Diagnosis and Treatment of Chronic Pain

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SECTION III
Treatments (Organic)

8 Transcutaneous Electrical Stimulation for Pain: Efficacy and Mechanism of Action

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Patients with chronic pain have long represented an onerous burden to the medical profession. Pain, although an essential sensory modality, all too frequently persists as a symptom of an underlying uncorrectable disease process, and becomes a disease in its own right. When the cause of pain cannot be treated, the means to obtain pain relief have traditionally been limited to analgesic medication, destructive operative procedures, and indirect measures such as physical therapy. These techniques have serious limitations and frequently aggravate the original pain. The lack of therapeutic options is compounded by the lack of means to assess objectively the presence and severity of the pain. It is unlikely that satisfactory solutions will ever be forthcoming until quantification of clinical pain is possible.

Despite this, progress has been made in the development of novel and effective alternatives in pain treatment, as is testified by the existence of this book. One of the major advances and major areas of interest in this field has been the use of electrotherapy for pain control. It has been

found that application of electrical current to the diencephalon,[1a] spinal cord, peripheral nerve, or skin may each have a place in the treatment of pain. The easiest and most benign of these procedures involves application of electric current to the skin. Its technique, usefulness, and mechanism of action will be the topic of this chapter.

Origins of Interest in Electrotherapy

Two developments served to stimulate interest in the use of electrotherapy for the treatment of pain, both occurring in the 1960s. The first was the revival of the original and heuristic concept of Henry Head[1,2] put forward and elaborated by Melzack and Wall[3] under the name, the "gate-control theory." According to this hypothesis, activity in the large primary afferents of the somatosensory system, which normally convey pressure and touch sensations, has an inhibitory effect on the noxious information conveyed by small fibers (C- and A-delta fibers). This inhibitory effect was presumed by Melzack and Wall[3] to take place in the dorsal horn of the spinal cord in the region of the substantia gelatinosa.

Not long after this publication there arose in the Western world growing awareness of the Chinese practice of acupuncture. Although skepticism as to the efficacy of this practice prevailed (as it does now) in scientific circles, considerable public pressure mounted to explore what relevance this ancient art might have for Western medicine.

This intermingling of science and folklore served to stimulate the search for alternate means to manage pain. The idea that pain could be controlled by non-noxious stimulation in contiguous and/or remote areas of the somatosensory system became of interest to clinicians, and initiated what has become a surge of research interest.

In 1967, Wall and Sweet[4] reported that electrical stimulation of the infraorbital nerve produced hypesthesia in the region innervated by this nerve. Since the stimulation itself was thought not to be painful, and because the electrical threshold of large fibers is considerably less than that of small fibers, it was thought that these results represented a demonstration of the inhibitory effects of large fiber primary afferent stimulation on pain perception. The gate-control hypothesis is no longer tenable in its original form, and whether this experiment, in fact, is demonstration of pain reduction by large fiber stimulation will be discussed later in this chapter. Nevertheless, the pioneering findings of Wall and Sweet[4] encouraged the application of electrical stimulation to the peripheral nerves of patients with chronic pain. The first implantable spinal cord stimulators were employed by Shealy as early as 1967, and the first implantable peripheral nerve stimulators were utilized by Long

in 1969. The early results of transcutaneous stimulation, and the use of implantable stimulating devices for chronic pain by Wall and Sweet, and Shealy and Long, were promising enough that a number of others have taken up these techniques, and neural modulation is now a major mode of therapy for patients with chronic pain.

History

The analgesic effect of electricity applied to the peripheral nervous system was not a discovery of the 1960s but rather dates to antiquity, as has been noted in a scholarly review of this subject by Kane and Taub.[5] According to Kellaway,[6] one of the first accounts of the application of electrotherapy for pain was made by Scribonius Largus, a Roman physician in the first century A.D. In the following passage the use of the electric fish in the treatment of the age old maladies, gout and headache, is described:

> For any type of gout a live black torpedo should, when the pain begins, be placed under the feet. The patient must stand in a moist shore washed by the sea and he should stay like this until his whole foot and leg up to the knee is numb. This takes away present pain, and prevents pain from coming on if it has not already arisen. Headache, even if it is chronic and unbearable, is taken away and remedied forever by a live black torpedo placed on the spot which is in pain, until the pain ceases. As soon as the numbness has been felt the remedy should be removed lest the ability to feel be taken from the part.[6]

It is of interest to note that the "torpedo " referring to the electric ray, is from the Latin, and literally means numbness or stiffness.

A practical application of electrical stimulation awaited the advent of the electric battery. Several reports of successful use of electricity for relieving pain during tooth extraction appeared.[7-9] As noted by Kane and Taub,[5] Althaus,[10] in 1859, described relief of pain from transcutaneous electrical stimulation applied to the peripheral nerve:

> I . . . applied a rapidly interrupted current to Dr R's ulnar nerve, placing one moistened conductor between the olecranon and the internal condyle, while the other conductor was placed in his hand. I began a current of low tension, such as was not powerful enough to produce contraction of the muscle animated by the ulnar nerve. After the current had acted a few minutes, I increased the intensity, so that a strong flexion of the fourth and little finger was produced. The action of this current was at first painful to bear, and the pain continued to increase during the first few minutes of application; but it soon became less, so that I could further increase the intensity of the current, without causing much inconvenience to Dr R, who became again gradually insensible to

> stronger shocks. The intensity of the current was then increased a third, fourth, and fifth time, and every additional increase was felt distinctly and immediately, but after a certain time the pain excited by very severe shocks was comparatively little. At least the normal sensibility of the ulnar nerve was so much diminished, that a current of such high tension was borne without inconvenience by Dr R, as would have been perfectly unendurable in the beginning of the experiment. Besides, Dr R mentioned a sensation of numbness in the fourth and fifth finger, and that he did not feel the board upon which his fingers rested. The intensity of the current was then diminished, and Dr R was now quite insensible of shocks which had caused him much inconvenience previously. After the current had ceased to act, numbness was still perceived by Dr R in his arm for a certain time. It is therefore obvious that a direct reduction of sensibility of the ulnar nerve was accomplished by electricity, but although the intensity of the current was very high and the velocity of the intermittences very considerable, no complete anesthesia of the skin was produced, as the skin of the hand is not only animated by the ulnar, but also by the median and radial nerve.[5]

Althaus stated that relief of pain from neuralgia was obtained with less intense stimulation. These observations, although made over one hundred years ago, are in agreement with those of others today.

Despite early successes, electrotherapy failed to gain wide support, although occasional reports attesting to its beneficial effects continued into the 1900s. For example, Peterson[11] unaware of previous reports of the analgesic effects of transcutaneous electrical stimulation, suggested that this technique may be used to induce local anesthesia during surgery. Thompson et al[12] described the effects of peripheral nerve stimulation of graded intensity on the sensory modalities subserved by the stimulated nerve. Using a rapidly alternating current with monopolar stimulation applied transcutaneously to the peripheral nerve, it was observed that the thresholds to touch and pressure were most susceptible to electrical stimulation, followed by pain, cold, and heat, in that order.

From this brief historical review it is clear that the idea of using electrical stimulation for control of both acute and chronic pain is an old one. Until most recently, this technique never gained wide acceptance, however, and the reasons for this were probably many. First, the original stimulators were large and awkward to use. Control over stimulus parameters was very limited, as was the availability of the stimulating devices. The control of pain with electrical stimulation never lasted very long, and control of chronic pain depended on frequent visits to the electrotherapist. Second, the emergence of pharmacological techniques for controlling pain lessened the need for electrical analgesia. It is likely, also, that people in the early part of this century and before were less inclined to bring complaints of chronic pain to their physician on a persistent basis. People today expect not to suffer from chronic pain, and this is reflected in the high incidence of operations for pain. The need for more effective means to control pain has evolved as a phenomenon of

our generation, paralleling the advance in standards of medical care in general.

Hardware and Techniques

The usefulness of transcutaneous electrical stimulation (TES) of peripheral nerves for the management of chronic pain came as a surprise to the initial users of this technique. Originally developed in an attempt to provide a means of screening patients in order to predict a favorable response to spinal cord stimulation, it soon became apparent that excellent pain relief with TES alone occurred in a small but significant number of patients.[13,14] Sweet and his associates carried out investigations using the stimulators that were utilized commonly in neurophysiological research.[15] Shealy[14] described the usefulness of a simple commercial device available on the open market, the "Electreat." This device consisted of an induction coil which delivered a spike pulse. It was equipped with a crude control for strength of current. Long and Hagfors[13] introduced the first transcutaneous stimulator especially designed for treatment of pain. This initial device was battery operated and employed a variable rectangular wave form with controllable current parameters.

Portable stimulating units, now provided by several companies, differ little in design and stimulus parameters. They are all battery operated and generally produce a spike or a rectangular waveform with variable frequency, voltage, and pulse width control.

Bipolar stimulation is delivered to the skin either directly overlying the area of pain or to the nerve which innervates the painful area. Each electrode should be greater than 4 cm^2 in size in order to minimize skin irritation. The electrodes should be flexible in order that they may be applied uniformly to the skin.[16] Most commercially available electrodes for this purpose are now made of silicone rubber imbedded with carbon particles. The electrodes are coated with a conductive jelly prior to application to the skin. Most units allow for manipulation of repetition, rate, power, and pulse width. These parameters may be adjusted on an empirical basis by both the physician and patient to provide maximal pain relief. Current outputs range from 0 to 70 mA, with voltage up to 90 V. Generally, the repetition rate may be varied from 5 to 200 Hz, while the pulse width can be varied from 50 μsec to several msec.[13]

The stimulus parameters used by patients who achieve excellent pain relief with TES were assessed by Linzer and Long[17] in a group of 14 patients. They found that current requirements ranged from 10 to 70 mA, which corresponds to a current density ranging from 0.5 to 8.5 mA/in^2. The charge per pulse was generally in a range from 1 to 3 μA/sec. Over 70% of the patients found best results with a pulse width ranging from 50

to 100 μsec. Repetition rate in over 80% of the patients was found to be most effective in a range from 10 to 60 Hz.

There are many ways to employ TES in the treatment of patients. Several basic principles must be observed. The patients must be carefully instructed in the use of the technique, and carefully observed so that problems which occur may be solved for them. The position of the electrodes and the parameters of stimulation used may be critical to successful use of TES, and must be carefully evaluated for each patient. The best results in chronic pain have been obtained when initial trials of TES are administered on hospitalized patients, which allows for careful patient instruction. Utilization by outpatients is feasible as long as the patients receive adequate evaluation and instruction in the use of the device. Facilities for the continued evaluation of the patients, monitoring of problems, and maintenance of the stimulating equipment must be available to obtain maximum benefits. At The Johns Hopkins Medical Institutions Pain Treatment Center, TES is one of the first therapeutic modalities offered to patients. It is safe, without major side effects, and does not interfere with diagnostic evaluation or the implementation of a comprehensive pain treatment program.

The procedures for applying TES are simple, and specially trained nurses or technicians are amply qualified to instruct patients in the use of these devices. It is important to distinguish between several categories of patients when attempting to assess the use of TES. In acute pain, such as that following a surgical procedure, the device is primarily employed by specially trained personnel to provide pain relief over a short period of time. The same is true of pains which may be classified as less serious or minor, for instance, athletic injuries, the acute low back or cervical syndromes, and minor soft tissue trauma. Chronic pain represents the greatest therapeutic challenge, and patients with chronic pain require a much longer period of time for evaluation and treatment if TES is to achieve optimal results.

The following principles have emerged from practical experience with over 1000 patients.

1. Electrodes may be placed in the region overlying a painful area (on occasion, this worsens pain, and the electrodes must be moved proximal to the pain) or over a major nerve which innervates the painful area.
2. Stimulation applied distal to the origin of pain almost never gives rise to satisfactory long-term benefits and sometimes aggravates the pain. Most patients who achieve effective pain relief feel tingling or some other sensation in the painful area when TES is applied.

3. Stimulating units should provide patients with flexible control of voltage, pulse width, and repetition rate, since the ideal stimulus parameters vary from patient to patient. However, the range is relatively narrow for optimum results, and it is also important to be certain that patients have explored the parameter areas most likely to give good pain control.
4. Stimulating units should be small so that they may be easily and inconspicuously carried. Application of electrodes and design of the device must allow the patient to undertake his usual daily activities while TES is being applied.
5. Patients who initially state that stimulation is ineffective will rarely achieve suitable pain relief with electrodes remaining in the same location. Before making this decision, a several-hour trial of stimulation is warranted. Failure of relief, when electrodes are in a location such that TES does not evoke paresthesias referred to the painful region, has no bearing on eventual success.
6. TES does not offer a cure for pain. Successful use of the technique is palliative, and does not replace the need for accurate diagnosis. Pain relief which lasts more than a few hours after termination of stimulation may be related to other factors such as muscular relaxation, humoral effect, psychogenic overlay, or the natural course of the pain.
7. Patients who have an initial favorable response to TES require at least several weeks to determine whether the technique is to have a lasting value. The patient should be free to rent a stimulating device for a variable length of time before the decision to purchase one is made by the patient and physician.
8. Patients require continued instruction with these devices and assistance with proper purchase. It is very important that this instruction be readily available for them if the results of therapy are to be maximized.
9. Patients who are first introduced to TES in the setting of a pain treatment center frequently have a favorable response which is not maintained during subsequent trials. This early success most likely represents a placebo response, and rarely lasts more than 48 hours. Most patients, attaining good relief of pain at the end of one month, continue to achieve this pain relief and continue to use the device on a long-term basis.

Pattern of Use

In Figure 8-1 the location site of electrodes used to treat chronic pain in four different patients is illustrated. These areas of stimulation may be varied somewhat to avoid skin irritation to any one area.

Figure 8-1 Four different patients are shown using transcutaneous nerve stimulation. From left to right, beginning with the top row, the conditions being treated are whiplash injury to the cervical spine, arthritis of the knee, ulnar nerve distribution pain due to ulnar nerve injury, and lumbar pain following unsuccessful lumbar disc surgery.

The length of time of stimulation and frequency of use varies considerably from patient to patient. The type of pain which the patient has is important in determining the pattern of use of the device. Patients with minor pain such as that accompanying chronic low back ailments or the cervical syndrome may often obtain pain relief with less than an hour of use. This relief characteristically will persist for a long period of time. Patients with acute pain such as that seen in the postoperative period utilize TES for longer periods of time, but often will not require continuous stimulation. Stimulation of the operative site for one to two hours out of each four- to six-hour period may give substantial pain relief. Patients with severe chronic pain typically use the device 8 to 16

hours per day. It is important that the electrodes be coated evenly with electrode jelly to minimize skin irritation and discomfort. The electrodes should be removed for at least eight hours per day to further minimize skin irritation.

Clinical Efficacy

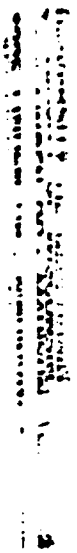
There is now a large body of evidence which confirms a role for the use of TES in the treatment of pain. We shall now consider the scope of this role and expectations for successful use of this technique.

It is inherently unsatisfactory to be able only to treat the symptom of a disease and not be able to correct the cause. Transcutaneous electrical stimulation is a technique to which the physician may resort to provide the patient with symptomatic relief and not one which will offer definitive treatment. Unlike other therapeutic options for the patient in chronic pain, however, TES is quite free from danger to the patient. The technique has no addictive potential and has little in the way of adverse side effects. Unlike neurosurgical ablative procedures, there is no threat of disruption of normal neurological function. It is easy to implement; if it fails to work little is lost.

Depending on the patient population, anywhere from 10% to 35% of patients suffering from otherwise intractable pain will achieve long-term excellent pain relief from use of TES.[18,19] The criteria for an excellent result vary from study to study, but at a minimum this means that a patient previously incapacitated with pain is able to obtain nearly complete relief from pain during this period. Between 30% and 50% of patients with chronic pain find TES to be a useful adjunct to other forms of pain therapy on a long-term basis.

The success of TES treatment in part depends on the origin of the pain. Patients with peripheral neuropathy, pain of central origin, and those with pain presumed to be secondary to psychogenic factors almost never achieve satisfactory pain relief using this technique. Patients with postherpetic neuralgia, phantom limb pain, stump pain, branchial plexus injury, peripheral nerve trauma, and arthritis are most consistently helped with TES. In a series of 39 patients with one of these diagnoses reported by Long and Hagfors,[13] 70% of the patients obtained excellent pain relief using TES on a long-term basis. Patients with chronic low back pain or cervical spine pain, with or without radiculopathy, constitute the majority of patients with chronic pain in most pain centers. In a group of 301 such patients, approximately 30% of the patients obtained excellent pain relief with TES. Patients with reflex sympathetic dystrophy or causalgia may have benefit if treated early in the context of their disorder.[20]

In addition to chronic pain, TES may have a role in the treatment of acute pain. Hymes and his associates[21] first called attention to the fact that postoperative pain could be greatly alleviated by the use of TES. First, in a retrospective study and then in a prospective fashion, these authors discovered that patients undergoing thoracotomy and laparotomy were significantly improved when TES was employed in the postoperative period. The need for narcotics was reduced and postoperative problems with atelectasis and ileus were considerably lessened. Van der Ark and McGrath[22] found that 77% of patients receiving TES for pain following thoracic and abdominal surgical procedures had substantial reduction in pain, as manifested by a reduction in verbal ratings of pain, and a reduction or elimination of narcotic intake. The usefulness of TES for control of pain resulting from such things as orthopedic injuries is limited in nonhospitalized patients by the cost and availability of stimulating units. The technique is quite useful in hospitalized patients and may reduce the need for analgesic medications. However, until it is as easy for the physician to order TES as it is to write an order for narcotics, it is unlikely that the technique will find widespread use in the hospital setting.



Mechanism of Action

Several hypotheses have been proposed to explain how TES relieves pain. These ideas may be divided into those in which direct effects on the peripheral nerve fibers themselves are postulated, and those in which it is proposed that TES modifies the transmission of nociceptive information in the central nervous system (CNS).

In the first proposal, it is postulated that the application of electrical current to the peripheral nerve at a location interposed between the source of the pain and the spinal cord induces an axonal blockade of activity in the primary afferent nociceptive fibers, and thereby prevents pain perception. The evidence that this mechanism plays at least some role in reducing pain during TES is considerable.

To understand better the effects of TES on normal pain perception, Campbell and Taub[23] studied the electrical parameters and stimulus locations necessary to alter normal pain perception. It was found that at levels of electrical stimulation necessary to induce cutaneous analgesia, there was loss of the A-delta elevation in the compound action potential recording. Effects on pain threshold were found only at points distal to the point of stimulation. It was further observed that stimulus frequencies greater than 10 Hz were necessary to obtain cutaneous analgesia. The electrical stimuli were not in themselves painful unless introduced suddenly, several minutes after any prior stimulation. The pain resulting

in this instance was brief, lasting a matter of seconds. These data were taken as evidence that electrical analgesia resulting from TES in normal subjects was due at least in part to an axonal blockade occurring in the primary afferent nociceptive fibers.

It was also postulated that a momentary activation of nociceptive fibers (which must precede axonal blockade) dispersed over time in patients with preexisting pain in the area innervated by the activated neurons may not be perceived. Thus, TES for clinical pain would not necessarily be expected to be even momentarily painful, despite the initial activation of nociceptive fibers prior to axonal blockade.

Corroboration of This Hypothesis

Further evidence for these ideas was presented by Ignelzi and Nyquist.[24] In this experiment, the effects of peripheral nerve stimulation on the compound action potential elicited by a subsequent supramaximal electric shock were studied in the cat. It was found that stimulation with electrical parameters similar to those used clinically to establish pain relief in humans led to a reduction in the height of the A-delta wave in the compound action potential recording. An example of these findings is shown in Figure 8-2. The first wave represents the A-beta wave adjacent to the electrical artifact. The second elevation is the A-delta wave. It is apparent that the degree of blockade of A-delta and A-beta units varies directly with the length of the conditioning stimulus. The degree of blockade is also increased by an increase in the voltage of stimulation. As found by Campbell and Taub,[23] blockade is antedated by an increase in conduction time.

It is possible that the reduction of the A-delta portion of the compound action potential in these two experiments merely represents a dispersion of the latencies of the single A-delta units, and therefore does not represent a conduction block. In addition, recording techniques did not allow identification of the wave associated with C-fiber activation. It is thus desirable to study the effects of electrical stimulation on individual A-delta and C units. This was accomplished by Torebjörk and Hallin[25] in human subjects.

Single units thought to subserve nociception which had conduction velocities in the C-fiber range were recorded from microelectrodes inserted percutaneously into peripheral nerves of unanesthetized human subjects. These units could be activated with electric shocks applied through intradermal electrodes placed near the receptive field of the respective C-fibers. Trains of electric shocks with a pulse width of 50 to 100 μsec were delivered through the electrode. The response latency of these units increased as the stimulus frequency was increased from 0.5 to

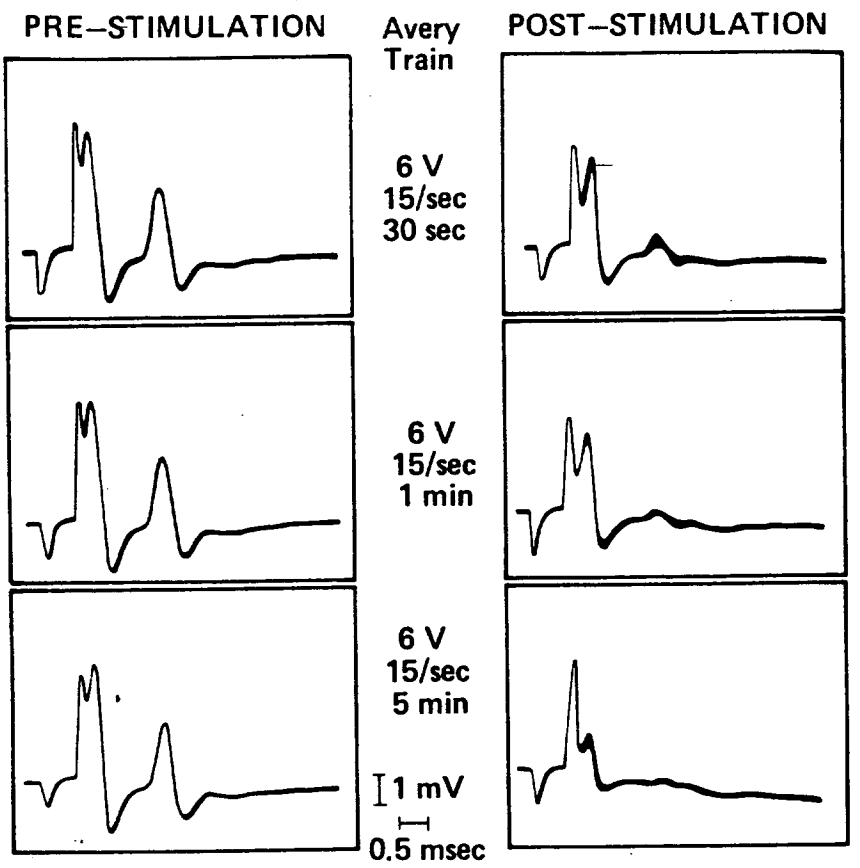


Figure 8-2 The effects of peripheral nerve stimulation on the A-delta component of the compound action potential. The compound action potential before and after a 30 sec, 1 min, and 5 min 6 volt 15/sec train of stimuli is shown. As the stimulus train is increased in duration, the A-delta wave becomes progressively smaller (from Ignelzi and Nyquist,[24] with permission).

10 Hz. At frequencies of 10 Hz pronounced blocking occurred. This was accompanied by loss of pain from the introduced shock and an elevation of pain threshold tested with pinprick stimuli. The recovery from such blocking was not systematically investigated, but the effect was still notable after 30 sec of rest from electrical stimulation. In the larger myelinated fibers, blocking and decreases in conduction velocity also occurred but required stimulus frequencies from 50 to 100 Hz. It is of interest to note in the report of Linzer and Long[16] that patients who had excellent pain relief with TES generally preferred stimulus frequencies between 10 to 60 Hz. Such frequencies may be expected to have a preferential blocking effect on small fibers and, therefore, reduce pain sensation.

Further corroboration of this hypothesis was presented by Wall and Gutnick[26] in an electrophysiological study of experimentally produced neuromas in rats. It was shown that a 100 Hz, six-second train of bipolar electrical stimulation applied to the peripheral nerve led to a marked increase of the electrical threshold, and loss of spontaneous activity in A-delta fibers which were presumed to innervate the neuroma (techniques did not allow for C-fiber recordings). This change in excitability lasted anywhere from minutes to as long as one hour. This contrasted with a more prompt return to normal in A-delta units which innervated histologically normal areas. The results of this experiment suggest, therefore, that pain arising from neuromas may be more susceptible to the blocking effects of TES than other types of pain. This conclusion is in agreement with studies in human patients with implanted peripheral nerve stimulators in which it has been found that chronic pain from peripheral nerve trauma responds most satisfactorily to stimulation.[27]

The phenomenon of frequency dependent conduction block of axons described here is analogous to the phenomenon of "Wedensky inhibition" originally described in 1903. Working with nerve-muscle preparations, Wedensky[28] found that a stimulus strong enough to elicit a contraction may fail to stimulate when it is repeated at certain relatively rapid rates. It has subsequently been demonstrated with single unit recordings that this results from a localized conduction block, ie, block of the propagation of the action potential in the axon.

Much has been learned recently regarding the mechanism and requirements of frequency related conduction block. The question has attracted additional interest because of evidence which suggests that conduction block may occur as a part of normal neuronal activity. For example, it has been shown that points of axonal branching and areas with increasing fiber diameter are especially vulnerable to frequency related conduction block.[29-33]

Theoretical and experimental evidence collected by several authors suggests that this phenomenon may be related to an increased concentration of potassium in the space outside the axolemma during repetitive firing of an axon.[34-38] From the Nernst equation it would be predicted that such a change would result in membrane depolarization. Inactivation of sodium conductance occurs both with increases in external potassium concentration and prolonged depolarization. Because sodium conductance is necessary for propagation of the action potential, these changes may lead to a conduction block. Adelman and Fitzhugh[34] modified the Hodgkin and Huxley equations to take into consideration changes in K^+ concentration during repetitive firing. They were able to predict and experimentally verify conduction block from repetitive firing of the squid giant axon using the modified equations. In addition the changes in spike amplitude and response latency observed prior to block were predicted from these equations.

It is predicted that factors in the environment of the axon which impede the diffusion of potassium from the axon will increase the susceptibility to frequency related conduction block. Smith and Hatt[39] demonstrated in the crayfish that an area of motor axon which passes through dense connective tissue was very susceptible to blockade with repetitive stimulation. Because the axon has no geometrical variation in this region, it was concluded by the authors that the dense connective tissue surrounding the axon acted as a barrier to the diffusion of potassium and may, therefore, account for the observed conduction block. Regardless of the mechanism, the importance of such things as connective tissue surrounding the axon in increasing the susceptibility to conduction block invites speculation that similar mechanism explains the susceptibility to conduction block of fibers which innervate neuromas (see previous discussion of experiment by Wall and Gutnick[26]).

Torebjörk and Hallin[25] have shown that C fibers are more susceptible to conduction block than the large myelinated fibers. This too can be explained in terms of the environment of the axon. Ruch and Patton[40] have stated that "the immediate extracellular space of the C fiber is peculiarly restricted in such a way that extracellular accumulation of potassium may well occur during repetitive activity." Thus, frequency related conduction block would be predicted to be more prominent in C fibers.

One final observation deserves mention. It has been observed that TES may relieve chronic pain without any other easily demonstrable effect on sensation. This observation has in the past posed difficulties for those who proposed that a peripheral axonal blockade of nociceptive afferents was important in producing TES-related analgesia. Because injured nerves are surrounded by increased amounts of connective tissue, it would be predicted that these fibers would be most susceptible to frequency related conduction block. It is, therefore, understandable how TES might alleviate pathological pain without interfering with other functions subserved by the stimulated peripheral nerve.

It deserves to be emphasized that in order for frequency related conduction block to occur, the fiber in question, in this case the A-delta and/or C fiber, must be initially activated before conduction block can occur. It remains to be demonstrated that C fibers may be activated using the electrical parameters utilized during TES. Until this is demonstrated the "frequency related conduction block hypothesis" must be regarded to be tentative, though there is circumstantial evidence to support it.

Anodal and Cathodal Blockade

A special type of axonal conduction block may be induced with DC currents of electricity. These have been termed cathodal and anodal block. Induction of a cathodal block requires that a subthreshold

depolarizing current be applied. Although there is an initial increase in excitability, a prolonged subthreshold stimulus may reduce sodium conductance to the point that a stronger than normal stimulus is required to activate the axon in this region. Induction of an anodal blockade requires that a hyperpolarizing current be applied. The potential shift required to reach threshold for activation is thereby increased.

These types of block are clearly different from those proposed to occur during TES. Anodal blockade has been used to produce local anesthesia in patients undergoing dental procedures.[41-44] For example, anodal current may be applied through the drill to the tooth pulp during restorations. The safety of this procedure has not yet been fully established, although commercial devices for utilizing this procedure are apparently available in the Soviet Union.[45] Unlike TES, this procedure blocks activity in the large fibers prior to including a conduction block in C fibers.[46] The electrical parameters are much different than those used in TES. Anodal block requires monopolar stimulation with a continuous DC current. TES, in contrast, involves bipolar stimulation with rapidly applied stimuli with brief pulse widths. It is, therefore, quite unlikely that either a cathodal or anodal block occurs during the type of TES under discussion in this chapter.

The Role of Central Mechanism

Not all sensory information entering the CNS from peripheral nerve fibers is perceived. There exists, therefore, control systems within the CNS that determine which and how much sensory information shall reach consciousness. Nociceptive information maintains a high priority in sensory experience as is commensurate with the importance of such information in minimizing harm to the organism from damaging stimuli. It has been postulated that TES may activate normally present CNS control systems, and thereby suppress the transmission of nociceptive information to CNS areas which subserve the sensation of pain and its affective attributes.

Just how such control systems may work, and what relevance known control systems may have in explaining the effects of TES has invited a surfeit of speculation. Certain ideas may be discounted, however. First is the idea that TES works by diverting attention from the pain. The fact that the stimulation must be applied to the nerve which transmits the nociceptive signal, and that when applied to an area remote to this nerve has no effect reduces the possibility that perceptual diversion plays an important role.

It has been popular to attribute the effects of TES-induced analgesia to an inhibitory effect of large primary afferent fiber activity on centrally located neurons, which is associated with pain perception. Two ex-

perimental approaches have been used to study this possibility. In the first approach, the effects of peripheral nerve stimulation on pain perception in the region innervated by that nerve were studied in human subjects. When Wall and Sweet[4] did this, they observed hypalgesia with levels of stimulation which were in themselves not painful. They concluded from this that the hypalgesia resulted from selective large-fiber stimulation. It has already been noted, however, that when electrophysiological measurements of the effects of such stimulation are made, there is evidence for inactivation of the primary afferent nociceptive fibers.[23,24] Nathan and Rudge[47] also found that stimulation of large primary fibers in itself had no effect on either pain threshold or pain tolerance in normal human subjects.

In the second approach, the effects of large-fiber stimulation may be studied in terms of their effects on central neurons, activity of which is associated with the perception of pain. This experiment is presently difficult to conduct because of uncertainties in regard to which central neurons subserve nociception.

The activity of spinothalamic neurons in response to C-fiber volleys as a function of the presence or absence of coincident A-fiber volleys has been studied. Price and Wagman[48] found in monkeys that central inhibition and facilitation can result from maximal stimulation of either A or C fibers without necessity of interaction between effects of these two groups. Manfredi[49] found that A- and C-fiber volleys had only an additive effect on the contralateral (and ipsilateral) anterolateral potential (presumed to be an index of activity in the spinothalamic tract) in the cat.

Nociceptive cells of the lamina I in the anesthetized cat have been described in which response to noxious cutaneous stimuli may be suppressed by such things as hair movement in the receptive field.[50] Peripheral nerve stimulation was also reported to suppress the response of lamina I nociceptive units.[51] There was a positive correlation between the amount of suppression and the intensity of electrical stimulation delivered to the peripheral nerve, but data were not provided by which it could be reliably determined whether large-fiber activation by itself could suppress the response of these nociceptive units. No such interaction has been demonstrated in the primate. This, in combination with the lack of notable effects of large-fiber activation on the subjective magnitude of pain judged by human subjects, reduces the possibility that such a central interaction is of much importance in normal pain perception, at least in humans.

The possibility that large fiber stimulation may affect higher order nociceptive neurons has been largely unexplored. This is recent evidence that a descending control system exists in the dorsolateral funiculus of the spinal cord, which may mediate pain relief elicited by periaqueductal and pretectal stimulation.[52] In a study of rats,[53] it was found that

bilateral sectioning of the dorsolateral funiculus blocked morphine-induced analgesia, but had no effect on analgesia produced by transcutaneous stimulation. This suggests that TES does not affect pain perception by way of actions of periaqueductal structures associated with morphine-induced analgesia.

In summary, there is evidence that TES-induced pain relief may be mediated by effects on the peripheral nerve itself. Evidence for centrally mediated effects of TES on pain perception is as yet scanty.

Conclusions

Transcutaneous electrical stimulation is a benign and simple form of therapy which may be effective in relieving pain which fails to respond to conventional therapy. There is a small incidence of skin irritation, and it may be cumbersome for the patient to carry the power supply and attach the electrodes to the skin on a daily basis. Despite this drawback, patients with chronic low back pain (one of the most difficult groups to help with any form of therapy) have a long-term success rate which is striking. In other forms of pain, expectations for success may be even higher. Patients with central pain or pain in which it may be difficult to apply the stimulation to the peripheral nerve proximal to the area from which the pain arises form a group which generally will not receive benefit from TES therapy.

Other techniques in which peripheral nerve stimulators are attached directly to the nerve[27,54] or in which epidural electrodes are placed over posterior roots (DM Long, unpublished data, 1977) offer a means of stimulation in which some of the problems encountered with TES may be overcome. The principal advantage of these techniques is that the stimulation may be applied more directly to the nerve. Problems with skin irritation are largely obviated and the intensity of the stimulus to the nerve is increased. Currently, these devices require an external power supply in order to activate the implanted electrodes. Research is now underway, however, to develop a power supply which may be permanently implanted and periodically recharged from an external source (R Fischell, unpublished data 1977). Such a device would be a great advantage to the patient who required long-term CNS stimulation for relief of pain.

In this chapter the mechanism by which TES relieves pain was considered in some detail. Although conclusions must as yet be tentative, there is evidence to suggest that a blockade of activity in the primary afferent nociceptive fibers plays at least some role in pain reduction. A mechanism by which such a blockade may occur is proposed to involve a rate related conduction block (analogous to "Wedensky inhibition"),

which in turn may be due to accumulation of potassium in the periaxonal space surrounding the primary afferent nociceptive fibers. Central mechanisms may also be important in understanding TES-related analgesia, but evidence at this time is sparse.

Whatever the mechanism, TES appears to be a valid way of treating many patients previously incapacitated by otherwise intractable chronic pain. It is safe, relatively inexpensive, and effective over long periods of time for many of these patients.

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