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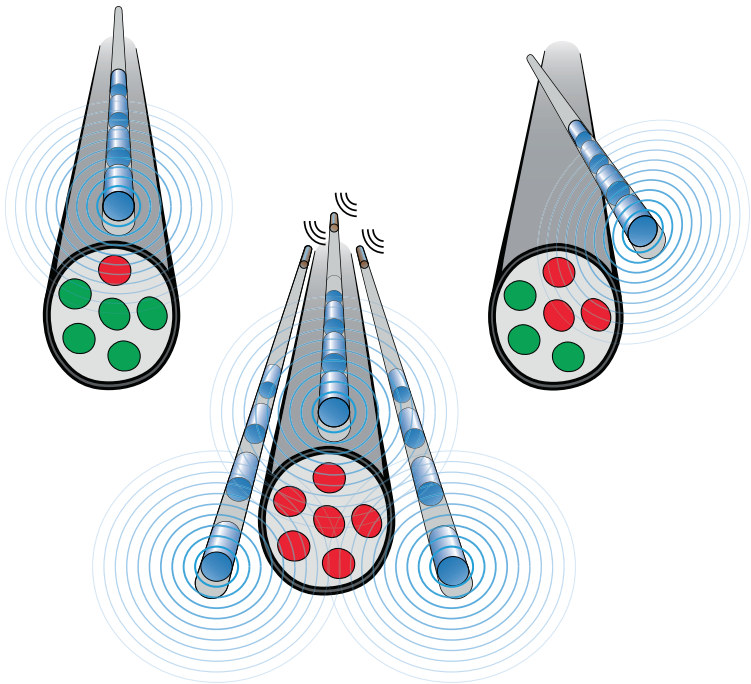
Stimulation of the Peripheral Nervous System

The Neuromodulation Frontier

Editor
K.V. Slavin



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Series Editor

L. Dade Lunsford Pittsburgh, Pa.

Stimulation of the Peripheral Nervous System

The Neuromodulation Frontier

Volume Editor

Konstantin V. Slavin Chicago, Ill.

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Series Editor's Note

As a series editor of *Progress in Neurological Surgery*, I would like to congratulate Dr. Slavin and the coauthors of this new update on the role of advanced stimulation technology in the management of patients with epilepsy, chronic pain, depression, treatment-resistant hypertension, obstructive sleep apnea, and other innovative indications.

The increasing adoption of peripheral nerve stimulation for a wide variety of patient conditions is a testament to the remarkable ingenuity and perseverance of this group of clinicians and investigators. Peripheral nerve stimulation techniques have continued to expand and have proven to be safe and effective for diverse conditions, often in clinical situations where virtually no other therapeutic option exists. The authors, who come from multidisciplinary backgrounds, work at centers with special expertise in the analysis and development of these technologies. The authors provide a striking example of how persistence and innovation pays off in terms of improving patient outcomes. This update on the current status of peripheral nerve stimulation should be a valuable resource to the field of neurosurgery and pain management specialists. I am sure it will become an important reference for specialists who care for these diverse patient problems that also include respiratory, gastrointestinal, genitourinary, and cardiac indications. The possibilities for neuromodulation have greatly expanded beyond its earlier role in the treatment of chronic pain and medically refractory epilepsy.

L. Dade Lunsford, MD, Pittsburgh, Pa.

Preface

In the most common impression, the term 'peripheral nerve' refers to the large nerves that travel through the trunk and extremities carrying motor, sensory, and autonomic information. These 'peripheral nerves' are then differentiated from 'cranial nerves' and used synonymously to the actual alternative of the cranial nerves, the spinal nerves. Even the most commonly used list of medical procedures, the Current Procedural Terminology (CPT) [1], differentiates interventions performed on 'peripheral' and 'cranial' nerves – thereby adding to the confusion in terminology.

Anatomy, however, is a precise science and anatomical terminology is very well defined. Even the most accepted compendium of anatomical terminology, the medical dictionary, provides clear division of the nervous system into central and peripheral parts, defining the peripheral nervous system as everything outside of the brain and spinal cord [2]. In vertebrates, mammals, primates, and humans, the central nervous system includes the brain and the spinal cord. According to the authoritative book *The Peripheral Nervous System* [3], the subject of the book's title is defined as the cranial nerves, spinal nerves, and peripheral ganglia which lie outside the brain and spinal cord. With this scheme, all nerves that originate from the cranial part of the central nervous system – the cranial nerves (with the exception of the olfactory and optic nerves which are considered parts of the central nervous system) – and all those that originate from the spinal cord – the spinal nerves – fall under the same category of the peripheral nerves, and this categorization is supported by their anatomy, histology, and physiology.

This discrepancy between a common misconception (i.e. peripheral nerves differ from cranial nerves) and the actual anatomophysiological similarity became obvious after the first volume of *Peripheral Nerve Stimulation* was published in 2011 [4]. Multiple clinical applications of cranial nerve stimulation remained omitted as most chapters concentrated on those nerves that travel through the trunk and extremities. Not surprisingly, those applications that dealt with indications other than pain (epilepsy, depression, sleep apnea, etc.) were not included in the book, as most of them specifically involve stimulation of the cranial nerves (vagus, hypoglossal). Along with these, the stimulation of the phrenic nerves used for respiratory insufficiency was left uncovered even though there is no controversy about phrenic nerve stimulation being

a 'true' example of peripheral nerve stimulation (PNS). Moreover, several applications of neuromodulation that would not fall under strict definition of PNS, but instead represent so-called 'peripheral neurostimulation' – i.e. stimulation of the trigeminal ganglion, dorsal root ganglion, sacral nerves, and nerve roots – are covered in this second part of *Peripheral Nerve Stimulation* from the popular and well-established series *Progress in Neurological Surgery*.

In addition to all of these new topics, this volume includes other important chapters. One of them deals with theoretical and technical aspects of peripheral nerve interface with neurostimulation devices. Others describe principles of wireless energy transmission that are used in modern miniaturized neuromodulation devices and characteristics of high-frequency PNS that results in a block of nerve conduction. Several chapters are dedicated to in-depth updates on the most common PNS indications, such as migraines, low back pain, and pain in extremities. Not surprisingly, the field of PNS is rapidly progressing, and as our experience grows, so does our understanding of surgical indications, proper patient selection, technical nuances of operative procedures, and complication-avoidance techniques. Instead of case reports and small retrospective single-surgeon or single-institution studies, we now have multicenter prospective studies that may be used in critical analysis of clinical evidence that could justify our interventions.

The growing clinical experience is paralleled by industrial developments. Instead of routinely using devices designed for spinal cord stimulation in PNS applications, there are now more than a dozen device-manufacturing companies that dedicate themselves to the creation of a new generation of electrodes and generators specifically designed for PNS use. Miniaturization, rechargeability, wireless interfaces, and customized designs – terms that only recently were considered futuristic and not applicable to PNS – are becoming reality at a very rapid pace.

The final chapter of this volume deals with regulatory aspects of PNS and related applications since over the last few years the field of peripheral neuromodulation has enjoyed several important approvals, mainly in Europe, Canada, and Australia, making PNS, once again, a legitimate intervention in the spectrum of available interventions, alongside spinal cord stimulation and deep brain stimulation approaches.

Even though this is yet another volume in *Progress in Neurological Surgery*, not all interventions covered here are performed by the neurosurgeons. The uniqueness of the neuromodulation field is that it blossomed at the intersection of multiple medical specialties, including neurosurgery, neurology, anesthesiology, physiatry, orthopedics, cardiology, urology, gastroenterology, otolaryngology, pulmonology, psychiatry, oral surgery, colorectal surgery, and others – the field of PNS undoubtedly brings together physicians from different backgrounds. One has to keep in mind, however, that the implantable nature of neuromodulation still requires surgery, and the substrate of our interventions is still the nervous system. And who would be better qualified for surgery on the nervous system than neurosurgeons? Being a neurosurgeon myself, I can already hear the criticism from my nonneurosurgical colleagues who perform the

overwhelming majority of neuromodulation procedures, including PNS and spinal cord stimulation, and who over the years have become much more comfortable with reaching the nerves all over the human body. And since I have taught hundreds of them how to make neuromodulation procedures safer, I feel confident that this volume will be of interest to the entire neuromodulation community, reflecting the interdisciplinary nature of our field and, among other things, reminding myself and other neurosurgeon readers what we may be missing!

Konstantin V. Slavin, MD, FAANS, Chicago, Ill.

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Technology for Peripheral Nerve Stimulation

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Abstract

Peripheral nerve stimulation (PNS) has been in use for over 50 years to treat patients suffering from chronic pain who have failed conservative treatments. Despite this long history, the devices being used have changed very little. In fact, current PNS technology was developed specifically for spinal cord stimulation. The use of technology developed for other applications in PNS has led to an unnecessary number of device complications and the limited adoption of this promising therapy. The following chapter provides an overview of PNS technology throughout the years, outlining both the benefits and limitations. We will briefly explore the electrophysiology of PNS stimulation, with an emphasis on technology and indication-specific devices. Finally, design and technical requirements of an ideal PNS device will be discussed.

Peripheral Nerve Stimulation Technology Throughout the Years

Compared to other types of medical devices, technological advances in peripheral nerve stimulation (PNS) have been rather few and far between. Only a few minor improvements have been made over the years and many of these improvements have been the result of the application of new technology developed in other neuromodulation therapies such as spinal cord stimulation (SCS). The following sections summarize PNS technology (fig. 1), with an emphasis on device complications and limitations.

Early Devices

The earliest recorded use of PNS was in 1962 by Shelden [1] who implanted 3 patients for the indication of pain due to trigeminal neuralgia. This was several years before the publication of the gate control theory [2] and was based on the rationale of

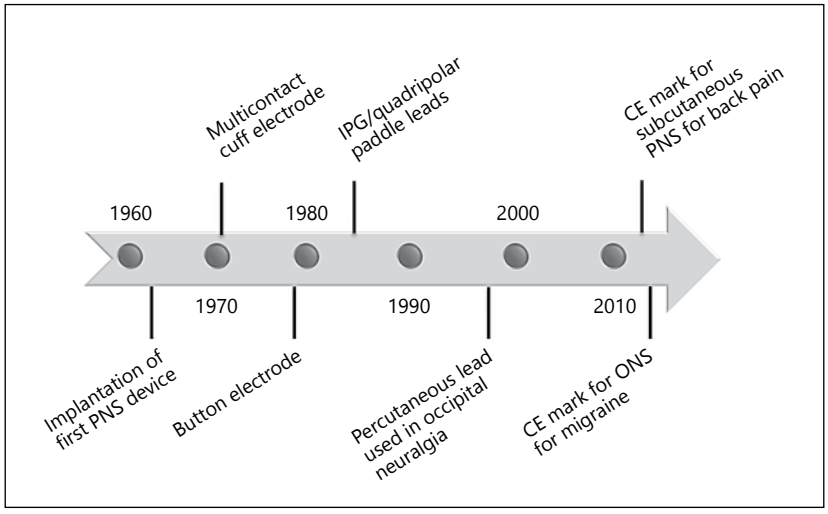

Fig. 1. Timeline of the significant technological changes since the inception of PNS. ONS = Occipital nerve stimulation.

depressing excitatory transmission by depolarization of the nerves [3]. The device was fully implantable and powered by an external radiofrequency (RF) generator. The RF device was capable of delivering 10 V at a frequency of 14.5 kHz. Shelden implanted platinum electrodes over the mandibular division of the trigeminal nerve in all 3 patients. One patient reported favorable outcomes up to 31 months after surgery. Single case reports by other researchers appearing around the same time [4] found stimulation of a variety of peripheral nerves was able to suppress chronic pain caused by complex regional pain syndrome and neural trauma.

PNS with RF generators and nerve cuff electrodes became much more common in the 1970s [5–8]. A device described by Long [5] in 1973 had the bipolar or monopolar electrodes wired directly to the RF-receiving coil. This required that the location of the receiving coil be determined by the position of the stimulating electrode. Long reported complete pain relief in 6 out of 10 patients. He found the device to be more efficacious in the upper extremities than the lower, likely due to increased difficulty in implanting electrodes in the hip area. Long did not report any complications due to the device. Patient selection was performed by a short period of percutaneous trial stimulation (in the order of minutes) with cordotomy electrodes connected to either a StimTech (StimTech Corporation, Minneapolis, Minn., USA) or Medtronic (Medtronic, Minneapolis, Minn., USA) external stimulator (1-ms pulse width, 10–25 pulses/s, 1–4 V).

Campbell and Long [6] continued to implant and reported a further 33 patients also using a bipolar nerve cuff and RF receiver. Electrodes were wrapped around the nerve corresponding to the area of the patient's pain (sciatic, brachial plexus, median, and ulnar nerves). They reported an overall success rate of 45%. Of the 17 failures, 12 were in patients with either low back pain with sciatica or pain from metastatic disease.

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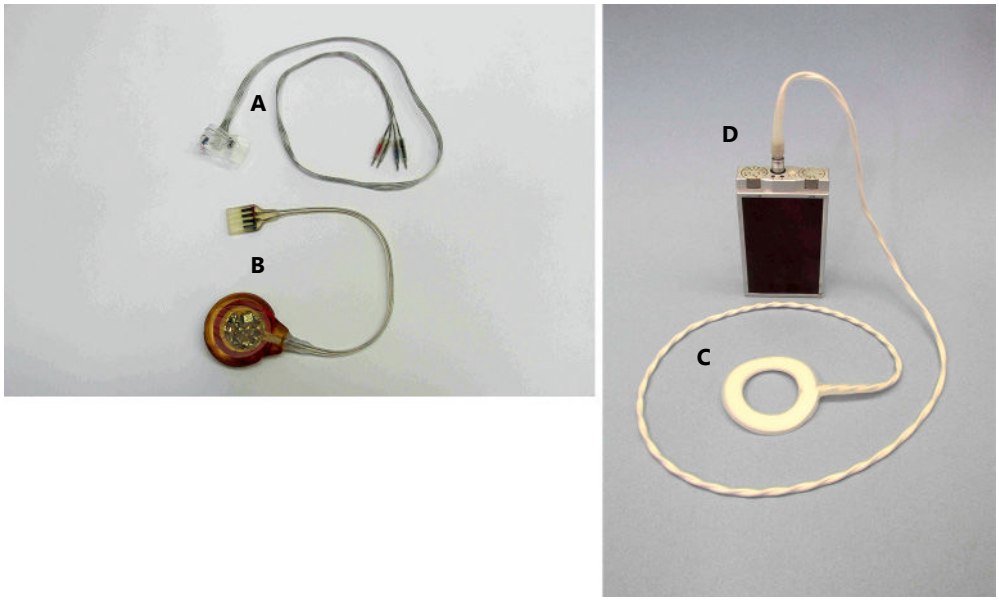

Fig. 2. Photograph of the Avery PNS system: (**A**) quadripolar cuff electrode, (**B**) radio frequency receiver, (**C**) external antenna, and (**D**) external stimulator (image courtesy of Avery Biomedical Inc., reprinted with permission).

Complications included two infections, 1 tissue reaction, 1 soreness over the receiver, 1 motor activation, and 1 wire disconnection.

In summary, the first generation of PNS devices showed the promise of peripheral stimulation to treat chronic pain, but they were limited by the hard-wired connection between the RF receiving coil and electrodes and the number of electrodes that could be stimulated at any one time.

Second-Generation PNS Devices

The next generation of devices employed quadripolar cuff electrodes developed by Avery Laboratories (Farmingdale, New York, N.Y., USA; fig. 2). As well as having multiple contact electrodes, this system had a connector between the leads and the generator, allowing greater flexibility in receiver location.

Law et al. [8] in 1980 reported on 22 chronic pain patients implanted with multiple contact cuff electrodes from Avery Laboratories. Despite the benefit of the extra contacts, the RF receiver was only capable of controlling two electrodes at a time (anode and cathode), and patients were therefore required to undergo a trial period during which the electrode lead was percutaneously passed to a switching box and the different combinations of electrodes were tested (fig. 3). When the optimal electrode configuration was determined, the switch box was disconnected and the selected

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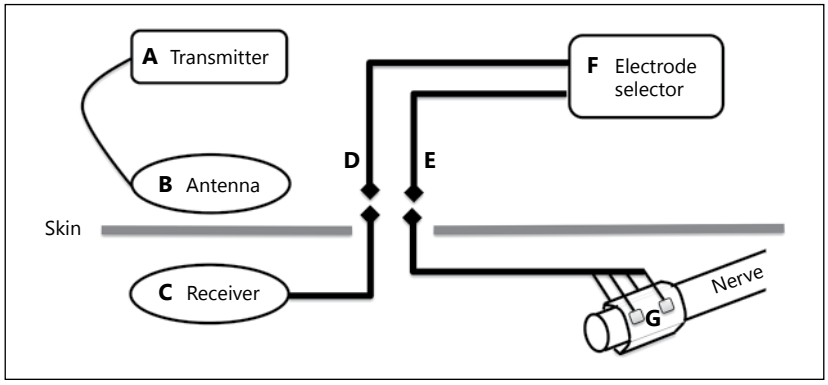

Fig. 3. Schematic representation of the components of the Avery PNS system. Before internalization of the lead, the electrodes (**G**) are connected by wires (**E**) and connectors (**D**) to the electrode selector (**F**); when the optimal electrodes are determined, they are connected to the internal receiver (**C**). Stimulation is transmitted to the receiver (**C**) via an antenna (**B**) attached to the transmitter (**A**).

electrodes were attached to the receiver and internalized. With this technique Law et al. reported a success rate of 62% for an average follow-up of 25 months. However, 50% of the patients required multiple operations to change the electrode selection. Other complications included equipment failure and repositioning of the connector, and a total of 6 patients required device removal, mainly due to lack of efficacy. It was clear from this early experience that electrode position played a critical role in the efficacy of treatment.

Waisbrod et al. in 1985 [9] reported on 19 chronic pain patients implanted with the Avery Laboratories device. Patients underwent a preimplantation trial using a percutaneous needle (stimulation 80–100 Hz, 0.3 V) for approximately 30 min. To qualify for implantation, each patient was required to have at least 50% reduction in pain. Patients were then implanted with a nerve cuff, attached to a cable buried subcutaneously. Two days later, patients returned to evaluate different electrode combinations for optimal pain relief. Waisbrod et al. reported a success rate of 84%. Complications included two skin erosions at the implant site, one necrosis of the cables, and one infection.

A series of 35 patients implanted with peripheral nerve stimulators from 1970 to 1979 was reported by Nashold et al. [10] in 1982. Electrodes were implanted on the median, ulnar, and radial nerves in the upper extremities and on the sciatic and tibial nerves in the lower extremities. Success in the upper extremities was higher (52.6%) than in the lower extremities (31%). They attributed their failures in the lower extremity to the stress of weight-bearing and anatomical positioning.

In 1979, Nashold et al. [11] replaced the cuff electrode with a newly developed PNS electrode with button contacts that could be sutured directly to the nerve. This new electrode eliminated complications associated with using a nerve cuff such as nerve compression and electrode rotation [12].

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The Avery system was used for many years; however, by the mid-1980s the RF receiver began being replaced with an implantable pulse generator (IPG) [13]. The RF device provided good pain relief, but a drawback was the need to have an external coil attached to the skin to operate. This often resulted in skin irritation and the need to wear the external controller reduced patient compliance. In addition, these devices could not be used 24 h/day, e.g. during bathing or other activities that involved water. The fully implantable generator eliminated these issues.

In 1990, Racz et al. [14] also described modifications in the lead implantation technique. Most notably, the electrode was covered with a thin fibrous membrane made from intramuscular septa in order to reduce the foreign body reaction related to direct electrode contact with the nerve. The focus of PNS up to this point was targeting specific nerves and implantation of electrodes very close to the nerves.

This focus continued with clinicians exploring the use of multipolar paddle leads commercially developed by Medtronic for SCS. Strege et al. [15] in 1994 reported on their initial experience using a 4-contact paddle lead with an RF stimulator (Resume/X-trel transmitter/receiver unit, Medtronic). This system, like that of Avery Laboratories, used a polyurethane-covered receiver unit implanted subcutaneously and required that a portable transmitter unit be carried at all times to activate the receiver through an antenna placed over the skin. Strege et al. later switched to a 4-contact IPG (Itrel System, Medtronic). This IPG could be programmed through the skin using telemetry and required no external unit to maintain stimulation. Both systems provided good results with a combined success rate of 62.5%. Complications included hardware problems with the generator, electrode migration, and foreign body reaction. The above technology continued to be used through the 1990s with good success and is still an option for patients with pain generated by a single easily accessible nerve.

Introduction of Percutaneous Leads for Peripheral Nerve Stimulation

The first documented use of percutaneous leads implanted to stimulate a peripheral nerve was in 1982 by Urban and Nashold [16], who described a technique combining SCS and PNS. They placed the percutaneous lead over the peripheral nerve by first inserting the lead epidurally and then advancing it through the intervertebral foramen (fig. 4). The peripheral electrode was placed percutaneously and positioned along the course of the anterior division of the spinal nerve anterolateral to the vertebral bodies. Their patients were implanted with the Avery percutaneous electrical bipolar nerve stimulator for PNS (50–400 μs, 7–200 Hz, and 0–14 V) and the Medtronic system for SCS (monophasic square wave 0.1- to 1-ms pulse width, 1–120 Hz, 0–10 V).

Urban and Nashold's study [16] examined stimulation from both epidural and peripheral leads in 23 patients with intractable leg pain. During implantation, patients were assessed to determine the location of the paresthesia with respect to their pain. After intraoperative assessment, 16 patients proceeded to chronic stimulation.

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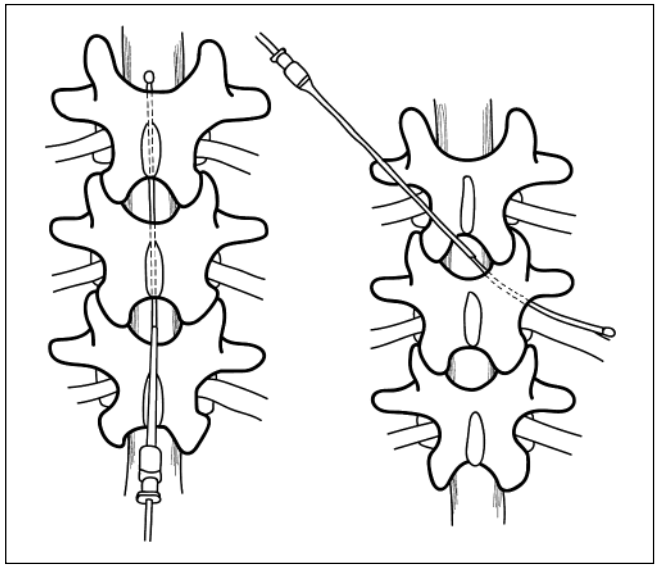

Fig. 4. Schematic illustration of the SCS (left) and PNS (right) electrode placement.

Peripheral electrodes were placed on the lumbar and first sacral nerves. The overall success rate for patients implanted with both SCS and PNS was 62.4%. One patient was lost to follow-up after 1 month. Only a few late complications of a minor nature were reported and the overall results were similar to those from conventional epidural spinal cord stimulator implantation.

Although Urban and Nashold [16] reported good success with the use of a percutaneous lead to stimulate a peripheral nerve, it did not become popular until 1999 when Weiner and Reed [17] treated occipital neuralgia by applying a percutaneous lead over the greater occipital nerves. This report prompted many clinicians to begin placing percutaneous leads in the periphery to treat a variety of disorders including trigeminal neuropathy [18], supraorbital neuralgia [19], cluster headache [20], and chronic migraine [21]. All the leads, anchors, and generators used in these studies were designed for SCS. Although there was an attempt to increase the lead spacing and development of a curved Tuohy needle [22], very little of the existing SCS device was modified for this new application. This led to a number of hardware complications related specifically to the implantation procedure including lead migration, lead breakage, pain at the lead site, and skin erosion [21, 23]. In 2007, Schwedt et al. [24] found that by 3 years all patients required revision surgery due to lead migration, and 42% also had their batteries reach end of life prematurely, likely due to higher than expected stimulation voltage requirements. This latter complication led to the adoption of rechargeable generators, but the lead migration and other lead-related issues remain open with the current technology.

In addition to the stimulation of the nerves of the head and neck, a number of researchers have placed percutaneous leads over the nerve roots using various

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techniques. The original transspinal approach of Urban and Nashold [16] has been modified to include simply guiding an epidurally placed lead laterally in the epidural space so that it lies over the targeted nerve roots. A transforaminal approach goes one step further by directing the lead out through the neural foramen [25]. An extraforaminal stimulation procedure avoids the spinal canal completely by placing the lead directly into the neural foramina [26]. It must be noted that all these techniques use current SCS technology and are associated with all the standard SCS complications, in addition to possible nerve root damage.

A more recent addition to the peripheral nerve approach is to not necessarily target a specific nerve, but to place leads in the periphery in the location of the pain [27]. Leads have been placed under the skin to successfully treat low back pain [28, 29], inguinal pain [30], axial neck pain [31], intractable abdominal pain [32], and postherpetic neuralgia [33]. The hardware used with all these techniques was designed for SCS. The result has been a number of complications such as lead migration, lead fracture, and connector failures, with many of these due to the high degree of motion exerted on the hardware in these locations. In addition, this technique is known to be prone to lead and anchor erosion because the location of the lead can be very superficial. To address the issue of lead migration, paddle type electrodes have been used successfully to treat migraines [34–36] and low back pain [37].

Other Devices

Some specialized devices designed specifically for peripheral nerve applications are starting to be developed. These include both percutaneous devices and fully implanted devices targeted for specific nerves.

Percutaneous electrical nerve stimulation is an approach that uses needle electrodes inserted under the skin whereby the tissue is stimulated for a period of time and then the electrodes are removed (Algotec, Crawley, UK). Percutaneous electrical nerve stimulation has been used to treat low back pain [38], diabetic neuropathy [39], and headache [40]. The therapy usually involves three 30-min treatments per week for 3 weeks. In 2000, Hamza et al. [39] found a statistically significant improvement in pain VAS scores before and after stimulation as well as improved physical activity, sense of well-being, and quality of sleep. No side effects were found with this treatment. However, this technique suffers from the same issues as RF-coupled systems in terms of diminished patient compliance and that effective pain relief requires patients to return to the clinic for multiple treatments.

An implantable device that has been developed to be used anywhere in the periphery is the microstimulator. Originally developed to be used to reanimate paralyzed muscle, this device was later redesigned by Boston Scientific to be used in the management of chronic pain conditions and renamed the Bion™ (Boston Scientific, Marlborough, Mass., USA; fig. 5). The microstimulator is a small cylindrical bipolar stimulator

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