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Stimulation of the Central and Peripheral Nervous System for the Control of Pain

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Summary: After suffering some setbacks since its introduction in 1967, stimulation of the spinal and peripheral nervous systems has undergone rapid development in the last ten years. Based on principles enunciated in the Gate Control Hypothesis that was published in 1968, stimulation-produced analgesia [SPA] has been subjected to intensive laboratory and clinical investigation. Historically, most new clinical ideas in medicine have tended to follow a three-tiered course. Initial enthusiasm gives way to a reappraisal of the treatment or modality as side-effects or unanticipated problems arise. The last and third phase proceeds at a more measured pace as the treatment is refined by experience. This review is divided into three parts as it traces the progress of spinal cord stimulation [SCS] and peripheral nerve stimulation [PNS]. The review commences with a discussion of the theory of SCS and PNS, and is followed by early reports during which it became apparent that the modality is essentially only effective in the treatment of neuropathic pain. The last section describes the modern experience including efficacy in specific types of pain and concludes with recent accomplishments that dramatize the relief of pain which can be achieved in nonoperable peripheral vascular disease or myocardial ischemia.

Over the years, a search for those transmitters that might be influenced by spinal cord stimulation focused on somatostatin, cholecystokinin (CCK), vasoactive intestinal polypeptide (VIP), neurotensin and other amines, although only substance "P" was implicated. More recently, in animal studies, evidence that GABAergic systems are affected may explain the frequent successful suppression of allodynia that follows spinal cord stimulation. During the past eight years, much attention has been directed to studies that use a chronic neuropathic pain model.

While PNS held significant promise as a pain relieving modality, early electrode systems and their surgical implantation yielded variable results due to evolving technical and surgical skills. These results dramatically reduced the continued development of PNS, which then gave way to a preoccupation with SCS. Modern development of SCS with outcome studies, particularly in relation to failed back surgery syndrome [FBSS] and the outcome of peripheral nerve surgery for chronic regional pain syndromes, has earned both modalities a place in the ongoing management of patients with intractable neuropathic pain.

The last section, dealing with pain of peripheral vascular and myocardial ischemia, is perhaps one of the more exciting developments in stimulation produced analgesia and as the papers discussed demonstrate, can provide a level of analgesia and efficacy that is unattainable by other treatment modalities. SCS and PNS has an important role to play in the management of conditions that are otherwise refractory to conservative or other conventional management. **Key Words:** Spinal-cord stimulation—Peripheral nerve stimulation—Stimulation-produced analgesia—Pain control.

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Stimulation-produced analgesia (SPA) is centuries old (Mayer and Liebeskind, 1974; Long, 1975). Natural sources of electricity, such as the electric eel and other fishes, have been used for the treatment of pain. In China, electric current applied to acupuncture needles has been in use for centuries and medical literature during the 19th century is filled with scientific and lay application of electrical stimulators promoted for treating pain (MacKay, 1841) (Long, 1986; Chapman, 1990). All but a few reports curiously ignored any association between the nervous system and the mystical properties that electricity held for the treatment of numerous human ailments. Although in 1959 Althaus (1959, 1970) reported that both analgesia and anesthesia occurred in the presence of paresthesia during electrical stimulation of major nerve trunks, he did not significantly influence current medical thinking. Although an interest in neuromodulation truly began with the publication of Gate Theory by Melzack and Wall (Melzack and Wall, 1965; Wall and Sweet, 1967; Shealey et al., 1970; Sweet and Wepsic, 1974; Long and Hagfors, 1975). It was the fortuitous association between Wall, Sweet, and Sweet's resident Shealey that set in motion any actual progress (Sweet and Wepsic, 1974; Shealey, 1975) and research and development that has resulted in the the present status of spinal cord and nervous system stimulation for the control of pain (Wall, 1973; Pineda, 1975).

Indeed, only 2 years later Shealey described the use of dorsal column stimulation (DCS), now known as spinal cord stimulation (SCS) for the control of chronic pain (Shealey et al., 1970). Because SCS failed to relieve many patients of their pain, interest in the use of peripheral nerve stimulation increased (Sweet and Wepsic, 1968; Picaza et al., 1975; Nashold et al., 1979). Indeed, it was the failure to control pain in many patients that stimulated clinicians to seek improved methods to screen their patients beforehand. While using a transcutaneous stimulation device, Shealey noted that some patients obtained control of their pain, obviating the need to implant a stimulator. Long and Hagfors (1975), who had designed and tested a stimulator, used a square-wave pulse with controllable amplitude and frequency and presented their data at the inaugural meeting of what subsequently became the International Society for the Study of Pain, 1973.

Although the use of transcutaneous nerve stimulation is another application of SPA, it has been more widely studied for the treatment of acute musculoskeletal syndromes (Long and Carolan, 1975; Sternbach et al., 1976; Procacci et al., 1977; Anderson, 1979; Ali et al., 1981; Morritz, 1982). Its use for specific peripheral nerve stimulation (PNS) is a separate topic and beyond the scope of this paper.

With regard to the mechanism of SPA and its introduction as a term in neurophysiology, the seminal paper is that of Mayer and Liebeskind (1974). It was Reynolds (1969), however, who demonstrated that focal stimulation of the lateral margin of the periaqueductal gray (PAG) prevented nociceptive responses in rats during abdominal surgery; later, Basbaum and Fields (1978; Willis, 1985) proposed a model describing descending pathways that modulate pain transmission. The components of this model include neurons in the PAG, the nucleus raphe magnus (NRM) forming the pathway from midbrain to the dorsal horn of the spinal cord, the role of which is to inhibit nociceptors by activating the inhibitory interneurons and prevent ascension of nociception. This inhibition may be both pre and postsynaptic. Projections from the locus ceruleus (LC) and the parabrachial complex (PB) and the magnocellular part of the nucleus reticularis gigantocellularis (Rmc) are also involved.

This system can influence the spinothalamic tract (STT), the main pathway for pain transmission in humans (Willis, 1985). Fields and Basbaum demonstrated that the neuropeptide transmitter substance P is affected by this descending influence which, participating in the "Gate mechanism" normally modulates pain transmission at the level of the dorsal horn (Basbam and Fields, 1978). To carry this analogy further, suppression of chronic pain from various parts of the body explains why stimulation of the dorsal columns (DC) of the spinal cord has been a particular target (Dimitrijevic et al., 1980; Barolat et al., 1991).

Primary cutaneous afferents corresponding to all parts of the body below the level of the stimulating electrode, and large fibers in particular, are considered to be selectively activated because of their low stimulation threshold. Stimulation of these fibers provides a tingling sensation (paresthesia) in the corresponding dermatome, thus enabling the physician to direct these paresthesias to the painful area by SCS (Law and Miller, 1982; Struijk et al., 1993*b*).

THEORY OF PNS AND SCS

Although the dorsal columns were assumed to be the primary target during dorsal-medial stimulation with an epidural electrode because they are closer to the electrode, theoretical evidence suggests that large dorsal root (DR) fibers have even lower stimulation thresholds than DC fibers of the same size (Coburn,

1985), possibly because DR fiber stimulation is due to the inhomogeneity, anisotropism, and the various orientations of DC and DR fibers. Although both DR and DC fibers relay primary sensory information, the DR fiber corresponds to a single dermatome whereas the DC contain fibers from a large number of dermatomes, particularly in the cervical spinal cord (Coburn, 1985; Struijk et al., 1993). Struijk et al. (1993) also showed that DR fibers are first excited at the lamina closest to their entry into the spinal cord.

The computer model predictions of Struijk and other investigators (Holsheimer and Struijk, 1991; Struijk et al., 1993*a*), have been confirmed by clinical data showing that with increasing stimulus paresthesias have onset in the dermatome that corresponds to the segmental level of the cathode. Indeed, this threshold decreases as the electrode is moved farther laterally—closer to the DR—whereas paresthesias have a segmental distribution (Barolat et al., 1991).

Because motor responses and other unpleasant sensations occur when a stimulus amplitude ~50% above the perception threshold is applied, the "window" (usage range) available for stimulation will determine that only a few dermatomes can usually be covered by paresthesias (Dimitrijevic et al., 1980). Obviously, the efficacy of SCS would be greatly improved if the usage range could be increased, enabling more DC fibers to be activated within this range. Other factors that influence SCS are the anatomic location, in particular the midcervical region and the midthoracic region, both of which are sites of primary regions for providing control of pain to the head, neck, and upper extremity or the spine and lower extremities (Barolat et al., 1991).

The influence of SCS is governed by contact length, contact width, contact spacing, and the effects on the threshold ratio DC/DR (Rattay, 1986; North et al., 1991; Tulgar et al., 1993*b*; Holscheimer et al., 1995). At least, computer modeling of SCS predicts that the preferential activation of spinal nerve fibers with different orientations may be controlled by the geometry of the rostral caudal contact array (Rattay, 1987*b*). DR fibers and segmental paresthesia activation will be favored by monopolar stimulation with a long cathode, whereas DC fiber stimulation and wide paresthesia coverage is favored by bipole or tripole (central cathode) with small contact lengths and spaces (Barolat et al., 1991; Holsheimer et al., 1994; Rukhoff et al., 1994).

These data suggest that recruitment of the descending inhibitory pathways requires excitation at a segmental level corresponding to the cathode and the anatomic area is a transverse section of the spinal cord in which the fibers recruited are determined by mediolateral position of the cathode. Position of the anode is not significant and plays no part in recruitment of DC fibers separated by a distance of >30 mm. Symmetrical stimulation of the dorsal columns requires that the center of the cathode be in the "physiological midline." Computer modeling has shown that the contact separation in respect to the recruited area and stimulus amplitude should correspond to ~1.4 times the distance between contacts and the dorsal columns, i.e., depth of cerebrospinal fluid (CSF) (Spincemaille and Wittens, 1989). This implies a smaller contact separation (3–4 mm) should be used for optimal cervical stimulation than for low thoracic stimulation (6–8 mm).

For mediolateral combinations, contacts will have a low spatial selectivity; those in a dorsal ventral direction will have a high spatial selectivity. Because the threshold stimulus is greatly influenced by the depth of CSF underneath the contact electrode, flexion and extension of the spine will influence the stimulus threshold (Nielson et al., 1976; Coburn, 1989; Spincemaille and Wittens, 1989; Holsheimer et al., 1994; Holsheimer et al., 1995). Likewise, because the stimulus threshold is inversely proportional to the fiber size, fibers <3 μm are unlikely to be recruited with low-thoracic stimulation (Struijk et al., 1993*b*).

Practical application of computer modeling was recently tested by Tulgar et al. (1993*a*). The usage range, or the difference between the perception threshold and tolerance threshold, is an important parameter used in epidural SCS therapy. The value for midthoracic levels is 0.5 V as compared with 0.26–0.42 V in the cervical region. If the usage range is <0.5 V, there is limited room to vary the intensity of stimulation when making threshold adjustments, often leading to discontinuation of stimulation. If, however, it is >1 V, too many changes in the stimulation parameters may cause the patient to alter stimulation settings, making it difficult to determine an optimal value.

In another study, Tulgar et al. (1993*b*) analyzed 266 combinations of contacts implanted in the midcervical and midthoracic regions. Their preliminary results showed that the topographical representation of the paresthesias did not correspond to the classical dermatomes (North et al., 1992). Using a unipolar combination, they noted that significant paresthesia at C4 in the midline represented the hand, forearm, and upper arm; with bipolar combinations, however, the hand and forearm were represented. With a unipolar combination at C4 in the lateral position, paresthesias

were felt in the anterior shoulder, forearm, upper arm, and hand, whereas with bipolar combinations they were represented in the hand, forearm, and upper arm. At T10, with a unipolar electrode in the midline, paresthesias were felt in the anterior and posterior thigh, leg, knee, ankle, and foot; with bipolar combinations, however, they were felt in the anterior and posterior leg, knee, and foot.

At T10, with use of unipolar lateral placement, the abdomen, anterior leg, knee, and anterior thigh were represented; with bipolar combinations, however, the anterior thigh, anterior leg, knee, and foot were stimulated. These data obviously suggest that further detailed studies are needed to improve our ability to predict the precise anatomicophysiologic sites for optimal therapeutic stimulation.

In an attempt to determine which neurotransmitters may be influenced by spinal cord stimulation, Meyerson et al. (1985), sampled the CSF for somatostatin, cholecystokinin (CSK), vasoactive intestinal polypeptide (VIP) neurotensin, and monoamine metabolites in 6 patients with PAG stimulation and in 14 patients with SCS stimulation. The only neurotransmitter shown to be influenced by central nervous system (CNS) stimulation was substance P (SP). Meyerson et al. (1985) concluded that while this may be significant in regard to SP-medicated transmission of nociception, the lack of other changes may indicate that pain-related substances are released in very small amounts, rapidly metabolized, and therefore not detected by a single sample of CSF, which was the case in this study.

In an experimental study of mononeuropathic rats, Cui et al. (1996) demonstrated that SCS may affect γ-aminobutyric acid (GABA)ergic systems by enhancing GABA-containing inhibitory interneurons. They also showed that SCS release of GABA may be responsible for the suppression of allodynia in rats, a situation not unlike the alleviation of pain in patients with peripheral neuropathy (Stiller et al., 1996).

Because most studies designed to investigate the mechanism of SCS have used acute noxious stimuli and because the primary purpose for neuromodulation is control of chronic neuropathic pain, Meyerson et al. (1994) have undertaken a series of studies based on the models of Bennett and Xie (1988) and Seltzer et al. (1990). These models are particularly suited to studies of this nature and have already provided data demonstrating that the late component of the flexor reflex evoked by high-intensity peripheral stimulation most likely represents activation of C-fibers and is not influenced by SCS (Garcia-Larrea et al., 1989). The threshold of the early component is markedly increased by SCS, however, and outlasted the period of SCS by as long as 40 min. The threshold for both early and late components of this reflex in the intact leg were unaffected by SCS. These effects were not dependent on lateral placement of the spinal cord electrode. The lack of any effect of SCS on the late component of the flexor reflex is at variance with other data showing that the late effect is suppressed by SCS (R111) without altering the stimulus threshold of the early effect (Garcia-Larrea et al., 1989).

What is not known, however, is whether the early component of this reflex in rats represents activation of A-beta or A-delta fibers (Lindblom and Meyerson, 1975; Lindblom and Berrillo, 1979; Campbell et al., 1988; Meyerson et al., 1994). Earlier, Ignelzi and Nyquist (1976). demonstrated that repetitive stimulation of the isolated peripheral nerve alters the conduction velocity and amplitude of A-alpha, A-beta, and A-delta activity (Ignelzi et al., 1976). However, Meyerson et al. (Meyerson et al., 1994) reasoned that if this component in the neuropathic leg represents allodynia, it is most likely mediated by A-beta fibers, and this is believed to be the case in humans. These data support the use of an experimental mononeuropathy for further studies of the mechanism of SCS.

PNS has undergone continuous development since Wall and Sweet implanted electrodes on the median and ulnar nerves of a patient in 1967. As proposed by the "Gate Hypothesis" (Melzack and Wall, 1965), activation of large myelinated nerve fibers is believed to interrupt the transmission of nociception in the spinal cord. Although nerve mapping was believed to be important for placement of the peripheral nerve stimulator electrodes (Krause and Ingham, 1920; White and Sweet, 1969) (J. L. Goldner, unpublished observations, 1955–1977). Sunderland (1945) reported that the orientation of sensory and motor fibers in peripheral nerves constantly changes in their course down the nerve, indicating that a predetermined standardized anatomic map cannot obtain. PNS lends itself as a modality for the treatment of neuropathic pain only if one nerve or at most two nerves to a region are involved. Because of the proximity of motor and sensory fibers in a peripheral nerve, the "usage range" is much smaller than is the case for SCS. The practical application of this means that a much lower and smaller window of amplitude is available to provide satisfactory analgesia.

Several early investigators reported that the failure rate for PNS in the lower extremity was higher than that for the upper extremity (Kirch et al., 1975; Picaza

et al., 1975; Campbell and Long, 1976; Sweet, 1976) because placement of the electrode on the posterior tibial nerve was subject to more stress and traction due to weightbearing. Furthermore, placement of an electrode on the sciatic nerve did not provide constant stimulation because some sensory fibers were deep within the nerve. The cuff-type electrodes, popular at one time, also induced complications.

EARLY EXPERIENCE

The development of SCS and PNS has occurred almost in parallel except that PNS, because of the relatively high incidence of failures and complications associated with its use, fell into disuse except in the hands of a few enthusiastic implanting surgeons. During the first 10 years of use of SCS, monopolar or bipolar electrodes predominated. Until a reliable flexible electrode that could be passed through a 16-gauge needle was developed, small button- or plate-type electrodes were introduced through a small laminotomy or ligamenta flavum incision (Waltz and Andreesen, 1981; Meglio et al., 1989*a*). However, toward the end of the 1970s, development of multiple-array electrodes increased the scope of SCS dramatically. During this period, the most significant difficulties were technical, related to breakage, surgical techniques associated with subdural insertion, and the unreliability of the early pulse generators. The advent of programmable microprocessor units and better implantable components has improved the reliability of SCS immeasurably.

Waltz and Andreesen (1981) reported the use of a multiple-lead linear array consisting of four circular platinum disc electrodes 3 mm in diameter and spaced 1 cm apart. For purposes of this report, the authors placed the electrode between C2 and C4 through a small laminotomy at C4. The introduction of percutaneously inserted electrodes in 1975 allowed parallel development of plate- and catheter-type electrodes for SCS (Hoppenstein, 1975; Lazorthes and Verdie, 1978; Urban and Nashold, 1978; Ray, 1982). One of the primary advantages of percutaneous electrode insertion was that it allowed a simple trial of spinal cord stimulation without the need for surgery. To the present day, both techniques are used with similar success. Most SCS is undertaken for chronic pain and, to a lesser extent, for cerebral palsy and motor disorders.

The early cuff-type electrodes initially used for PNS gave way to button-type electrodes which were actually sewn to the epineurium of the affected nerve (Nashold et al., 1979). Most morbidity is associated with electrode approximation (Nashold et al., 1982), electrode displacement, and lead failure (Hassenbusch et al., 1996). The results of sustained benefit in four small uncontrolled studies published in the 1970s, representing data collected for 68 months, were 61, 53, 45, and 50%, respectively (Sweet and Wepsic, 1968; Kirch et al., 1975; Picaza et al., 1975; Campbell and Long, 1976). These data, while reflecting the technology and experience of the period, also helped provide support for its further development. In keeping with the prediction of Nashold et al. (1982), standardized criteria for PNS and the early elimination of other pathology such as arterial, venous, and compressive factors (entrapment) and the development of sensory nerve mapping will ultimately improve the clinical outcome of this treatment method.

From the beginning, physicians realized the need to screen patients adequately psychologically before undertaking SCS or PNS. Several articles have emphasized this need, and even Shealey described the need to discuss psychological factors when selecting patients for neuromodulation (Shealey, 1975; Daniel et al., 1985; Bel and Bauer, 1991; North et al., 1991*b*).

The Minnesota Multiphasic Personality Inventory (MMPI) was originally believed to be helpful in assessing the three basic clinical scales of hypochondriasis, depression, and dysthymia (Spiegelmann and Friedman, 1991). However, these indices appear to have no correlation with the suitability for SCS. Nonphysiological conditions such as Waddel's signs, features of somatization, abnormal learned behavior patterns, major drug habituation and untreated major depression, either singly or together, may contribute to a lack of efficacy and therefore are relative contraindications. In addition to use of the psychological evaluation, some investigators consider it important to demonstrate the relief of symptoms first by nerve block in the neuropathic extremity. The principle underlying such an approach is the demonstration on several (at least three) occasions, with or without a placebo injection, that a source of nociception is distal to the site of neural blockade. Obviously, when a patient has many neuropathic pains, with both "central" and "peripheral" components, such an exercise will prove futile. More important to a general psychological assessment of the suitability of a patient for implantable technology would be multifactorial criteria weighed as a result of an interdisciplinary assessment. Such criteria would include pain ratings, the personality of the individual, the presence of nonphysiologic signs (as just described), and factors such as compensation or

litigation, which may influence the outcome of neuromodulation. However, one must also be extremely careful to ascertain whether withholding treatment because of pending litigation will be deleterious to the medical and psychological outcome of the patient; therefore, each case must be treated on its own merits. Although psychological factors are frequently used as the ultimate exclusionary criterion when a decision is made regarding implantable technology, observation of the response to trial stimulation is still the best indicator of prognosis, and accurate interpretation of this response should be the best determinant of the ultimate success of either SCS or PNS.

MODERN EXPERIENCE

Many studies of SCS and PNS have demonstrated their efficacy (Nielson et al., 1976; Nashold Jr. et al., 1979; Meglio et al., 1989; Probst, 1990; Meyerson et al., 1991; North et al., 1991, 1994; Barolat, 1993; Hassenbusch et al., 1996). Patients suitable for neuromodulation are those with chronic pain due to failed back surgery syndrome, arachnoiditis, spinal cord and head injury, peripheral mononeuropathy or plexopathy, chronic regional pain syndromes [CRPS type I reflex sympathetic dystrophy (RSD) or type II (causalgia)], (Stanton-Hicks et al., 1995) ischemic vascular pain, and intractable angina (Long et al., 1981; Lazorthes et al., 1995; Barolat et al., 1989; Robaina et al., 1989; Sanchez-Ledesma et al., 1989; deJongste and Staal, 1993; Broggi et al., 1994; deJongste et al., 1994; Horsch and Claeys, 1994). Some of these will now be reviewed.

Barolat (1993), in a large series of 509 patients, of whom 227 had chronic pain due to CRPS, failed back surgery syndrome, arachnoiditis, spinal cord injury, severe nerve injury pain, and other miscellaneous pain conditions, reported that 73.2% of these patients were successfully using their electrodes at follow-up. Implanted electrodes had to be surgically removed due to infection in 3.7%, in one third of cases after surgical revision $\leq$10 days after the original implant. Barolat stresses the importance of careful topographical electrode placement and of paying strict attention to the surgical technique.

In another study, North et al. (1994), using disinterested third-party assessments, achieved an outcome efficacy of >70% in 102 failed back surgery patients in a 5-year period. This result is similar to the results of Long et al. (1981), who reported a 10-year experience of SCS and PNS for chronic pain control. In two separate studies, North et al. (1993) reviewed their two decades of experience with SCS for chronic intractable pain. Their study population included 320 patients with intractable pain who underwent implantation of temporary or permanent spinal cord stimulators between 1971 and 1990. All patients were screened with a temporary electrode to demonstrate that satisfactory relief of pain could be obtained before the permanent device was implanted; 78% (249) of the group underwent 298 permanent implants, the higher figure representing reimplantation after satisfactory treatment of a wound infection, electromechanical failure, or an upgrade to a more improved device: 64% (or 205 patients) were subsequently interviewed.

The 205 patients represented three diagnostic categories, 153 with failed back surgery syndrome (FBSS), 11 with spinal cord injury, and 41 with pain syndromes of peripheral origin, the latter representing peripheral nerve injuries, postamputation pain syndrome, and CRPS. This study is important to understanding and progress of SCS in several respects.

Fifty-two percent (171 patients) representing a mean 7-year follow-up reported at least 50% continued relief of pain; 60% of those patients stated they would undergo the procedure again. North et al. (1994) used a disinterested "third-party interview," which removed investigator bias from data acquisition while increasing the integrity on the results. The rate of return to work was high in comparison with that in other published studies of SCS. Of patients aged <65 years who received permanent implants, 54% were actively working postoperatively as compared to 41% preoperatively.

North et al. (1994) noted that although it is important to achieve stimulation paresthesias in the topographical representation of the patient's pain, such achievement did not necessarily coincide with pain relief. The researchers did emphasize that electrode position is critical to the satisfactory relief of symptoms and that multiple electrode arrays are technically advantageous. The second study of North et al, compared the results of SCS and reoperation in patients with FBSS using a prospective randomized protocol (North et al., 1991). Eighty-one patients were entered in the study, the primary outcome measure being the frequency of cross-over from one treatment to the other. The other ratings were pain relief, medication use, work status, activities of daily living (ADL), functional capacity by physical therapy measurement, and psychological testing. Fifty-one patients consented to randomization; the remaining 30 have chosen reoperation outside the study, although

retaining the option of SCS should reoperation be unsuccessful. At 6 months, 27 of the randomized patients became eligible for cross-over, 15 having reoperation and 10 (67%) having SCS. Of the 12 who underwent SCS initially, 2 (17%) requested cross-over for reoperation. Of the 19 patients who at 6 months requested reoperation outside the study, 8 (42%) requested "cross-over" to SCS. Both groups included patients who, although they did not fail the primary outcome measure, are not treatment "successes."

Summarizing the results so far, North et al. (1991) report a statistically significant advantage in favor of SCS over reoperation for FBSS. The primary outcome measure in the study is the frequency of cross-over from one treatment to the other. If one considers the available interventions for FBSS (i.e., surgery, neuroaugmentation, SCS, and neurosurgically ablative procedures), this particular study does address some of the criticisms of existing clinical studies by using outcome of SCS as an alternative to major neurosurgery for FBSS. Although rehabilitation and physical therapy are standard treatments for the management of patients with FBSS, their relationship to the overall success of treatment is not answered by this study. The study design, however, represents a significant step in the appropriate evaluation of neuromodulation for FBSS.

Meglio et al. studied the results of SCS in a 9-year period: from 1978 to 1986. Their patients included those with obstructive vascular disease of the extremities (Meglio et al., 1989*a*), previous herpes zoster infection in 10, incomplete traumatic spinal cord lesion in 15, root and/or nerve damage in 9, cancer in 11, and a diagnosis of FBSS in 19. Meglio et al. reported that pain associated with incomplete spinal cord lesions did not respond to SCS. However, patients who have spinal cord lesions but whose main goal is the improvement of motor control or bowel and bladder function could be considered candidates for SCS. Sixty percent of patients with postherpetic neuralgia responded and remained stable throughout the period observed (Meglio et al., 1989*b*). SCS was successful in relieving low back pain in most patients during the first 3 months, but after 12 months <30% still had 50% relief of their symptoms. Also noted was a lack of correlation between radiological evidence of arachnoiditis and low back pain. Patients with ischemic pain reported >82% stable analgesia at 36 months.

In a large, 17-year retrospective study of SCS in Sweden, Meyerson et al. (1991) reviewed the long-term effects in 86 of the original 143 patients who received questionnaires. Most patients received their SCS for peripheral neuropathy, and a few had lumbosacral or cervical radiculopathy. Fifty-six patients still use their stimulators regularly, 48 for as long as 5 h/day and 3 for 5–24 h/day. The remainder used their stimulators for 1 h/day. Meyerson et al. noted a complication rate similar to that of North et al., 1991 due to technical failure, but reported that all complications were corrected by minor surgery under regional anesthesia. They concluded that SCS is an indispensable tool for treatment of chronic neuropathic pain and that it merits far greater application.

Similar results published most recently by Lazorthes et al. (1995) of a 20-year experience emphasize that with improved screening and psychological evaluation the success rate can be expected to increase to 68%. Their indications for treatment with SCS are arachnoiditis and epidural scarring, peripheral neuropathy, phantom pain, brachial plexopathy, spinal cord lesions, vascular pain, and cancer pain with radicular or plexus involvement. Lazorthes et al. (1995) noted that for ipsilateral upper limb pain radicular stimulation is preferable but that if the nerve lesion extends to the preganglionic portion such as brachial plexus avulsion or postherpetic neuralgia, thalamic stimulation should be considered after failure of a trial of SCS.

In another study, Richardson et al. reviewed the results of SCS in a 3-year period in 36 patients with acute and chronic intractable pain (Richardson et al., 1979). Eleven of the patients were diagnosed with "acute" intractable pain of <1-year duration and 25 were described as having chronic intractable pain for >1 year. The authors evaluated the success of SCS by noting the decrease in use of opiate and nonopiate analgesics, the decrease in pain behavior, the improvement in socioeconomic activities, familial interrelationships, and an improvement in motor skills, particularly ambulation. The SCS was most successful in patients with diabetic amiotrophy, postamputation or stump pain, and arachnoiditis. Pain caused by metastatic neoplasia was not relieved.

The study of Richardson et al., like many earlier reports, emphasized the value of trial SCS which, if successful, will predict the success of permanent analgesia in >50% of patients. PNS was developed in parallel with SCS and, although interest in PNS waned during the 1970s, it resurfaced during the 1980s with the advent of improved equipment and better surgical techniques (Cook et al., 1976; Long et al., 1981; Nashold Jr. et al., 1979, 1982; Linderoth et al., 1991; Turner et al., 1995). Introduction of the flat and oval electrodes, particularly those with four electrode con-

tacts (Resume type, Medtronic), provided significantly better outcomes.

In a prospective consecutive series involving a third-party "disinterested observer" as described by North et al. (1991), Hassenbusch et al. (1996) evaluated PNS in the treatment of CRPS type I (RSD). They reported long-term good to fair relief of symptoms in 63% of patients. As a measure of outcome, 20% of the 32 patients who were studied for the 3-year period returned to work.

In contrast to the previous experience with cuff and button electrodes, the technique in which an inline plate-type Resume electrode [described by Racz (1988, 1990)] that was physically separated from the target nerve by a thin layer of tissue (fascia, tendon) was shown to be particularly advantageous.

In a review of 10 years of experience, Long et al. (1981) emphasized some of the early failures related to the selection criteria that omitted inclusion of adequate psychological screening. By 1974, control for opiate addiction, comprehensive pain evaluation, and the use of psychological testing instruments markedly improved the outcomes. PNS was used for peripheral mononeuropathy and brachial plexopathy. Of the 30 patients additionally entered in the study, 79% were described as having satisfactory relief of symptoms at 7 years and 22 (73%) still had satisfactory pain relief at 10 years. However, many patients were not receiving adequate stimulation due to a defect in the PNS system. Indeed, mechanical defects, particularly those related to a fracture in the electrode wire, interfered with its function and with the success of this modality. Long et al. (1981) make the valid point that PNS is not an alternative to narcotic use and will either fail or be less than successful if implanted in patients who have severe behavioral or psychiatric problems. They also emphasized that outcome markers of return to work, stabilization of family, and improvement in social competence are more important factors in themselves than the mere subjective endpoint of pain relief.

Nashold Jr., et al. (1979), used the following outcome criteria: (a) >90% relief of symptoms, (b) increased physical activity, (c) no requirement for analgesic medication, and (d) continued need for PNS, in a review of their more than 10-year experience. Most patients had had their symptoms for 5–14 years and seem to qualify as having had a neuropathic pain. Nineteen stimulators were implanted in the upper extremity on the median, ulnar, or radial nerves, and 17 were implanted on the sciatic nerve in the lower extremity.

Nashold Jr. et al. claimed a success rate of 52.6% for the upper extremity and of 31% for the lower extremity. They note that their results have improved consistently as a result of patient selection and criteria already discussed. They also emphasized that because of the surgically skilled nature of the procedure, it should be practiced only by an experienced operator.

Spinal cord stimulation has been used successfully in the treatment of CRPS type I (RSD) and type II (causalgia). Barolat et al. (1989) studied 18 patients with CRPS I who were refractory to more conservative therapies (including medications, intrathecal opioids, sympathectomies). Four patients experienced no relief with the trial and therefore were not implanted. Of the remaining 14 who had permanent stimulators placed, 11 noted significant improvement (5 with moderate pain relief and 6 with good pain relief). Three of the patients with good pain relief were able to discontinue all narcotics, and 3 were able to reduce their usage significantly. Sanchez-Ledesma et al. (1989) reported a series of 24 patients with CRPS: 11 with type I and 13 with type II. Eight of the patients with type I and 11 of the patients with type II received permanent implanted stimulators. All these patients reported at least a 50% reduction in pain, and 89% of the patients reported excellent results (>75% pain relief) with long-term follow-up.

Broseta et al. (1982), studied a series of patients with nerve injuries or amputations that resulted in intractable burning dysesthesias. All patients obtained good pain relief (75–100% pain relief, minimal narcotic requirements, and return to work) in the short-term follow-up, and 8 of the 11 patients reported good to excellent pain relief at long-term follow-up. Even better results were reported by Robaina et al. (1989), who studied 8 patients with CRPS type I of the upper extremity. All had spinal cord stimulators permanently implanted. Seven of the 8 patients reported good to excellent pain relief (>75% pain relief); the eighth patient reported fair pain relief. The results of these and other studies indicate that SCS is beneficial in the most patients with CRPS.

In a literature review of SCS for chronic low back pain (the conclusions of which also apply to PNS), Turner et al. (1995), concluded that apart from the article by North et al. (1994), which is a preliminary report of a randomized cross-over trial currently in progress, no other prospective randomized trials were available for analysis. As a consequence, no conclusions regarding the efficacy of SCS for FBSS can be drawn and each study must be viewed on its own merits. Turner et al. (1995) found that criteria for the selection of patients for permanent SCS still varies

nonresectable peripheral vascular disease (1994). According to the Fontaine classification, 114 patients had stage III and 63 had stage IV disease. Clinical diagnosis was confirmed by ankle/brachial blood pressure index (ABI) of <0.40 and a toe blood pressure of <30 mm Hg; TcPO2 was used as a measure of changes in the skin circulation. In all, 77.9% (138 patients), 102 with stage III and 36 with stage IV disease had >75% reduction of their pain. At 6-month follow-up, 75% pain relief was noted in 62% (110 patients), but in 17 of the remaining 28 patients the initial improvement produced by stimulation had decayed. Severe ischemic pain again developed, requiring above-knee amputation in 1 patient with stage III and 5 patients with stage IV disease. Horsch and Claeys (1994) concluded that the main effect of SCS for ischemic pain is an improvement in the microcirculation, as evidenced by the change in $TcPO_2$ (Sciacca et al., 1986; Jacobs et al., 1988; Robaina et al., 1989).

The most dramatic effect of SCS in peripheral vascular disease is limb salvage. SCS has a salutary effect on ischemic ulceration <3 cm^2, but in even larger ulcers (>3 cm^2) SCS may decrease the spread of ulceration. This allows more conservative treatment of ischemic limbs and a reduction in the need for extensive debridements and amputation (Jacobs et al., 1990; Horsch and Claeys, 1994; Jivegard et al., 1995). Jivegard, et al. identified a limb salvage rate of 62% with SCS in comparison with 45% in their control group while Jacobs, et al. obtained a one and two year salvage rate of 80% and 56% respectively (Jivegard, et al., 1995).

Angina Pectoris

Oxygen deprivation and the failure of metabolite removal that results from reduced coronary perfusion is responsible for myocardial ischemia. This may be a result of either a reduction in the oxygen supply or an increase in its demand. The underlying cause in most cases is impaired coronary blood flow due to obstruction by underlying Arthromitus changes or to vasospastic factors.

The relief of pain either through use of vasodilators such as nitroglycerin or prophylaxis by reducing the myocardial oxygen demand and sympathetic efferent discharge through use of β-adrenoceptor blocking agents, and use of acetylsalicylic acid through its effects on platelet dysfunction are common treatment strategies.

In addition to patients with acute anginal pain, however, another group of patients who are either not considered appropriate candidates for invasive revascularization procedures and who are resistant to all medical treatment have been shown to respond favorably to SCS. One such group consists of patients who have angina pectoris with no objective signs of ischemia and who have normal coronary arteriograms. This group of signs and symptoms is termed syndrome X, and such patients are assumed to have small vessel disease.

Mannheimer (1984) reported that transcutaneous electrical nerve stimulation (TENS) was effective in some patients with angina pectoris. Initially, this was not accepted by the medical community, but since in some patients all other conventional strategies at the time had been exhausted, TENS, and later SCS, began to receive attention as having therapeutic potential (Mannheimer et al., 1982, 1988, 1989, 1993; Sanderson, 1990; Sanderson et al., 1992).

Resistance to the use of SCS remains entrenched, mainly due to a concern that the mechanism inhibits only impulse transmission of nociceptive information, thereby removing warning signals, from the cerebral cortex without affecting the primary mechanism, i.e., myocardial ischemia (Foreman et al., 1989; Chandler et al., 1993).

Although stimulation-induced alleviation of angina pectoris appears to be associated with an antiischemic effect, SCS has not been demonstrated to increase or redistribute myocardial blood flow (Mannheimer, et al., 1988; de Landsherre et al., 1992). Recent evidence shows that coronary blood flow velocity increases during the use of TENS both in patients with coronary artery disease and in those with normal coronary circulation (Chauhan, et al., 1994).

Although the exact mechanism of stimulation-induced relief of angina is unknown, SCS has been in use for treatment of cardiac ischemia since 1984. Although the standard treatment of angina pectoris is medical, with use of β-adrenoceptor and calcium blocking agents both to reduce myocardial oxygen demand and to increase its supply, nitroglycerin is the preferred treatment for acute myocardial ischemia. A few patients who remain refractory to medical and surgical treatment and continue to experience myocardial ischemia despite having normal coronary arteriograms (syndrome X) have responded well to the use of SCS (Eliasson et al., 1993); although the mechanism of pain relief is unclear, many studies have demonstrated improvement in myocardial function during SCS. Kujacic et al. (1993), using adenosine-induced left ventricular dysfunction, demonstrated significant improvement in patients with SCS as com-

pared with a control group. Lactate production, a reflection of pathological myocardial metabolism during atrial pacing is the gold standard for evoked myocardial ischemia (Thadani et al., 1979; Ihlen et al., 1983; Remme, 1992).

In a recent study of 28 patients with severe angina pectoris and coronary artery disease who were paced during treatment with SCS, Eliasson et al. (1996) observed reduced lactate production, less angina, and increased tolerance to pacing. At the maximum pacing rate, however, all patients experienced anginal pain similar in degree to that experienced during control pacing. Although lactate extraction reverted to production and myocardial oxygen consumption increased in magnitude to control values, the rate–pressure product increased to a point at which it was equal to its maximum control workload. This measurement has been shown to correlate well with myocardial oxygen consumption (Cohen et al., 1966). Although only a few patients were included in this study, the results are very promising.

Eliasson et al. (1996) concluded that SCS apparently produces beneficial effects on angina pectoris in patients with normal coronary arteriograms by reducing anginal symptoms and increasing exercise performance. They suggest that these effects occur by reducing myocardial ischemia. Mannheimer et al. (1993) also studied the effects of spinal cord stimulation in patients with pacing-induced angina pectoris. They showed an increased tolerance to atrial pacing, an increase in myocardial lactate metabolism, and a decrease in the magnitude and duration of ST changes during SCS. Other investigators (de Landsherre et al., 1992; Chauhan et al., 1994) speculate that the mechanism of SCS may be twofold: At rest, it is due to an increase in coronary blood flow and during periods of increased cardiac work or stress it is a result of a decrease in myocardial oxygen consumption.

In another study, Eliasson et al. (1994) evaluated the effects of SCS on patients with severe coronary artery disease and angina pectoris using electrocardiography (ECG). The particular aim of this investigation, using ambulatory ECG, was to determine whether SCS conferred any potentially unfavorable effects through analgesia or other undetermined aspect. The study protocol required a 24-h ECG recording before SCS implant; a second 24-h ECG recording was obtained, one without SCS and one with three 30 min periods of SCS during the recording period. SCS was also permitted for the relief of anginal attacks. The last two recordings were made on 2 consecutive days. All patients were admitted to the hospital during the actual study periods. SCS was not permitted for 48 h before the second part of the study; the time between the initial 24-h ECG with control recording and treatment recordings was 8 ± 8 months. The study findings did not support the view that SCS treatment in patients with severe coronary artery disease and angina pectoris might conceal any warning symptoms or aggravate myocardial ischemia. No increase in frequency of ischemic episodes, total ischemic burden, or number of arrhythmic episodes was noted during the course of treatment. The overall frequency of anginal attacks, as compared with their frequency during control, was reduced by stimulation, and this decrease was paralleled by the reduction in absolute numbers of ischemic episodes and the ischemic burden. These results did not reach statistical significance, however, possibly because of the small population sampled.

This protocol abolished ischemia in 6 patients during the hours that SCS was not in use. Ischemia was reduced in 3 of the remaining 4 patients. Eliasson et al. (1994) noted the potential for rebound ischemia after exercise when SCS is temporarily withheld and is possibly counterbalanced by the sustained antiischemic influence observed during the study. They concluded that the EKG is a useful monitor of SCS influence on myocardial ischemia and symptomatic ischemia as expressed by the reduction in total ischemic burden, the duration of ischemia, and the number of ischemic episodes, reduction of anginal attacks, and need for glyceryl trinitrate.

Another significant prospective, randomized clinical study of the efficacy of SCS in intractable angina pectoris determined that SCS significantly improves exercise capacity and quality of life. deJongste et al. (1994), in conjunction with the Working Group on Neurocardiology of the University of Groningen, The Netherlands, designed the endpoints of the study to correspond with exercise capacity by treadmill testing and quality of life, using standardized questionnaires. The control and final testing of patients took place after 6–8 weeks. Measured were the number of anginal attacks and use of sublingual nitroglycerin for a 2-week period both at baseline and during weeks 6–8. Subjects were randomized into one of two groups, one having the SCS implanted and adjusted within 2 weeks of group assignment; in the other group (control), the SCS was implanted after week 8 of the follow-up period. Patients excluded from SCS during their control period received stimulators under similar controls after 8 weeks. Long-term assessments were made at 14, 26, and 52 weeks of SCS; the results

were compared with their baseline values. Objective data including the left ventricular ejection fraction was assessed by radionuclide angiography at baseline and after 6 weeks of SCS. Other measures included 24-h ambulatory ECG recordings; these were analyzed for their average, minimal, and maximal heart rate and for ischemic episodes and arrhythmic events. ST segments were analyzed by laser. Ischemia was considered significant if 1 mm of ST depression was recorded during minute separated by at least 1-min intervals (deJongste et al., 1994).

Important aspects of the study related to exercise tolerance and quality of life have already been discussed. These results clearly show that SCS increases the anginal pain threshold, enabling an increase in exercise tolerance that is confirmed by the reduction in both symptomatic ischemia and clinically recognizable signs: ST segment depression during exercise. These findings have been verified by other observers (deJongste et al., 1994; Sanderson et al., 1994). Particularly germane to inherent criticisms of the technique are the observations that although electroanalgesic modulation of pain is fundamental to SCS, in this instance SCS did not suppress angina completely but significantly improved the quality of life for patients. deJongste et al. noted that the prolonged effects of SCS, which appeared to last for an entire day after only three daily applications for 1 h each day implies a supraspinal effect of SCS.

The long-term follow-up of 1 year showed all the exercise variables to be improved as compared with baseline variables. The time for an anginal episode and the time for ST segment depression at maximum exercise to occur showed a second-order trend. All other variables demonstrated a linear trend. SCS apparently can be an effective treatment for patients with intractable angina who have proved refractory to all other standard therapy. Ultimately, investigations that address both mortality and morbidity are needed. There have been two major concerns with the use of SCS in treatment of angina pectoris. First, the effects of SCS were speculated to be due in actuality to a placebo effect. However, the placebo effect decreases with time, whereas the therapeutic effects of SCS in angina pectoris remain unchanged even after years of use. Furthermore, if the simulation is interrupted (i.e. depletion of battery charge, dislodgment of lead), the beneficial effects of stimulation disappear and the frequency and duration of anginal attacks increases. With resumption of stimulation, the previous status quo is immediately restored. Second, researchers expressed concern that SCS only interrupted transmission of nociception from the heart without affecting ischemia might deprive the patient of a "warning signal." This might prevent the patient from taking appropriate action to terminate the ischemic episode, leading to the potential complications of arrhythmia, heart failure, myocardial infarction, or even certain cardiac death. Recent studies, however, have demonstrated that although SCS does decrease the number and frequency of ischemic episodes, it fails to mask pain of angina pectoris during an ischemic episode (Mannheimer et al., 1993; Eliasson et al., 1994).

A timely review of current studies and the indications for and contemporary clinical experience with SCS in the treatment of severe angina pectoris was recently published by Eliasson et al. (1996). One group of the researchers first described use of TENS and SCS for this purpose (Mannheimer et al., 1982). Safety aspects in addition to those already cited (Mannheimer et al., 1982, 1985, 1986, 1988, 1989, 1993, 1994; de Landsherre et al., 1992; Sanderson et al., 1992; Kujacic et al., 1993) confirm that the antianginal effect of SCS in severe coronary artery disease is secondary or is associated with an antiischemic effect. However, de Landsherre et al. (1992), using positron emission tomography (PET), detected no significant differences in regional myocardial perfusion in patients exercising under the influence of SCS.

Summarizing the clinical experience to date, we conclude first that chest pain must be related to current, reversible myocardial ischemia as determined by conventional exercise tests, myocardial nuclear imaging techniques, stress echocardiography, and long-term ECG monitoring (Holter technique). Second, a holistic evaluation should determine the cerebral status of prospective patients since most of them will have already undergone coronary bypass graft operations. The syndrome of diffuse cerebral damage with impairment of intellect or cognitive function may alter the perception of pain and give rise to pain behaviors that may determine a poor response to conventional therapeutic treatment (Shaw et al., 1986; Smith et al., 1986). Third, once the requirements for SCS are determined, the patient's spouse or nurse attendant must be familiar with the stimulation parameters so that they can be adjusted to obtain optimal topographic paresthesias in the appropriate dermatomal distribution of referred pain. Fourth, long-term follow-up showed that 80% of patients still obtained good effect from treatment, with reduced frequency of attacks and consumption of coronary vasodilators. Fifth, although placebo effects may contribute to the positive outcome, these decrease with time and are

widely. Although complications were reported to range from 20 to 75% of patients in all studies, they were mostly minor and most were electromechanical. Infection was reported to have having a mean incidence of 5%. Methodological problems in all of the studies reviewed received the greatest criticism, primarily due to their potential for statistical bias. Many of the studies did not report the total time of stimulator use by patients, and none reported an association between the amount of stimulator use and frequency of patients' symptoms. Therefore, we cannot draw conclusions as to which symptoms were actually influenced by SCS. Meta-analysis or any literature synthesis in itself is an imprecise tool, particularly when one is dealing with an evolving technology such as SCS (Turner et al., 1995). Neither is it possible to determine from the analyzed data whether the newer systems are associated with fewer complications than those reported in earlier publications. Although Turner et al. (1995) have suggested that randomized controlled trials of SCS would be optimal, it is difficult to conceive how such studies with sham stimulation and without paresthesias could be effective. However, the design of a randomized trial of SCS might be a more realistic type of investigation but would require cooperation with the third-party payor, a situation which today is highly unlikely. This type of review or complete meta-analysis, while providing interesting information, cannot replace the data that are acquired by carefully designed clinical trials. Healthcare agencies such as the Agency for Healthcare Policy and Research (AHCPR) could provide the impetus to initiate the types of outcome studies that will ultimately be mandatory for evaluation of developing and existing therapy.

PAIN OF VASCULOPATHY

SCS in peripheral vascular disease

In 1976, Cook et al. demonstrated the remarkable improvement of lower limb blood flow in a group of patients treated with SCS for multiple sclerosis. Both neuropathic pain and pain of ischemic origin are now recognized as primary indications for SCS. In addition to the proposed neurophysiological mechanisms that underlie pain control by SCS, the relief of pain arising from peripheral vascular disease occurs in parallel with improvement in ischemic circulation and is therefore independent of central or supraspinal control of pain. Its mechanism is most likely the facilitation of transmission through the ventral roots of the spinal cord, including preganglionic efferent sympathetic pathways (Krainick and Thoden, 1975; Linderoth et al., 1991, 1994; Coburn, 1992; Illis, 1992; Illis and Krainick, 1992; Linderoth, 1992, 1993). The effect is believed to be suppression of sympathetic vasomotor control (Augustinsson et al., 1992; Linderoth, 1993).

Ischemic conditions that have a significant vasospastic component respond more favorably to SCS (the greater the remaining vascular compliance, the more effective the stimulation). Ischemia that is secondary to degenerative or arthrosclerotic disease processes precludes an effective response to stimulation.

Although both neuropathic and ischemic pain can be alleviated by SCS, basic differences between the two pain mechanisms are apparent. First, the location of the paresthesias is more critical in neuropathic pain than in ischemic pain. In neuropathic pain, thoracic or cervical stimulation may be effective in relieving leg pain if the paresthesias cover the affected areas. SCS-induced unilateral paresthesias for patients with vascular pain, however, may produce bilateral vasodilatation, a temperature increase, and excellent relief of pain. Second, in neuropathic pain, paresthesias may not be accompanied by a subjective temperature change (either increase, decrease, or no change). Typically, in pain of ischemic origin, the stimulation-induced paresthesias, when effective, are accompanied by a subjective feeling of warmth (Linderoth et al., 1987). Third, the time to effective relief of pain is significantly longer. Although pain relief in neuropathic states occurs almost immediately ($\leq$10 min) after stimulation is initiated, 2–3 days may elapse before the effects of SCS are realized. Although microcirculatory changes occur rapidly, reperfusion and its effect on ischemic tissues may require a much longer period before ischemic pain is relieved. For this reason, ischemic vasospastic pain will respond much more rapidly to SCS than will ischemic pain due to degenerative or obliterative processes (Robaina et al., 1989).

Although SCS-induced relief of ischemic pain is the result of reperfusion in affected vascular beds (Linderoth et al., 1987; Jacobs et al., 1988, 1990), some researchers believe that it results from interruption of nociception (Broseta et al., 1986; Hosobuchi, 1990). Initially, the mechanism of stimulation-produced microvascular changes in the peripheral circulation was believed to derive from antidromic activation of primary afferent fibers, including unmyelinated, high-threshold, small-diameter fibers (Hilton et al., 1980). This view is unlikely for a several reasons: (a) Stimulation intensities are too low to stimulate these fibers:

TABLE 1. *Fontaine classification of stages of peripheral vascular disease*

Stage	Symptoms
I	No symptoms
II	Intermittent claudication
III	Rest and night pain without tissue involvement
IV	Grade III + tissue loss (ulcers, gangrene)

(b) stimulation frequencies exceed the maximum firing rate of these fibers; (c) patients do not experience the stimulation as painful; and (d) sectioning of the dorsal roots does not abolish the effects of stimulation (Linderoth et al., 1991). An alternative hypothesis proposes that SCS alters autonomic activity through a spinal cord effect. An increase in preganglionic sympathetic activity is generally believed to be associated with ischemic disease, the effect of SCS being to blunt this response (Augustinsson et al., 1985; Linderoth et al., 1987). Several associated autonomic changes, including changes in heart rate, skin temperature, and bladder tone, occur during SCS (Augustinsson et al., 1982; Broseta et al., 1986).

This hypothesis has been challenged, however, by the observation that SCS is effective in many patients who have undergone previous chemical or surgical sympathectomies (Broseta et al., 1986; Jacobs et al., 1988; Hosobuchi, 1990; Jacobs et al., 1990). This argument was recently challenged by animal studies demonstrating that if the sympathectomy is complete the stimulation-induced vasodilatory response is abolished (Linderoth, et al., 1991; Naver et al., 1992).

The sequelae of peripheral vascular disease, pain, ulceration, gangrene and even amputation are all related to a decrease in blood flow, i.e., ischemia of the limb. Unlike in angina pectoris, the mechanism of stimulation-induced response in peripheral vascular disease appears to be directly related to the increase in peripheral blood flow. Dooley et al. demonstrated arterial dilatation as measured by plethysmography with SCS (Dooley et al., 1976; Law and Miller, 1982). Subsequent studies have borne out this observation by using Doppler (Broseta et al., 1985; Broseta et al., 1986) and xenon clearance methods (Tallis et al., 1982).

Patient selection is critical to the use of SCS for peripheral vascular disease. Patients considered appropriate for SCS are those in whom medical management of their ischemia has failed and who, in addition, are not candidates for vascular reconstructive surgery. The main subjects to be selected are patients in group III of the Fontaine classification (Table 1).

SCS has been provided for patients in stage II and IV with less successful results. Patients with stage II disease have a decrease in pain in response to SCS stimulation, but not to the same degree as those with pain at rest (stage III) (Augustinsson et al., 1992). Patients with stage IV disease also respond to stimulation, and ischemic ulcers <3 cm^2 have been demonstrated to heal well in response to stimulation (Fiume et al., 1989). Ulcers >3 cm^2 rarely heal, but there may be an improvement in the demarcation of ischemic tissue, an improvement in circulation of the base of the ulcer, and a decrease in extension of ulceration. Unfortunately, no improvement in gangrenous conditions is realized (Broseta et al., 1986).

The most common indication for SCS in peripheral vascular disease is pain at rest. Younger patients with primary vasospastic disorders (i.e., Raynaud's disease) (Robaina et al., 1989; Francaviglia et al., 1994) respond more favorably than older patients with degenerative or obliterative vascular conditions, but even these patients show efficacious responses. The disease states responding most favorably to SCS are collagen vascular disease (Francaviglia et al., 1994), diabetes mellitus and diabetic arteriopathy (Franzetti et al., 1989), arteriosclerosis, and complex regional pain syndromes (Type I and Type II) (Barolat et al., 1989). Numerous studies have confirmed the efficacy of SCS for the relief of ischemic pain (Tallis et al., 1982; Fiume, 1983; Tallis et al., 1983; Broseta et al., 1985; Broseta et al., 1986; Barolat et al., 1987; Bracalle et al., 1989; Franzetti et al., 1989; Hosobuchi, 1990; Francaviglia et al., 1994). Negative prognostic factors for SCS are advanced age, subtotal vessel occlusion by obliterative or degenerative processes, diabetes mellitus, and hypertension (Augustinsson et al., 1992) (Jivegard et al., 1995).

Although an important effect of SCS is the relief or decrease in ischemic pain, the more significant effect may be the increase in blood flow, especially at a capillary level, that has been demonstrated by several studies (Tallis et al., 1982; Broseta et al., 1985; Broseta et al., 1986). The secondary effect on skin temperature and increased oxygen delivery as measured by transcutaneous oxygen tension ($TcPO_2$) has been demonstrated by several investigators (Broseta et al., 1985; Broseta et al., 1986; Barolat et al., 1987). Fiume, et al., noted that only patients who had an increase in $TcPO_2$ actually had an improvement in their ischemic symptoms (primarily pain reduction) (Fiume, 1983).

One of the first significant investigations of SCS for ischemic vascular pain was that of Horsch and Claeys, who from 1986 to 1992 evaluated 177 patients with

negligible after 2–3 months (White et al., 1985). Sixth, SCS is a safe and effective method for the treatment of severe angina pectoris and appears to achieve its effect through both antianginal and antiischemic properties. Finally, patient selection is of the utmost importance to determine suitability of SCS.

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