervous system effects cannot be excluded.

Other cutaneous stimuli have been reported to alter

local pain threshold in man. Wall, and Cronley-Dillon (1960) reported that vibration (60 hz, peak to peak amplitude 3/16 in) raised the threshold to warmth and pain (tested with heat and electric shock) in the areas stimulated. Melzack, Wall, and Weisz (1963) studied the effects of vibration on local touch, prick, and pain thresholds to electric shock. Some subjects showed an increased threshold to touch and prick when vibrated, but no effect on mild pain, and a decreased threshold to severe pain. It would appear that vibration has a variable effect on pain threshold.

The observation of previous investigators (Wall, and Sweet, 1967; Meyer, and Fields, 1972) that it was possible to stimulate peripheral nerves electrically without producing pain, and yet produce a temporary local relief of pain in patients with chronic pain syndromes, was thought to be compatible with the gate control hypothesis, i.e., with the notion that a central inhibitory effect was at the basis of the hypalgesia produced. It was proposed that electrical stimulation of peripheral nerves in man produced hypalgesia while stimulating large myelinated fibers only. The portion of the primary afferent spectrum stimulated was inferred from the lack of a report of pain, and no action potential data were presented. The data presented here make an alternate view likely; that in those clinical situations in which relief of pain was reported, a peripheral effect, i. e., peripheral blockade of smaller myelinated fibers, had occured, preventing transmission of information

derived from A delta nociceptors.

In the study presented here pain was experienced initially during continuous stimulation, but only transiently. Once intensities of stimulation sufficient to produce A delta blockade were reached, pain was not reported. It is possible that where pain prexsists chronically, a brief period of pain produced by electrical stimulation is apt to be overlooked. It remains to be seen whether analgesia can be produced by stimulation of large myelinated fibers alone, but it appears unlikely to be the case.

The brief "jab" of pain experienced when the skin was pierced during electrically induced local analgesia in our study may, perhaps, be attributable to stimulation of peripheral receptors provided with C fiber primary afferents, as these were not blocked at the intensities of stimulation used.

The gate control hypothesis, as presented in the introduction, maintains that large fiber stimulation raises the threshold to pain. The study presented here is the first experiment to directly test this hypothesis, and the results are non-confirmatory. Electrical stimulation raised the threshold to pain only at that point where evidence indicates that A delta fibers were being blocked. The gate control hypothesis actually predicts that as the intensity of electrical stimulation is increased from mild to moderate and intense levels the pain threshold should decrease, since A fibers begin to "adapt producing a relative increase in

small-fiber activity" (Melzack, and Wall, 1965, p. 975). The opposite result was found in this study.

Because it might argued that the 10-12 v stimulus was not the appropriate intensity to achieve maximal large fiber input relative to small fiber input, pain and touch thresholds were tested as a function of a wide range of intensities of electrical stimulation during pilot studies. The results were always the same--it was not until high intensity electrical stimulation was used that an elevation of pain threshold could be demonstrated. This result was somewhat surprising to the author, since many have relegated the gate control model to the status of a theory. Other studies however, have provided data which do not fit the gate control hypothesis.

(1) Melzack and Wall contend in their paper that large fiber inhibition of pain is a common sense phenomena, since rubbing an area which has been hurt seems in many cases to relieve the pain. If this is indeed true there are many ways rubbing could relieve pain. The most obvious is that rubbing may alter excitability characteristics of receptors in the involved area. If the gate model were to hold, then it would be predicted that vigorous rubbing or pinching might make the pain worse. By self introspection the opposite result has been found. The most serious flaw with this "common sense" evidence for the gate model is that in fact, rubbing leads to volleys in both A and C fibers (Douglas, and Ritchie, 1957,1962; Iggo, 1960). Since there

are many more C than A fibers, and since the majority of C fibers are sensitive to nonnoxious stimuli, especially mild mechanical stimulation, one might expect that rubbing would induce a larger C volley than A volley. If the gate model were true, then rubbing should actually increase pain.

(2) As pointed out by Taub (1973) the gate model was proposed at a time when the existence of nociceptors was in doubt. To explain pain sensation it was thus necessary to invoke a facilatatory effect of small fiber input on the overall effects of both large and small fiber input. Subsequent studies have shown that nociceptors comprise a significant fraction of small fibers (Bessou, and Perl, 1969; Bessou, Burgess, Perl, and Taylor, 1971; Perl, 1968). Furthermore C fibers are quite sufficient when fired in isolation to elicit ventral root reflexes (Franz, and Iggo, 1968). Wagman and Price (1969, 1970) noted in a study of lamina IV and V neurons in Macaca mulatta that the effects of isolated C fiber effects on dorsal horn cell activity were more prolonged than A fiber input alone. This prolonged excitatory action of small fibers was felt by the authors to be by itself sufficient to trigger ascending pathways leading to the sensation of pain. A and C fibers were found to be able to exert many of their central effects independently, and that "the presence or absence of one these groups neither severely decreased nor augmented the central effects normally observed for the other group."

(3) Since as has been indicated earlier the anterolat-

eral quadrant of the cord plays an important role in pain sensation, some insight into the relative roles of small and large fibers in pain sensation may be achieved by observing the contralateral anterolateral potential (CAP) as a function of large and small primary afferent fiber stimulation.(Collins, and Randt, 1956; Hagbarth, and Kerr, 1954; Oscarrson, 1958). The gate model would predict that large fiber stimulation would inhibit the CAP. Manfredii (1970b) showed however that the effects of stimulation of various size fibers in cats were simply additive. In addition it was found that volleys segregated to A delta-C fibers were not remarkably different from those produced by whole nerve stimulation. In other words the A beta fiber contribution to the CAP was small. Thus activity within the slow fiber range is quite sufficient to activate the ascending anterolateral pathways leading, it is assumed, to the sensation of pain. Similar results were obtained by Manfredi in the ipsilateral anterolateral tract. The spinocervical tract is postulated to possibly contribute to pain sensation in the cat (Taub, 1964). As Manfredi points out (1970b), the discharge pattern of dorsolateral tract axons shown in figures by Mendell and Wall (1965), indicate that mixed A and C volleys are merely additive to effects of separate A and C fiber volleys. This evidence again makes it quite unnecessary, and indeed uncalled for to postulate the small/large fiber interactions in the dorsal horn as is proposed by the gate model.

(4) The gate control model postulates that large fiber

input inhibits the overall effects of large and small fiber input on central transmission cells by producing primary afferent depolarization (PAD) within the terminal arborizations of at least the large fibers (small fiber terminal arborizations have not been recorded from). PAD is thought to produce the negative dorsal root potential (DRP) (Lloyd and McIntyre, 1949; Wall, 1958; Eccles, Eccles, and Magni, 1961) originally noted by Barron and Matthews (1938). Furthermore PAD is postulated to result from presynaptic inhibition mediated by the substantia gelatinosa, which in turn is thought to be caused by the excitatory influence of large fibers on the substantia gelatinosa. Whether by presynaptic or post synaptic effects, the gate model maintains that large fibers should have some inhibitory effect on central transmission cells. Wagman and Price (1969, 1970) found however that in Macaca mulatta, A and C fibers when stimulated separately had qualitatively similar effects on lamina IV-V cells. As previously indicated Manfredi (1970b) found the effects of isolated A and C volleys on CAP to be merely additive.

(5) A late small positive DRP was first described by Lloyd (1952). Mendell, and Wall (1964), and later Mendell (1970, 1972) and Hodge (1972) have shown that similar positive DRPs can be produced by small fiber input into the cord. It has been shown to correspond to primary afferent hyperpolarization (PAH) (Mendell, and Wall, 1964; Wall, 1964; Anden et. al. 1966; Lundberg, and Vyklicky, 1966;

Cangiano et. al. 1969; Dawson et. al. 1970; Mendell, 1970, 1972; Chan, and Barnes, 1971; Hodge, 1972), and it is generally thought to provide a mechanism for presynaptic facilitation. Though some controversy has surrounded the existence of the positive DRP (Zimmerman, 1969; Franz, and Iggo, 1968; Vyklicky, 1969), Hodge (1972) and Mendell (1972) have provided convincing evidence that it does indeed exist. Its relevance to pain sensation however has been brought to serious question. Hodge (1972) obtained intracellular recordings from A alpha afferent fibers in the dorsal root entry zone of the lumbar cord as a function of afferent volleys containing the A alpha component, A alpha and A delta, or A alpha-delta and C components. Efficacy of primary afferent input on second order neurons was tested by measured monosynaptic mass discharge from the spino-cervical tract in response to inputs from A alpha, A alpha-delta, and A alpha-delta and C volleys. A surprising finding was that the presynaptic terminals of A alpha fibers showed three responses: (1) No PAH or PAD; (2) PAD; (3) PAD plus PAH. Of 14 cells found to fall into the third group (roughly one third), 2 had PAH in response to A alpha stimulation alone. Thus PAH is not due solely to small fiber input. Though small fiber conditioning volleys were found to have a facilatatory effect on spinocervical tract mass discharge, this effect was of small magnitude being never greater than 135% of control (the issue of what relevance spino-cervical tract activity has to pain sensation was not dealt with). It was

concluded by Hodge that this effect was not large enough, and did not have the proper temporal characteristics to account for the marked high frequency second order neuron responses that occur subsequent to noxious stimuli, and repetitive C fiber volleys. Mendell (1972) in a similar study confirmed that large afferents could produce a positive DRP (PAH). It was further shown that stimulation of flexor reflex afferents, contrary to what would be expected from the gate model, elicited mainly PAH in the presynaptic terminals in proprioceptive afferents, and PAD in presynaptic terminals of cutaneous afferents. These results suggest that PAH may have nothing at all to do with pain sensation.

(6) Szentagothai (1964) challenged the concept that the substantia gelatinosa has any thing to do with pain. In his extensive study of the substantia gelatinosa he was unable to find any anatomical indication of an influence of the substantia gelatinsosa on the transmission by synaptic mechanism to the crossed spino-thalamic tract in cats.

The gate control model not only goes beyond what current data on spinal cord mechanisms justify (Taub, 1973), but in fact contradicts many aspects of what is known about spinal cord physiology. Pain sensation is undoubtedly influenced and governed by many CNS controls, as well as being influenced by other external stimuli. The parameters of these external stimuli, their efficacy, as well as the nature of governing CNS mechanisms remains to be demonstrated.

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