45 Years of Neuromodulation

January 2013

Hello

My name is Keith Mullett. I was privileged to be a Medtronic employee for 37 years from my hire date, 15 May 1972, until my retirement, 30 April, 2009. My entire Medtronic career was with the Neurological Division, half at the Division Headquarters in Minneapolis and half at the Bakken Research Center in Maastricht.

19 November 1965, Volume 150, Number 3699 SCIENCE

Pain Mechanisms: A New Theory

A gate control system modulates sensory input from the skin before it evokes pain perception and response.

Ronald Melzack and Patrick D. Wall

The nature of pain has been the subject of bitter controversy since the turn of the century (*1*). There are currently two opposing theories of pain: (i) specificity theory, which holds that pain is a specific modality like vision or hearing, "with its own central and peripheral apparatus" (*2*), and (ii) pattern theory, which maintains that the nerve impulse pattern for pain is produced by intense stimulation of nonspecific receptors since "there are no specific fibers and no specific endings" (*3*). Both theories derive from earlier concepts proposed by von Frey (*4*) and Goldscheider (*5*) in 1894, and historically they are held to be mutually exclusive. Since it is our purpose here to propose a new theory of pain mechanisms, we shall state explicitly at the outset where we agree and disagree with specificity and pattern theories.

Specificity Theory

Specificity theory proposes that a mosaic of specific pain receptors in body tissue projects to a pain center in the brain. It maintains that free nerve endings are pain receptors (*4*) and generate pain impulses that are carried by A-delta and C fibers in peripheral nerves (*6*) and by the lateral spinothalamic tract in the spinal cord (*2*) to a pain center in the thalamus (*7*). Despite its apparent simplicity, the theory contains an explicit statement of physiological specialization and an implicit psychological assumption (*8, 9*). Consider the proposition that the skin contains "pain receptors." To say that a receptor responds only to intense, noxious stimulation of the skin is a physiological statement of fact; it says that the receptor is specialized to respond to a particular kind of stimulus. To call a receptor a "pain receptor," however, is a psychological assumption: it implies a direct connection from the receptor to a brain center where pain is felt (Fig. 1), so that stimulation of the receptor must always elicit pain and only the sensation of pain. This distinction between physiological specialization and psychological assumption also applies to peripheral fibers and central projection systems (*9*).

The facts of physiological specialization provide the power of specificity theory. Its psychological assumption is its weakness. As in all psychological theories, there is implicit in specificity theory the conception of a nervous system; and the model is that of a fixed, direct-line communication system from the skin to the brain. This facet of specificity theory, which imputes a direct, invariant relationship between stimulus and sensation, is examined here in the light of the clinical, psychological, and physiological evidence concerning pain.

Clinical evidence. The pathological pain states of causalgia (a severe burning pain that may result from a partial lesion of a peripheral nerve), phantom limb pain (which may occur after amputation of a limb), and the peripheral neuralgias (which may occur after peripheral nerve infections or degenerative diseases) provide a dramatic refutation of the concept of a fixed, direct-line nervous system. Four features of these syndromes plague patient, physician, and theorist (*8, 10*).

1) Surgical lesions of the peripheral and central nervous system have been singularly unsuccessful in abolishing these pains permanently, although the lesions have been made at almost every level (Fig. 2). Even after such operations, pain can often still be elicited by stimulation below the level of section and may be more severe than before the operation (*8, 10*).

2) Gentle touch, vibration, and other nonnoxious stimuli (*8, 10*) can trigger excruciating pain, and sometimes pain occurs spontaneously for long periods without any apparent stimulus. The fact that the thresholds to these stimuli are raised rather than lowered in causalgia and the neuralgias (*10*), together with the fact that referred pain can often be triggered by mild stimulation of normal skin (*8*), makes it unlikely that the pains can be explained by postulating pathologically hypersensitive "pain receptors."

3) The pains and new "trigger zones" may spread unpredictably to unrelated parts of the body where no pathology exists (*8, 11*).

4) Pain from hyperalgesic skin areas often occurs after long delays, and continues long after removal of the stimulus (*10*). Gentle rubbing, repeated pin pricks, or the application of a warm test tube may produce sudden, severe pain after delays as long as 35 seconds. Such delays cannot be attributed simply to conduction in slowly conducting fibers; rather, they imply a remarkable temporal and spatial summation of inputs in the production of these pain states (*8, 10*).

Psychological evidence. The psychological evidence fails to support the assumption of a one-to-one relation-

Dr. Melzack is associate professor in the department of psychology at McGill University, Montreal, Canada. Dr. Wall is professor in the department of biology at the Massachusetts Institute of Technology, Cambridge.

19 NOVEMBER 1965 971

Fig 1

Pat Wall 1925 – 2001
Ron Melzack 1929 -

I point to 1965 as the beginning of Neuromodulation. It was that year that psychologist Ron Melzack (Fig 1, right), Canadian from McGill University, and physiologist Pat Wall (left), Englishman working at Massachusetts Institute of Technology, combined to publish this paper, "Pain Mechanisms: A New Theory".

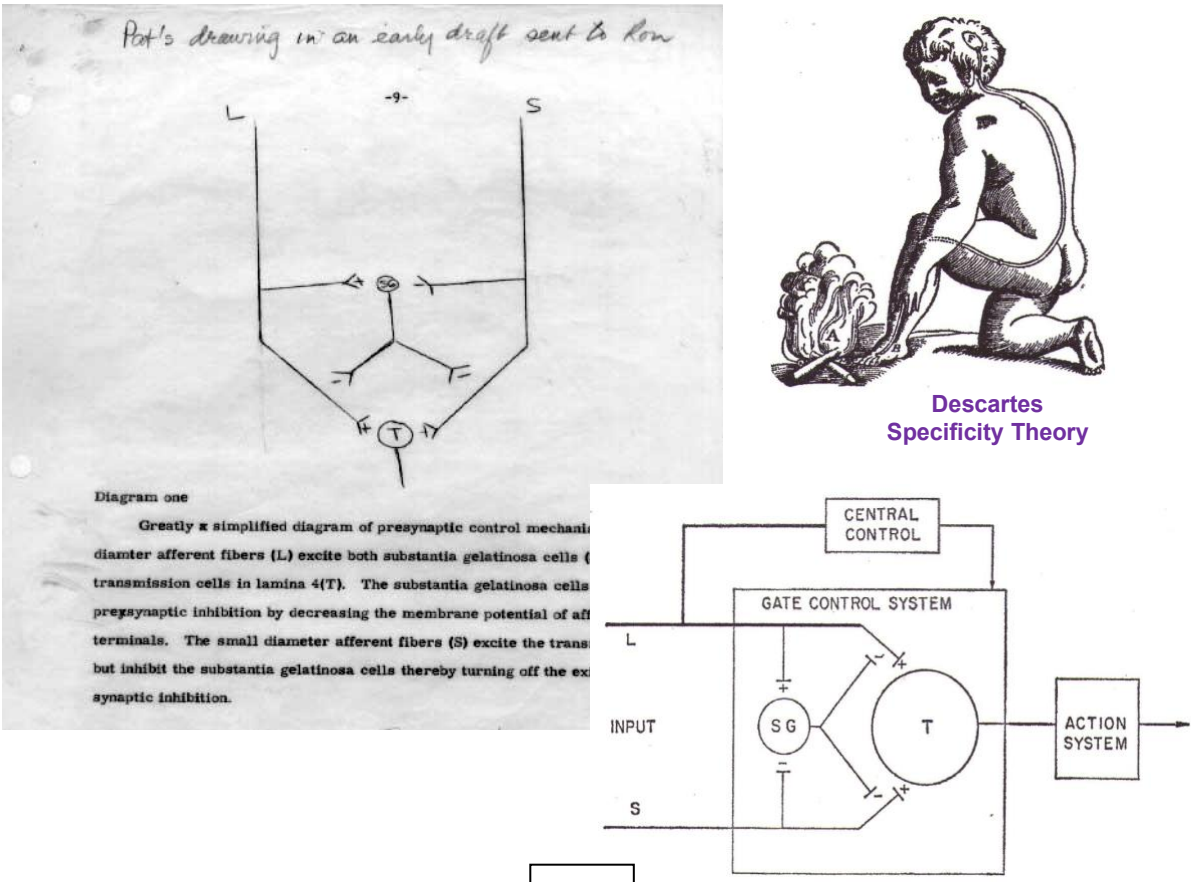


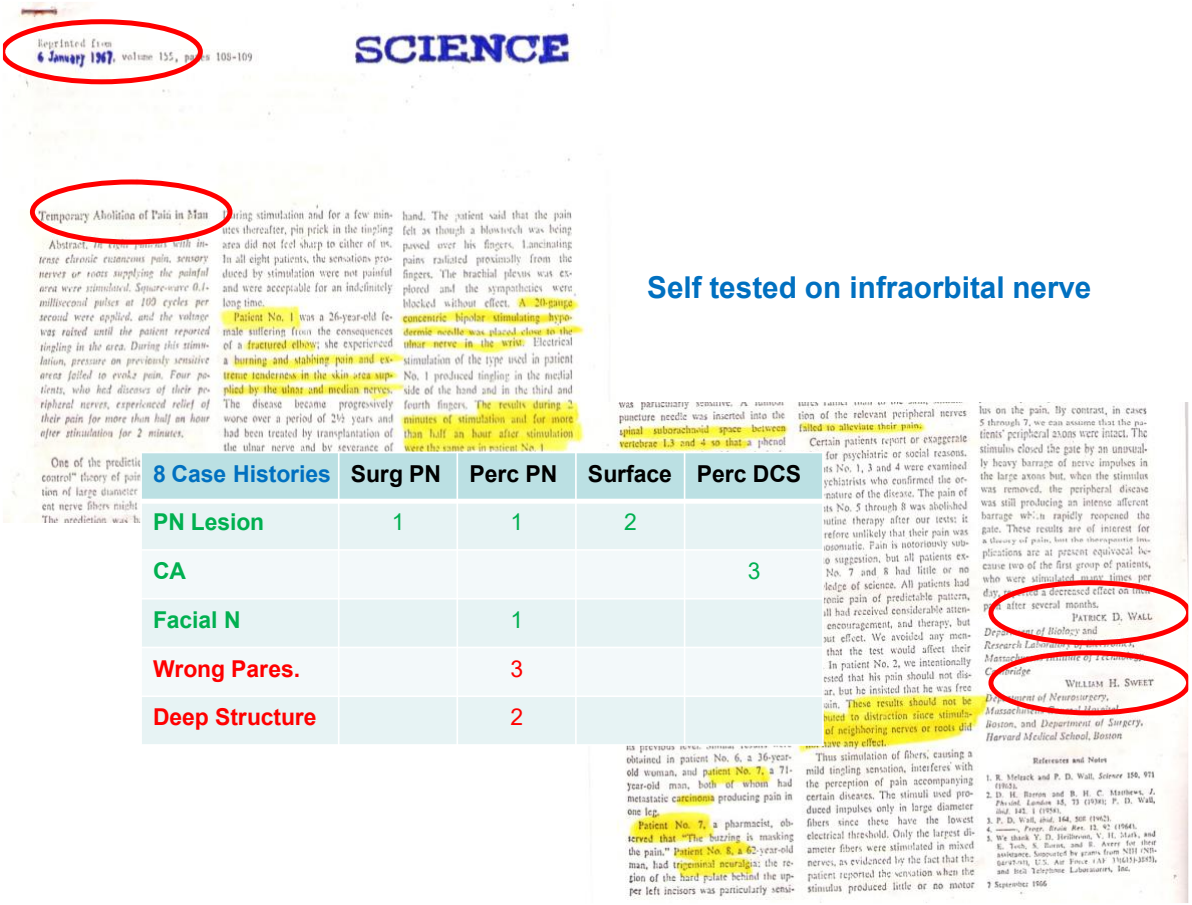
Fig 2

Prior to this publication, the most common understanding of pain perception was the Specificity Theory as described by Descartes (Fig 2, upper right); that is, in the presence of a noxious input (fire), specific pain receptors in the periphery were activated and a signal was then conducted along specific pathways to a specific point in the brain where pain was perceived. With this understanding of the pain perception system, in the presence of chronic pain, it was logical to think of severing or cutting the pathway to stop the perception pain. Hence, all of the –otomies and –ectomies developed by neurosurgery to treat chronic pain.

However, the Specificity Theory didn't explain all pain types, phantom limb pain for example, and the destructive surgical procedures sometimes resulted in unwanted side effects including a secondary pain, sometimes worse than the original pain being treated.

Melzack & Wall's alternative theory, known as the Gate Control Theory, is shown in an early sketch "sent by Pat to Ron" (Fig 2, top left). When published it was turned sideways (lower right). It proposed that mainly painful signals carried on the small diameter (S) C-fibers could be pre-synaptically inhibited by mainly non-noxious sensory signals carried on the large diameter (L) A-β fibers via an intermediate neuron in the substansia gelatinosa (SG) of the spinal cord blocking, or at least downward modulating, the painful signals to the brain.

With this concept of the pain system, physicians attempting to treat chronic pain could use a new, much less destructive strategy, the electrical stimulation of the large diameter A-β fibers to activate the gate instead of cutting a pain pathway.



Reprinted from 6 January 1967, volume 155, pages 108-109

SCIENCE

Temporary Abolition of Pain in Man

Self tested on infraorbital nerve

8 Case Histories	Surg PN	Perc PN	Surface	Perc DCS
PN Lesion	1	1	2	
CA				3
Facial N		1		
Wrong Pares.		3		
Deep Structure		2		

Fig 3

A little more than a year later, Wall and his neurosurgical colleague, William Sweet, from Mass General Hospital in Boston published the first series of “Temporary Abolition of Pain in Man”. After testing the stimulation on their own infraorbital nerves to assure themselves that it was safe, they temporarily stimulated 8 patients with peripheral or facial nerve lesions or cancer. One (1) electrode was placed on a peripheral nerve surgically, 2 were placed on peripheral nerves percutaneously, 2 were with surface electrodes, and 3 with percutaneously placed dorsal column electrodes. All patients reported substantial decrease in their pain as described in the case histories in this paper. However, in 3 patients they were unable to obtain paresthesias in the proper area and in 2 patients with “deep structure” pain, stimulation had no effect (Fig 3).

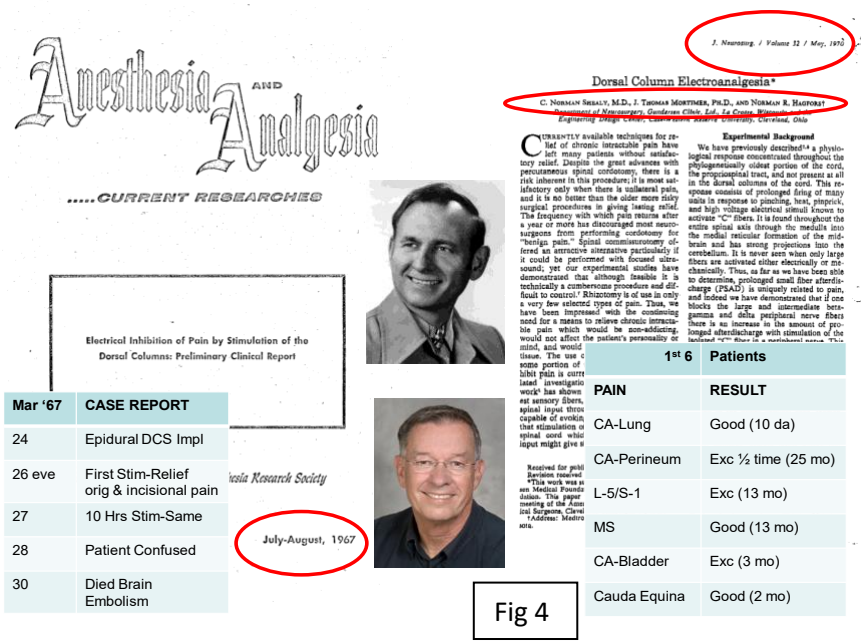


Fig 4

However, it was C. Norman Shealy (Fig 4, upper), neurosurgeon from Cleveland, and his bioengineering student, Thomas Mortimer (lower), who reported on the first case of dorsal column stimulation (DCS) to treat pain chronically. Tom had just finished his MS degree in electrical engineering at Case Institute of Technology and his advisor, Jim Reswick, steered him into a PhD on Dorsal Column Electroanalgisia with Shealy. Shealy selected a man with lung cancer and pain in the chest and abdomen. Mortimer built the implantable electrode in the lab which Shealy implanted over the dorsal columns in the epidural space sutured to the dura mater. The wires were threaded to 2 insulated jacks placed just under the skin where they were accessible by needles placed through the skin to contact the jacks.

The first patient was implanted on 24 March, 1967. Two days later Tom connected the stimulator via the implanted jacks and the patient reported immediate total relief of his original pain as well as the incisional pain from the laminectomy required to implant the electrode. The following day, Tom again connected the system which the patient used for 10 hours with complete pain relief. Unfortunately, on the 3rd day the patient seemed confused and died of a brain embolism 2 days later.

Based on this initial success, Shealy and Mortimer decided to build a more viable system for the second patient. Mortimer had interviewed with Medtronic for a job previously before deciding on the PhD route. He now contacted Medtronic engineer, Norm Hagfors, and with his advice, designed and built a radio frequency system for the second patient, a woman with cancer of the perineum. Shealy had by this time, about 9 months after Patient 1, moved to the Gunderson Clinic in LaCrosse, Wisconsin. The 2nd system was implanted and again the patient reported excellent pain relief during the 1st day of stimulation. Mortimer told me he now was confident his PhD was “in hand”. However, the next day the patient reported no pain relief. Mortimer tested the system and tried many different parameter settings to no avail and suddenly the PhD seemed to be “slipping through his fingers”. The next day the patient again reported pain relief which was absent the following day. At 25 months, she was still reporting excellent pain relief half the time with minimal relief on the other days (Fig 4, right, Patient 2).

Mortimer persisted with his thesis and based on these two patients and a lot of animal studies on the design of implanted electrodes was granted his PhD and went off to Sweden for post doctorial studies. Shealy turned to Medtronic to build his DCS Stimulators from Patient 3 onward. The 1st 6 patients were published by Shealy, Mortimer & Hagfors in Journal of Neurosurgery in 1970 (Fig 4).

2nd Generation
(1973-75)

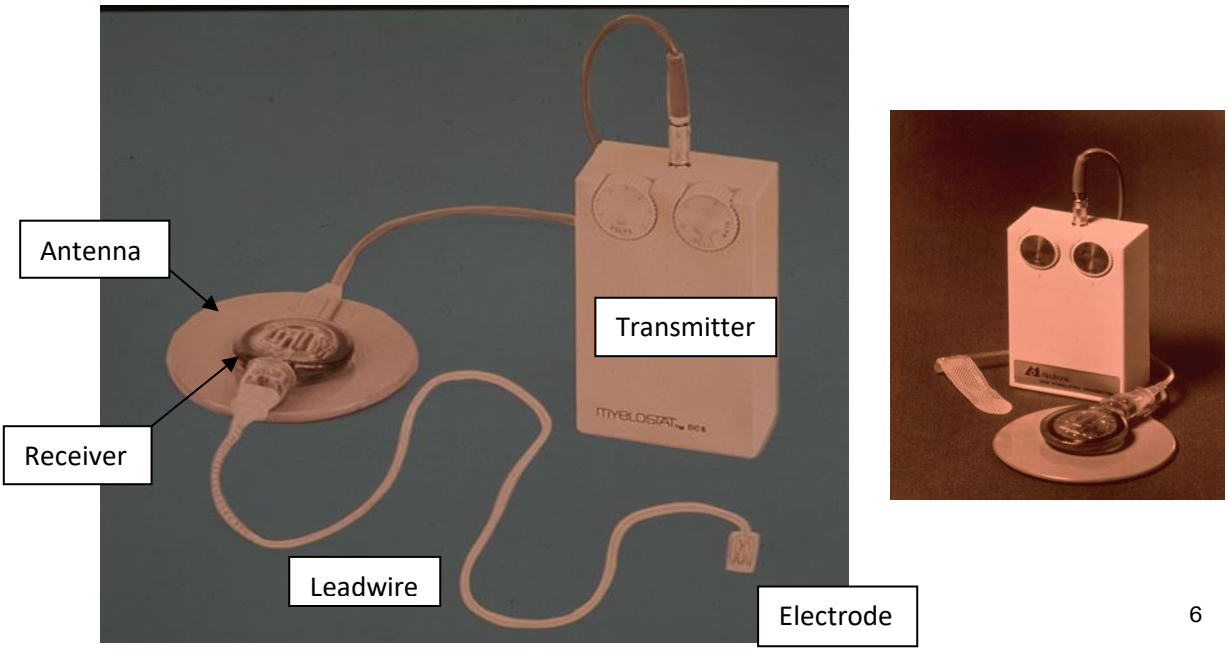


Fig 5

Cardiac pacemakers of the era used mercury zinc batteries manufactured by the Mallory Company. They were large and in the cardiac pacing application lasted about 2 years. Neurostimulation, as practiced at the time, required 5 times the energy of a cardiac pacemaker. Two years divided by 5 would obviously result in a very short battery life time. Thus a different approach was needed.

The solution was a radio frequency system. The patient carried a “box” called a transmitter which contained the batteries, pulse generating circuitry, radio frequency (RF) coding circuitry, and the controls. This RF signal was sent to the antenna taped to the surface of the skin over the implanted receiver. The receiver was a passive (no battery) device that received the RF signal, decoded it into a pulse train, and delivered it through a leadwire to the implanted electrode which delivered the stimulation to the dorsal columns.

The original electrodes were large, 3 plate (5mm X 5mm each) devices in a guarded bipolar configuration. Surgeons, attempting to get stimulation more focused on the dorsal columns, requested small electrodes which could be implanted in the sub-dural, extra-arachnoid space, such as the 2nd generation system (Fig 5, left). This was a monopolar, tinsel wire electrode with the wire exposed in the face of the silicon for stimulation. The indifferent electrode was on the receiver.

A similar system is shown configured for peripheral nerve stimulation (PNS) with a “wrap-around” bipolar electrode (Fig 5, right).

FAILURES

Type

- Paresthesias don't help
- Paresthesias don't cover
- Don't like the paresthesias
- Root pain

How to predict failures (&successes)

Fig 6

Several years after these initial enthusiastic reports, physicians began to realize that the outcomes were not always positive (Fig 6). Some patients began to report that their system was not providing the relief expected. Some of these were undoubtedly failures from the beginning which were not recognized by hopeful patients and enthusiastic doctors. Some were early successes that later failed due to body tissue changes, electrode movement or failure, or other reasons. Surgeons began to ask, "How can we predict failures" (and in the process, successes).

CSD (1971)

TNS (1973)

Electreat®(1970)
(dates from 1918)

"Two things cannot occupy the same space at the same time. Shooting electricity in forces the pain out"

Percutaneous Screening Lead

Fig 7

It was Norm Shealy who re-discovered an old device marketed as early as the 1920's. The device was marketed with claims far beyond its capabilities. Nevertheless, it was an early TENS device. It probably did provide a degree of pain relief which the Electreat Company informed its customers was due to the fact that "Two things … (Fig 7, left).

Shealy used the device to help select patients more likely to be successful with DCS and to eliminate those who appeared would be non-responders. Medtronic soon built a "Cutaneous Stimulation Device (a misnomer - it's not the skin but the nerve endings under the skin that are stimulated) for physicians to use for screening patients. However, some patients reported that the CSD stimulation relieved their pain and they saw no reason for spinal surgery. By 1973, Medtronic and several other companies introduced their Transcutaneous Nerve Stimulators (TNS) for chronic patient use. The name later changed to Transcutaneous Electrical Nerve Stimulator or TENS as we know it today.

In the same era, the first leads for temporary insertion into the sub-dural space became available for surgeons to be even more accurate in patient selections (Fig 7, bottom).

Dr. Norm Shealy
Self-Health Systems

Norm Shealy says today that "while the science of medicine is indispensable to the physician, it is the art of practicing medicine that heals the human body and soul." For over 4 decades, Norm Shealy as been at the forefront of Alternative Medicine and Alternative Health Care.

J. Thomas Mortimer, Ph.D. (Emeritus)
Professor Emeritus
Department of Bioengineeriing
Case Western Reserve University

Fig 8

So where is Norm Shealy today (2013)? Several years after the above events, he left neurosurgery stating that while neurosurgery is a valid discipline, he felt it was overused and he preferred not to be part of that overuse. Instead he refocused his career on Alternative Medicine. If you Google his website you will see the statement above which I'm sure our founder, Earl Bakken, would call "high tech, high touch".

And Tom Mortimer? After completing his post-doc year in Sweden he returned to his alma mater, now Case Western Reserve University where he headed the Neural Control Laboratory until his retirement about 10 years ago. He recently told me "I only realized in the last few years that maybe I did something important during the early years of my career.

DBS 1969

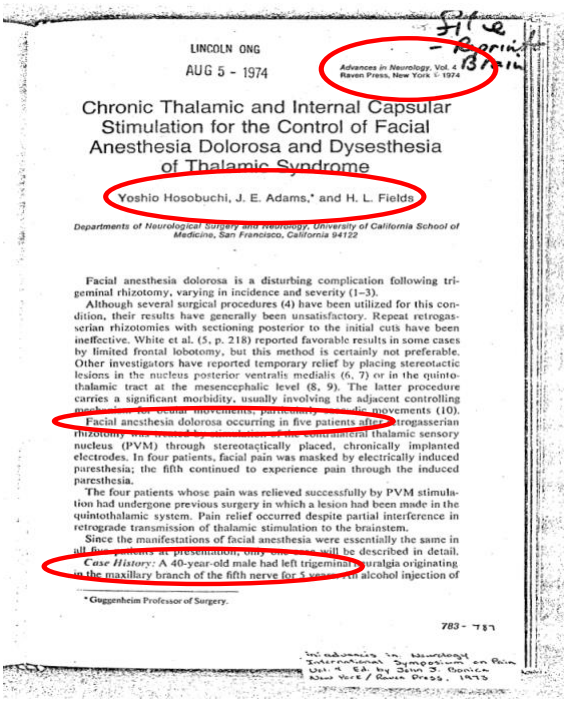
Yoshio Hosobuchi,MD
Neurosurgeon, UCSF

- **Patient:** Facial Anesthesia Dolorosa
- **Planned procedure:** Thalamotomy of the PVM Nucleus
- **Observation:** Intra-operative pain relief during stimulation
- **Revised procedure:** Percutaneous connection to Electrode
- **Short term FU:** Pain relief persisted for 9 mo.
- **Follow-up procedure:** Connection to "DCS" Receiver
- **Long term outcome:** 20 years pain relief

Fig 9

During this era one of the "-otomies" used by neurosurgeons was thalamotomy, the lesioning of the thalamus to stop pain. In order to be sure that the lesioning electrode was properly placed, surgery was performed under local anesthesia and the patient was intra-operatively stimulated. When the patient reported paresthesias in the appropriate place, a lesion was made. Some physicians observed that patients reported that, during stimulation, not only did they feel the paresthesias, but that pain disappeared.

It was Yoshio Hosobuchi from UCSF who first, in a patient scheduled for thalamotomy, with the patient's consent, left the lesioning electrode in position after report of pain relief. Several months later, with the electrode still in place and wire coming through the skin, Hosobuchi requested Medtronic to convert a DCS System for Deep Brain Stimulation (DBS) use. About 9 months after the original procedure, the electrode was converted for chronic stimulation with an implantable system (Fig 9). I had the privilege to meet the patient 20 years later in 1989 when he attend Medtronic's annual Holiday party in Minneapolis to tell his story. The results of the first DBS implants were published by Hosobuchi et. al in Advances in Neurosurgery in 1974 (Fig 10).



LINCOLN ONG
AUG 5 - 1974

Advances in Neurology, Vol. 4
Raven Press, New York © 1974

Chronic Thalamic and Internal Capsular Stimulation for the Control of Facial Anesthesia Dolorosa and Dysesthesia of Thalamic Syndrome

Yoshio Hosobuchi, J. E. Adams,* and H. L. Fields

Departments of Neurological Surgery and Neurology, University of California School of Medicine, San Francisco, California 94122

Facial anesthesia dolorosa is a disturbing complication following trigeminal rhizotomy, varying in incidence and severity (1–3).

Although several surgical procedures (4) have been utilized for this condition, their results have generally been unsatisfactory. Repeat retrogasserian rhizotomies with sectioning posterior to the initial cuts have been ineffective. White et al. (5, p. 218) reported favorable results in some cases by limited frontal lobotomy, but this method is certainly not preferable. Other investigators have reported temporary relief by placing stereotactic lesions in the nucleus posterior ventralis medialis (6, 7) or in the quintothalamic tract at the mesencephalic level (8, 9). The latter procedure carries a significant morbidity, usually involving the adjacent controlling [illegible] for ocular movements, particularly [illegible] movements (10).

Facial anesthesia dolorosa occurring in five patients after retrogasserian rhizotomy was relieved by stimulation of the centromedian thalamic sensory nucleus (PVM) through stereotactically placed, chronically implanted electrodes. In four patients, facial pain was masked by electrically induced paresthesia; the fifth continued to experience pain through the induced paresthesia.

The four patients whose pain was relieved successfully by PVM stimulation had undergone previous surgery in which a lesion had been made in the quintothalamic system. Pain relief occurred despite partial interference in retrograde transmission of thalamic stimulation to the brainstem.

Since the manifestations of facial anesthesia were essentially the same in all [illegible] at presentation, only one case will be described in detail.

Case History: A 40-year-old male had left trigeminal neuralgia originating in the maxillary branch of the fifth nerve for 5 years. [illegible] alcohol injection of

* Guggenheim Professor of Surgery.

783 - 787

In Advances in Neurology
International Symposium on Pain
Vol. 4, Ed. by John J. Bonica
New York / Raven Press, 1975

12

Fig 10

1st Generation
(1969-73)

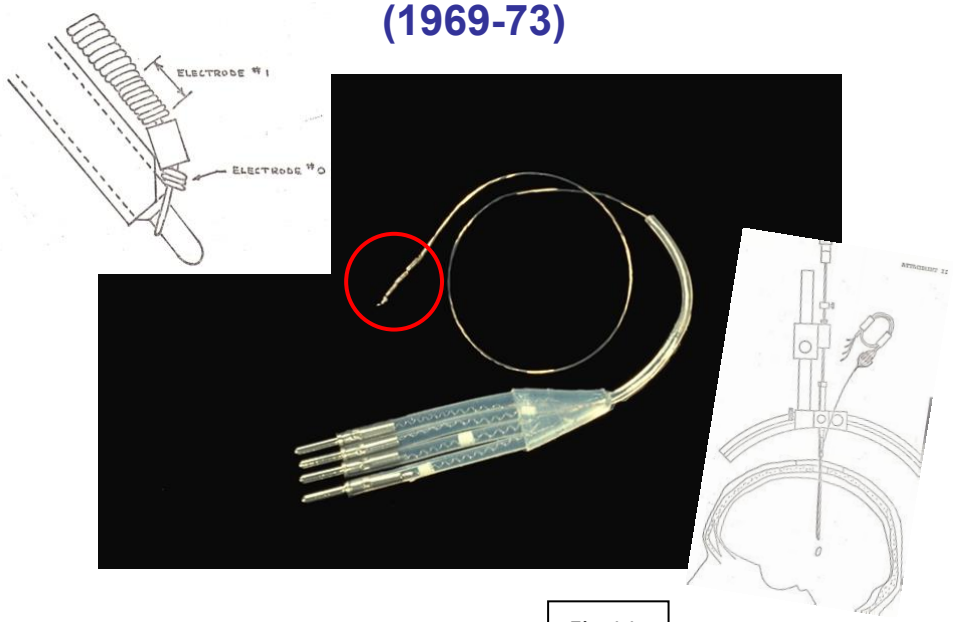
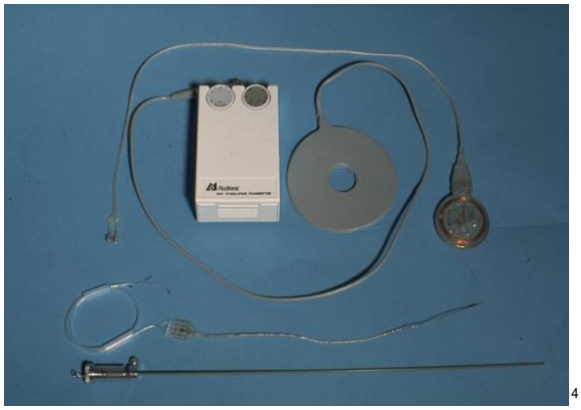


Fig 11

The lesioning electrode used by Hosobuchi was a stainless steel Schryver Electrode. Medtronic modified the electrode to use platinum iridium wires, later, pure platinum, more suitable for long term use in contact with brain tissue. The configuration remained the same as the lesioning electrode. Four (4) electrodes at the tip (Fig 11, red circle) were introduced stereotaxically into the brain. Electrode 0, the loop at the tip, was looped over the tip of the stylet to pull the electrode into the brain. When test stimulation assured that the electrode was in the correct location, the stylet was slightly retracted freeing the loop before the insertion tool was removed from the brain leaving the electrode at target (Fig 12, right). Redesign of the connector reducing its size resulted in an improved system for clinical study (Fig 12, left).

2ND Generation
(1973-80's)



Circa 1978

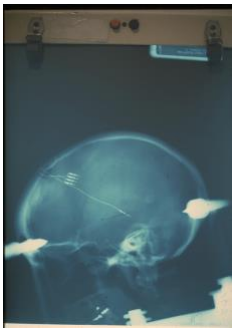


Fig 12

Dr. Donald Richardson
Neurosurgeon
Tulane Medical Center

Huda Akil Ph.D
Professer
Senior Research Scientist and
co-Director, Mental Health
University of Michigan

Pain reduction by electrical brain stimulation in man.
Part 1: Acute administration in periaqueductal and periventricular sites.
Richardson DE, **Akil** H.
J Neurosurg. 1977 Aug;47(2):178-83.

…periaqueductal gray matter, the accompanying side effects render it impossible to stimulate this site…

Pain reduction by electrical brain stimulation in man.
Part 2: Chronic self-administration in the periventricular gray matter.
Richardson DE, **Akil** H.
J Neurosurg. 1977 Aug;47(2):184-94.

The results are discussed in terms of … naturally occurring opiate-like factors such as the enkephalins and endorphins.

Fig 13

In the early 1970's at Tulane University, Don Richardson and his Research Associate, Huda Akil, were assessing in animals the effect of stimulation of the periventricular gray (PVG) and periaqueductal gray (PAG) areas adjacent to the third ventricle and the aqueduct of Sylvius. Prior research had suggested these endorphin rich areas may contribute to pain relief through descending inhibitory systems. After several of his laboratory built human test electrodes failed, Richardson approached Medtronic for access to the DBS System. Collaboration resulted in a 2-part article published in the Journal of Neurosurgery in 1977. Part 1 discussed acute stimulation of the PVG/PAG concluding that, while PAG stimulation effectively reduced pain, side effects such as autonomic responses rendered it impossible to use therapeutically. Part 2 discussed chronic stimulation of the PVG concluding that effective pain relief could be achieved in this location and "discussed the results in terms of the opiate-like factors" (Fig 13).

DBS Study Group – 1974-76

John Adams	San Francisco
Donald Becker	Richmond, Va
Rolf Breest	Paris
Charles Burton	Minneapolis
George Ehni	Houston
Phil Gildenburg	Tucson Az
Russell Hardy	Cleveland
Yoshio Hosobuchi	San Francisco
Uli Krainick	Freiburg
Richard Lewin	Beverly Hills
John Loeser	Seattle
Donlin Long	Baltimore
Bjorn Meyerson	Stockholm
John Miles	Liverpool
John Mullan	Chicago
Don Richardson	New Orleans
Ian Turnbull	Vancouver

Fig 14

In 1974 Medtronic organized a Study Group of physicians interested in DBS to work together and share methods and results (Fig 14). A similar group was organized for DCS.

And so ends the “Early Years of Neuromodulation”.

Milestones & Developments

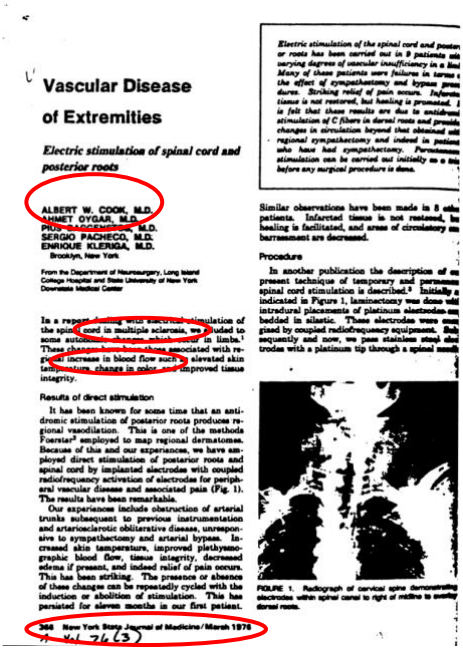
1965-73	EARLY YEARS	
1965	Melzack & Wall	Gate Theory of Pain
1967	Shealy, Mortimer	1st Chronic DCS
1969	Hosobuchi, Adams	1st DBS – Thalamus
1973	Richardson & Akil	1st DBS – PVG / PAG
1973-76	EXPANSION YEARS	
1973, 1976	Cook, Dooley	PVD
1974	Cooper	Cerebellar Stimulation (Spasticity)
1969	Rancho Los Amigos (LA)	Foot Drop
1974	Bobechko	Scoliosis

Fig 15

18

Now comes the “Expansion Years”.

Physicians now had access to neuromuscular stimulating devices. There was no shortage of ideas of how to use them. Four of these projects are discussed below.



Vascular Disease of Extremities

Electric stimulation of spinal cord and posterior roots

ALBERT W. COOK, M.D.
AHMET OYGAR, M.D.
PHILIP ANGEMENIS, M.D.
SERGIO PACHECO, M.D.
ENRIQUE KLERIGA, M.D.
Brooklyn, New York

From the Department of Neurosurgery, Long Island College Hospital and State University of New York Downstate Medical Center

Results of direct stimulation

Procedure

FIGURE 1. Radiograph of cervical spine demonstrating

South Med J. 1976 Oct;69(10):1309-11.

Modification of blood flow to the extremities by electrical stimulation of the nervous system.

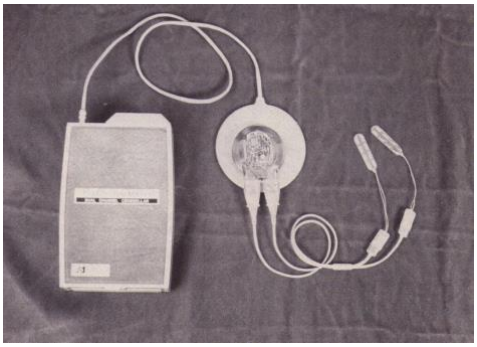
Dooley DM, Kasprak M.

Abstract

Sixteen patients who had electrical stimulation applied to various portions of the nervous system were examined for increase in blood flow to the extremities. Clinical observations and a one-channel plethysmograph were used to measure arterial dilatation. Seven patients had transcutaneous stimulation applied over the cervical or thoracic spinal cord, peripheral nerves, or low lumbar region; eight had electrical stimulators implanted over the spinal cord in attempts to relieve intractable pain or some of the symptoms of multiple sclerosis; and one patient had electrical stimulators implanted over the C-6 dorsal roots for small artery disease of the upper extremities. Twelve of 13 patients who had electrical stimulation applied to the spinal cord or dorsal roots had significant arterial dilatation in one or more extremities. Electrical stimulation applied to the ulnar nerves did cause arterial dilatation. One patient did not show any change in the central arterial pressure curve during transcutaneous stimulation of the cervical spinal cord.

Fig 16

Very soon after the initial DCS implants for pain, several physicians observed that DCS seem to improve spasticity in patients with multiple sclerosis. As early as 1973, Al Cook, neurosurgeon from New York observed increase in peripheral blood flow in MS patients being stimulated for their spasticity which he reported in the New York State Journal of Medicine in 1976. In the same year, Don Dooley from Miami reported on 16 patients. Fifteen (15) of the 16 were implanted to treat pain or spasticity and one was implanted for small vessel disease of the upper extremity, the first reported patient to be treated with DCS specifically for peripheral vascular disease (PVD). This technique would picked up by several European centers including Meglio and Fiume (Rome), Augustinsson (Gothenburg), Tallis (UK), and Broseta (Salamanca).



1974

1922-85

August 1976
Neurology. 1976 Aug;26(8):744-53

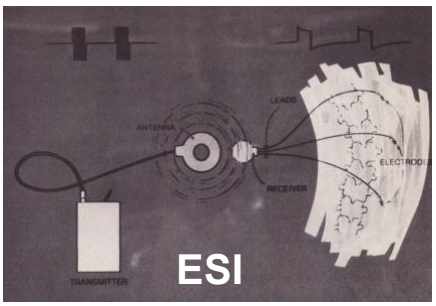
Chronic cerebellar stimulation in cerebral palsy.
Cooper IS, Riklan M, Amin I, Waltz JM, Cullinan T.

August 1976
Arch Neurol. 1976;33(8):559-570

Chronic Cerebellar Stimulation in Epilepsy Clinical and Anatomical Studies
Irving S. Cooper, MD, PhD; Ismail Amin, MD; Manuel Riklan, PhD; Joseph M. Waltz, MD; Tung Pui Poon, MD

Fig 17

Irving Cooper, neurosurgeon at St. Barnabas in the Bronx, NY asked Medtronic to support his work with cerebellar stimulation to treat the spasticity resulting from cerebral palsy (Fig 17). He and his colleagues also noted improvement in seizures in some of these patients. This work resulted in several publications in the decade beginning in the mid '70's.



Walter P. Bobechko, MD
Chief of Orthopedic Surgery
Hospital for Sick Children
Toronto

Electrospinal instrumentation for scoliosis: current status.

Bobechko WP, Herbert MA, Friedman HG.
Orthop Clin North Am. 1979 Oct;10(4):927-41.

Jens Axelgaard, PhD
Director, Spinal Research
Rancho Los Amigos Rehab. Engineering Center
Downey, CA

Lateral electrical surface stimulation for the treatment of progressive idiopathic scoliosis.

Axelgaard J, Brown JC.
Spine (Phila Pa 1976) 1983 Apr;8(3):242-60

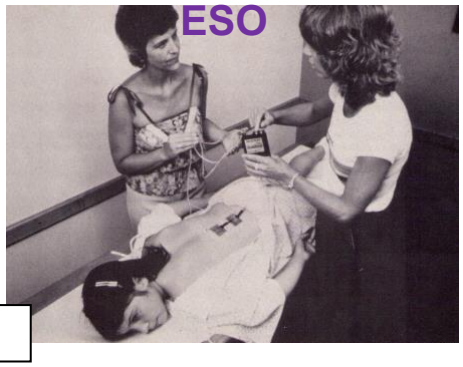


Fig 18

Walter Bobechko from Toronto requested Medtronic support for a stimulator to treat scoliosis. He hypothesized that the scoliotic curve resulted from weakened muscles on the convex side of the curve which could be strengthened by exercise, pulling the spine straight eliminating the need for unsightly braces and avoiding a future Harrington rod procedure. The Electrospinal Instrumentation (ESI) system was implanted and studied at various centers in North America and Europe (Fig 18, left). Axelgaard at Rancho Los Amigos Hospital in Los Angelis suggested that the same could be achieved with an external muscle stimulator avoiding surgery all together. The Electro Spinal Orthosis System was studied at several US centers (Fig 18, right).

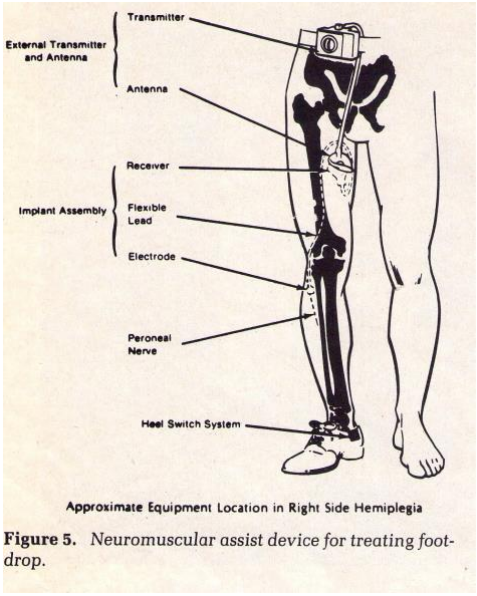


Figure 5. *Neuromuscular assist device for treating foot-drop.*

Appl Neurophysiol 1977;40:235-239

Experience with Implanted Electrodes at Rancho Los Amigos Hospital

Donald R. McNeal, Robert Waters, James Reswick

Rancho Los Amigos Rehabilitation Engineering Center, Downey, Calif.

Abstract

Implanted units, manufactured by Medtronic, Inc., have been implanted in 31 patients for treatment of drop foot. ….. for periods of up to 7.3 years…..

Fig 19

The group at Rancho also collaborated with Medtronic on an implanted Foot Drop System. A radio frequency switch in the shoe was activated upon heel lift. The RF signal was received by the transmitter on the patient's belt and retransmitted by a second RF link to an implanted receiver connected to an electrode on the peroneal nerve. The stimulated nerve resulted in toe lift avoiding the stumbling gait of foot drop patients. Upon heel strike, the system shut off allowing the foot to settle into normal position. Thirty-one (31) patients were reported in Applied Neurophysiology in 1977.

So, what happened to these "expansion ideas"?

SPASTICITY: Several centers continued to pursue DCS for spasticity, most notably Joe Waltz, at St Barnabas. However, the availability of the implantable baclofen pump proved to provide a much more profound response in the patient population and today (2013), very little stimulation is done on an off-label basis.

PVD: Physicians, mainly in Europe, continue to treat patients and study the effects of DCS for PVD. Significant numbers of patients are treated at a few specific centers in Europe. The therapy is not approved in the US.

EPILEPSY: Work continues on stimulation for epilepsy (see later in this paper).

SCOLIOSIS: Progression of a scoliotic curve is not linear; in fact, the curve can stop progression or even reverse spontaneously. Randomized studies would have been necessary to prove an outcome, difficult to implement on adolescent girls, the main population with scoliosis. Insufficient studies were performed and the general perception was that stimulation provided marginal benefit at a great cost (surgical, hospital staff time, and financial).

FOOT DROP: The system won a "10 wonders of the Engineering World" award. It never won a "wonders of the sales world" award. Many patients have footdrop resulting from stroke. These patients have multiple problems functioning and solving one, footdrop, does not lead to full rehabilitation. The system remains archived.

It is possible, of course, that several of these discarded ideas may have proven valuable, but---see following page.

1976

U.S. Congress passed the Medical Device Act
– Regulations Promulgated by FDA in 1979

- "Trying things" less easy
- Clinical proof demanded
- Industry faced with choices

Choice to focus on SCS for Chronic Pain

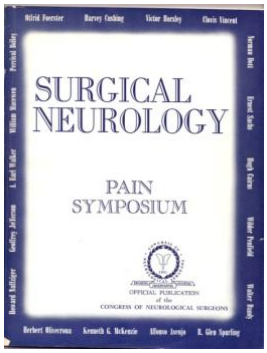
- Time to make SCS work and work right

Fig 20

Figure 20 speaks for itself.

In 1973, Medtronic sponsored a symposium on Neuromodulation. The proceedings were published in Surgical Neurology Supplement 2 years later. Among the papers were 2 by Dr. Rueben Hoppenstein. He pointed out the major drawback of DCS, acknowledged the use of percutaneous temporary electrodes for screening, but most importantly, announced the first reported implant of a percutaneously inserted, chronic stimulating electrode.

Minneapolis
1973
Published 1975



Reuben Hoppenstein, MD, FACS
Neurological Surgeon
Mount Sinai Hospital, NY

MUCH of the resistance from both patients and physicians to implanting dorsal column stimulation (DCS) devices stems from the fact that a laminectomy under general anesthesia must be performed. Debilitated patients and

fied. With the advent of percutaneous stimulation of the spinal cord using a penetrating electrode[3] and my personal experience with percutaneous on-surface stimulator (POSS) of the spinal cord,[1] new avenues for pain control have been opened and have already been used in one patient to control trigeminal neuralgia by placing a bipolar electrode percutaneously on the ipsilateral ventral column at C1-2.[2]

sub-arachnoid

Fig 21

Not only was the electrode placed in the sub-arachnoid space, it was also placed transversely and Dr. Rubinstein reported that both ventral and dorsal placements resulted in pain relief (Fig 22). This raised questions about what the real stimulation target was and led to the change of terminology from dorsal column stimulation (DCS) to spinal cord stimulation (SCS). Although most of Hoppenstein's work was in collaboration with Avery Laboratories, he did do the first Medtronic percutaneously inserted, chronic SCS.

In the addendum to the paper in Surgical Neurology, he reported on 10 patients with percutaneously inserted chronic electrodes, 8 of which were explanted for various reasons. In spite of the failures, he predicted that percutaneous was the way of the future (Fig 22). He was right.

Percutaneous Implantation of Chronic Spinal Cord Electrodes for Control of Intractable Pain: Preliminary Report

Reuben Hoppenstein, M.D.

Department of Neurosurgery, Mount Sinai Hospital and Medical School, Departments of Orthopedics and Surgery, Hospital for Joint Diseases, and Beekman Downtown Hospital, New York, New York

A percutaneous technique is described for implanting a dorsal or ventral column stimulator for pain control with minimal surgical trauma. If the patient does not respond to percutaneous on-surface spinal stimulation, a percutaneous cordotomy can be carried out, as the needle is already in the correct position. Stimulation of the cord at the C1-2 level can be used for treatment of trigeminal neuralgia.

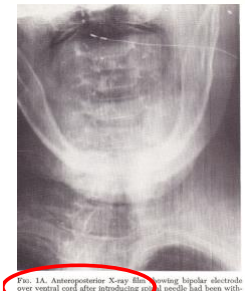


FIG. 1A. Anteroposterior X-ray film showing bipolar electrode over ventral cord after introducing spinal needle had been withdrawn. Note electrode has been [illegible] advanced to avoid [illegible] removal with needle.

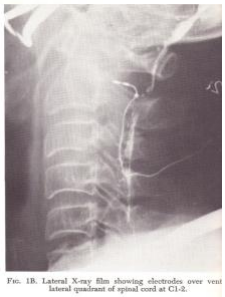


FIG. 1B. Lateral X-ray film showing electrodes over ventral quadrant of spinal cord at C1-2.

'74 ADDENDUM
10 additional patients

8 explants for:
- •Tissue irritation
- •Lead movement
- •CSF Leak

Despite poor results, it is still the author's belief that further investigation is warranted and further modifications of the electrode are being attempted.

Acknowledgment

I would like to acknowledge the invaluable assistance and technical advice of Mr. Roger Avery, who built all of the equipment used.

Fig 22

MDT NEURO BURNS

1977

Fig 23

But, wait. Time out! Medtronic Neuro burns down.

In 1975, Medtronic decided that the neurological research programs could no longer exist as a research arm of a cardiac pacing company. It was time to stand on our own as a business division. I suspect there was some nostalgia amongst senior management who, knowing that Medtronic had started in a garage in northeast Minneapolis, thought Neuro should do the same.

Our garage was a former grain storage warehouse in northeast Minneapolis. Neuro moved into the first 2 floors and began to organize itself as a business. One Saturday morning less than a year later I got a call from my boss, Ed Schuck. “Get down to the office. Neuro has burned!” Indeed, it seems that a vagrant had moved into the unoccupied 7th floor of the building and decided to cook his dinner over an open fire on the wooden floor with disastrous results.

Neuro mainly suffered water damage from the fire department but the building was condemned and Neuro moved out to a modern building in the suburb of Roseville.

It was time to get back to the business of designing a percutaneous lead.

PISCES®

- Percutaneously Inserted Spinal Cord Epidural Stimulator
- Scribonius Largus, court physician to the Roman emperor Claudius (47 ad)

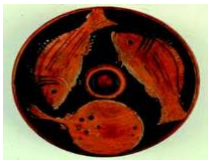


Fig 24

The name, PISCES, was selected as an acronym, but also to remind us that the ancient physicians already had insight into electrical stimulation and used electrical fish to treat their pain patients (Fig 24).

The original PISCES electrode was a loose wound, silicon rubber insulated, monopolar electrode. It was held stiff for insertion by a stylet which was removed when adequate placement was achieved. The lead frequently dislodged from its position falling into the left or right gutter. Any tug on the distal portion of the lead led to tip movement. An improvement, the addition of sigmoidal curves in the body of the lead, intended to act as a spring taking the force of the any distal movement failed to improve performance (Fig 25, left).

The solution lay in exactly the opposite strategy. The first successful PISCES family leads used a tight wound, octofilar coil with two wires attached to each of 4 electrodes. The lead was insulated with stiffer polyurethane insulation. The first leads were introduced in 1978 and today's percutaneously inserted leads are direct descendents of that lead including the MRI safe leads introduced in 2013.

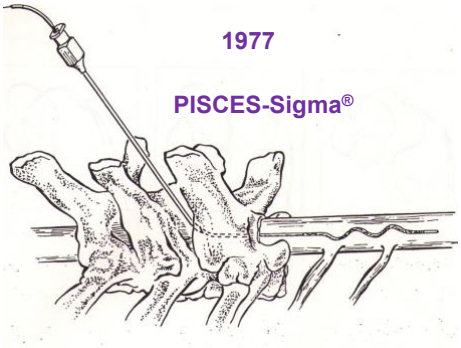


Fig 25

Results

•Trial with permanent lead possible

•Implant under local anesthesia possible

•Ever less invasive methods developed

•New user base – Anesthesiologist

Fig 26

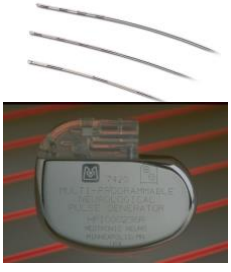
The development of PISCES leads meant that physicians could trial the patient and convert to chronic implant without needing a second surgery to place a permanent lead. Further, it was no longer necessary to perform a laminectomy under general anesthesia to place the lead. Finally, and very importantly, it opened up a large group of physicians, the anesthesiologist, to the technique (Fig 26).

Thus the late '70's and early 80's can be viewed as the decade which consolidated SCS as a viable therapy available for appropriate patients. Major advances included (Fig 27) percutaneously inserted chronic leads already discussed. The advent of lithium battery technology allowed the development of fully implantable systems to replace their RF forefathers, and ever improving and less invasive surgical procedures were developed.

Perhaps the most significant improvement was the increased understanding of the pain patient leading to better patient selection. Acknowledgement for this goes to John Bonica, anesthesiologist from Seattle (Fig 27, bottom). As early as the 1950's Bonica pioneered the concept of multidisciplinary pain centers which were further promoted by the International Association for the Study of Pain (IASP) of which he was a founder. What may not be known is that he financed his medical education as a professional wrestler under the name "The Masked Marvel" and was post-humously inducted into the Wrestling Hall of Fame in 2002. After his wrestling career ended he said that injuries received in the ring gave him increased empathy for the pain patients he later treated.

Advances (70's-80's)

- **Stimulation Systems**
  - Percutaneously Inserted Leads 1974
  - Fully Implantable Systems 1983
- **Surgical Technique**
  - Epidural placement
  - Less invasive procedures
- **Patient Selection**
  - Multidiscplinary Pain Center 1950's
  - IASP 1973
  - Professional Wrestling Hall of Fame 2004



JOHN J. BONICA, M.D.
1917-94

Fig 27

Milestones & Developments

1965-73	**EARLY YEARS**	
1965	Melzack & Wall	Gate Theory of Pain
1967	Shealy, Mortimer	1st Chronic DCS
1969	Hosobuchi, Adams	1st DBS – Thalamus
1973	Richardson & Akil	1st DBS – PVG / PAG
1973-76	**EXPANSION YEARS**	
1973, 1976	Cook, Dooley	PVD
1974	Cooper	Cerebellar Stimulation (Spasticity)
1969	Rancho Los Amigos (LA)	Foot Drop
1974	Bobechko	Scoliosis
1976-85	**CONSOLIDATION YRS**	
	Industry	Perc. Leads & IPG's
	Medical Profession	Surgical Techniques
	Medical Profession	Patient Selection & Management

32

Fig 28

And so we close the next phase of the evolution of Neuromodulation, the "Consolidation Years" (Fig 28).

And now for more Expansion. Success with SCS in the decade up to 1985 provided the resources to look ahead (Fig 29).

Milestones & Developments

1965-73	**EARLY YEARS**	
1973-76	**EXPANSION YEARS**	
1976-85	**CONSOLIDATION YRS**	
1985-90	**MORE EXPANSION**	
1987,88	Giles, Mannheimer	Angina
1987	Benabid	Tremor
1988	UroSystems	Incontinence

33

Fig 29

Angina Pectoris

Pain. 1987 Mar;28(3):365-8.

Dorsal column stimulation for pain relief from intractable angina pectoris.

Murphy DF, Giles KE.

Abstract

Dorsal column stimulation was undertaken in 10 patients referred to the Pain Relief Clinic for management of otherwise intractable angina pectoris. All patients were on maximal medical therapy and were determined to be unsuitable for coronary artery revascularization by the referring cardiologists. Dorsal column stimulation was beneficial in all patients by decreasing the frequency and severity of anginal attacks. The mechanism of action of dorsal column stimulation in this condition is uncertain.

Br Heart J. 1988 Jan;59(1):56-61.

Epidural spinal electrical stimulation in severe angina pectoris.

Mannheimer C, Augustinsson LE, Carlsson CA, Manhem K, Wilhelmsson C.

Abstract

The short term effects of epidural spinal electrical stimulation were studied in 10 patients with angina pectoris of New York Heart Association functional class III or IV. The antianginal pharmacological treatment given at entry to the study was regarded as optimal and was not changed during the study. The effects of epidural spinal electrical stimulation were measured by repeated bicycle ergometer tests. Treatment with epidural spinal electrical stimulation increased the patients' working capacity, decreased ST segment depression, increased time to angina, and reduced the recovery time.

Fig 30

In the late 1980's several reports were received of SCS used in Angina Pectoris (Fig 30). Giles and colleagues in Australia were the first to report favorable results in 10 patients. Mannheimer et. al (Gothenberg) published their series of 10 patients a year later. Many cardiologists argued that symptomatic pain relief in angina patients removed a critical warning necessary to patient survival. Advocates of stimulation argued that patients with intractable angina used pharmaceuticals to stop symptomatic pain and that stimulation not only blocked pain but improved cardiac blood flow directly improving the underlying disease. Studies to show this ensued and continue today (2013) with the scope of evaluation broadened to include heart failure.

Tremor

Appl Neurophysiol. 1987;50(1-6):344-6.

Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease.

Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J.

Abstract

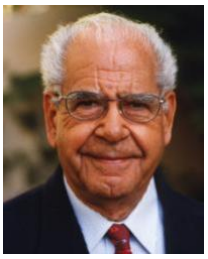
Stereotactic thalamotomy of the thalamic nucleus ventralis intermedius (VIM) is routinely used for movement disorders. During this procedure, it has been observed that high-frequency (100 Hz) stimulation of VIM was able to stop the extra pyramidal tremor. In patients with bilateral tremor of extra pyramidal origin, who were resistant to drug therapy, the therapeutic protocol associated (1) a radiofrequency VIM thalamotomy for the most disabled side, and (2) a continuous VIM stimulation for the other side using stereotactically implanted electrodes, connected to subcutaneous stimulators. VIM thalamotomy relieved the tremor in all operated cases. Side effects were mild and regressive. VIM stimulation strongly decreased the tremor but failed to suppress it as completely as thalamotomy did. This was due in part to the fact that programmable stimulator frequency rate is limited to 130 Hz, while it appeared that the optimal stimulation frequency was 200 Hz. This therapeutic protocol appears to be of interest for patients with bilateral extra pyramidal movement disorders.

Fig 31

In 1987 Alim-Louis Benabid from Grenoble reported the first cases of DBS for intractable tremor. Thalamotomy was known to be very effective in arresting the tremor from Parkinson's disease (PD), essential tremor, and other tremor syndromes. However, when applied bilaterally, unacceptable side effects occurred limiting its utility to unilateral therapy. Benabid demonstrated that unilateral thalomotomy followed by contra-lateral stimulation of the ventral intermediate (Vim) nucleus of the thalamus resulted in bilateral control of tremor with few side effects.

Benabid also demanded that Medtronic design and provide an improved DBS electrode. A custom monopolar PISCES style lead modified for DBS was built at the Bakken Research Center (BRC) in Maastricht followed by another custom design, this one quadripolar. This lead and variations of it became the standard Medtronic DBS lead for clinical trials and eventual market release (see Fig 38).

Incontinence



Clinical Report

J Urol. 1989 Aug;142(2 Pt 1):340-5.

Neural stimulation for control of voiding dysfunction: a preliminary report in 22 patients with serious neuropathic voiding disorders.

Tanagho EA, Schmidt RA, Orvis BR.

Abstract

.... Of 22 patients with serious neuropathic voiding disorders treated during the last 6 years results were available for evaluation in 19 (2 were lost to followup and 1 was withdrawn from the protocol because of an infection at the receiver site). In 8 patients (42 per cent) complete success was achieved. These patients have regained reservoir function, are completely dry and void with electrical stimulation.

Animal Studies

Invest Urol. 1977 Jul
Intraspinal sacral root stimulation for controlled micturition.
Heine JP, Schmidt RA, Tanagho EA.

April 1992
MEDTRONIC ACQUIRES ASSETS FROM UROSYSTEMS

… Medtronic Inc … has acquired certain assets of UroSystems Inc of California …. … include a licence from the University of California and the UroSystems clinical evaluation programme which uses the Medtronic device 'Itrel II' spinal cord stimulation system.

Fig 32

There has long been interest in stimulation for control of micturition dating to at least 1970. It was Emil Tanagho and colleague, Rick Schmidt, from UCSF who first reported on successful control of voiding disorders in humans by sacral nerve stimulation (SNS). Both urgency and retention responded to stimulation. The small California company, Urosystems, purchased Itrel II neurostimulators from Medtronic and configured a system for SNS for Tanagho and other members of the study. In 1992, Medtronic acquired the assets of Urosystems which formed the basis for the Interstim Division and product line (Fig 32).

Milestones & Developments

1965-73	EARLY YEARS	
1973-76	EXPANSION YEARS	
1976-85	CONSOLIDATION YRS	
1985-90	MORE EXPANSION	
1990-Present	SCS-Standard of Care	
	DBS-Application Development	
	SNS-Establishing the Therapy	

37

Fig 33

And so we now enter the last 2 decades of neuromodulation.

For **SCS**, the goal was to take the increasing acceptance of SCS for pain management to **"Standard of Care".**

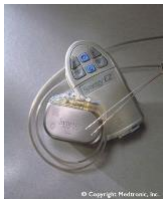
For **DBS**, the goal was to establish DBS for Movement Disorders while pioneering **new applications**.

For **SNS**, the goal was to increase the **acceptance and utilization** of the therapy.

SCS-Standard of Care

1990-Present

Technique intensive	Training & Education	ECMT
Outcomes variable	Clinical Evidence	CRPS Kemmler PROCESS v. d. Abeele EVIDENCE North
Pain is individual	Technology	Rechargeability Flexible Programming Multi-Lead Systems MRI Safe Leads



Neuromodulation 2005: Spinal Cord Stimulation vs. Conventional Medical Management: A Prospective, Randomized, Controlled, Multicenter Study of Patients with Failed Back Surgery Syndrome (PROCESS Study)
Krishna Kumar MD, FRCSC…..

38

Fig 34

In spite of improved hardware and surgical techniques, SCS remains a **technique intensive** therapy. Therefore, **training** is an essential part of the development of the therapy. Training can be in many forms – physician to physician, company representative to physician, or more formally in meeting format. The establishing of European Continuing Medical Training (ECMT) in 1995 was a major step forward towards "Standard of Care" in Europe. Jan Gybels (Fig 34, upper right) from Leuven, Belgium was ECMT's first President. As of the end of 2012, ECMT has trained over 2500 physicians since its founding.

It is the nature of pain medicine, in fact most of medicine, that **outcomes are variable**. Therefore, we must always talk of what percent of patients will receive which percent of pain relief. It is important that physicians understand these limits and communicate them to potential patients. Therefore, **clinical evidence** is essential to achievement of "Standard of Care". Three notable randomized studies have been published: Kemler et. al, Kumer et. al, and North et. al.

Kemler, Maastricht, the Netherlands, compared SCS plus physical therapy (PT) to PT alone in patients with reflex sympathetic dystrophy.

Kumer, Regina Canada, was the lead investigator in a Medtronic study of SCS plus Optimal Medical Therapy (OMT) vs. OMT alone. (Acknowledgement here to Carine van den Abeele in the Medtronic European Clinical Group. Without Carine, the study would never have been started let alone completed.)

North and colleagues at Johns Hopkins hospital in Baltimore conducted a study comparing SCS to reoperation in patients with prior back surgery for pain.

N Engl J Med. 2000 Aug 31;343(9):618-24.
Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy.
Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnée CA, van den Wildenberg FA.

Neuromodulation 2005: Spinal Cord Stimulation vs. Conventional Medical Management: A Prospective, Randomized, Controlled, Multicenter Study of Patients with Failed Back Surgery Syndrome (PROCESS Study)
Krishna Kumar MD, FRCSC…..

Neuromodulation. 2011 Jul-Aug;14(4):330-5
Spinal cord stimulation versus re-operation in patients with failed back surgery syndrome: an international multicenter randomized controlled trial (EVIDENCE study).
North RB, Kumar K, Wallace MS, Henderson JM, Shipley J, Hernandez J, Mekel-Bobrov N, Jaax KN.

And finally, **pain is very personal**. Therefore, therapy must be carefully **tailored to patient** need. Improved flexibility of programmers, dual channel stimulators capable of driving multi-lead systems, and rechargeability help the physician achieve the right therapy for each patient. MRI safe leads introduced in Europe in 2013 assure that patients will not be blocked from receiving necessary diagnostics in the future (Fig34).

A New Spin-Off from SCS

Earlier (Fig 5) peripheral nerve stimulation (PNS) was mentioned. Repeated reports in the early years described PNS as more effective than DCS. However, PNS is limited to pain within a single nerve distribution. Most candidates for Neuromodulation presented with broader pain patterns making PNS impractical. Furthermore, surgical insertion of a cuff electrode around a peripheral nerve is not a trivial surgery and complications did occur. Thus PNS was little used in the intervening years.

Neuromodulation. 1999 Jul;2(3):217-21.
Peripheral neurostimulation for control of intractable occipital neuralgia.
Weiner RL, Reed KL

Fig 35

In 1999, Rick Weiner, Dallas, USA, reported on a series of patients suffering from various headache syndromes stimulated with electrodes placed subcutaneously over the occipital nerve (Fig 35). Several physicians picked up the idea and began to explore the concept of subcutaneous electrode placement for stimulation of peripheral nerves for other pain types, particularly low back pain which is difficult to treat with SCS. Today, peripheral nerve field stimulation (PNFS) remains a growing investigational interest.

DBS-Application Development

1965-73	EARLY YEARS	
1973-76	EXPANSION YEARS	
1976-85	CONSOLIDATION YRS	
1985-90	MORE EXPANSION	
1990-Present	SCS-Standard of Care	
	DBS-Application Development	
1979-Present	Physician Sponsored Studies	DBS for Pain
1993	Benabid	DBS for PD
'90's	Kupsch and others	Movement Disorders
1987-2004	Fisher, Velasco, Boon	Epilepsy
1999	Nuttin	OCD
2003-5	Malone, Mayberg	Depression

Fig 36

39

DBS for Pain was market released prior to the Medical Device Act of 1976. In 1979 the FDA called for clinical evidence of safety and efficacy to be submitted. Although Medtronic had clinical data from the study groups, it did not meet the standards required by the FDA and, therefore, the company withdrew the product from the market. Physicians who wanted to continue to study the therapy had to file physician sponsored studies with their regulatory agencies. A few physicians did and continued to advance the therapy. After market release of DBS for tremor, physicians could purchase the system and use it off label for pain. Medtronic does not market DBS for pain but a few physicians, most notably, Tipu Aziz from Oxford, did continue treating and studying pain patients off-label (Fig 37).

Neurosurgery. 2012 Nov 10.

Long-term Outcomes of Deep Brain Stimulation for Neuropathic Pain.

Boccard SG, Pereira EA, Moir L, Aziz TZ, Green AL.

Abstract

RESULTS: 197 patients were referred over twelve years, of whom 85 received DBS for various etiologies: 9 amputees, 7 brachial plexus injuries, 31 after stroke, 13 with spinal pathology, 15 with head and face pain, and 10 miscellaneous. Mean age at surgery was 52 years and mean follow-up 19.6 months. Contralateral DBS targeted the periventricular gray area (PVG; n=33), the ventral posterior nuclei of the thalamus (VPL/VPM; n=15), or both targets (n=37). Almost seventy percent (69.4%) of patients retained implants 6 months after surgery. 39 of 59 (66%) of those implanted gained benefit and efficacy varied by etiology, improving outcomes in 89% after amputation and 70% after stroke. In this cohort, sustained >30% improvements in VAS, MPQ, SF-36, and EQ-5D were observed in 15 patients with >42 months follow-up, with several outcome measures improving from those assessed at one year. CONCLUSION:: DBS for pain has long-term efficacy for select etiologies. Clinical trials retaining patients in long-term follow-up are desirable to confirm findings from prospectively assessed case series.

Fig 37

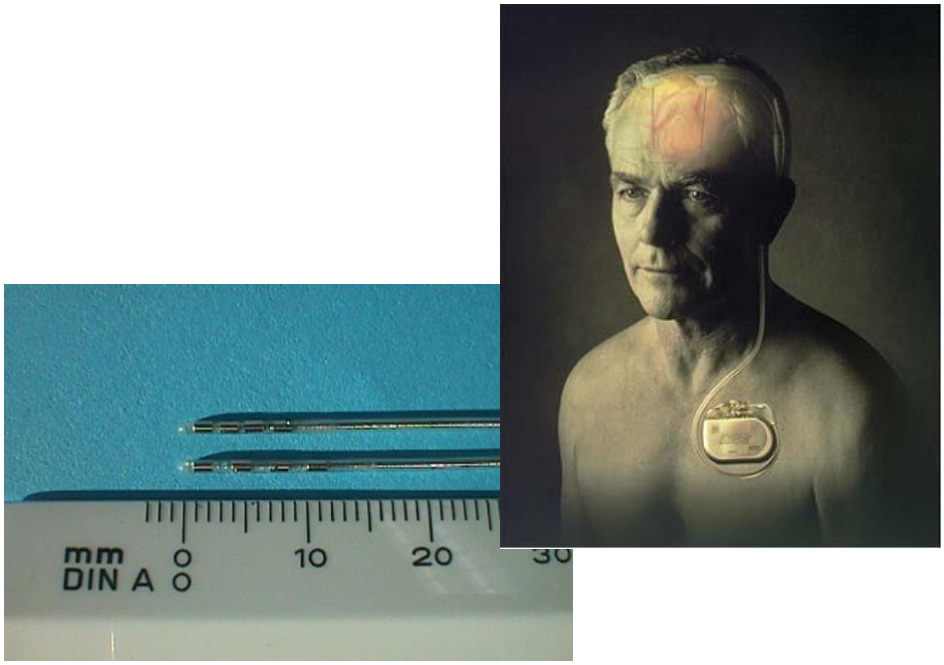


Fig 38

Encouraging clinical reports from Benabid on results of DBS in treating tremor in about 1990 led Medtronic to a series of improvements in the DBS system. As noted earlier, Benabid's demands for an improved electrode led to custom electrodes which then became the standard electrodes used for clinical studies and released to the market. Paralleling this was the development of a dual channel stimulator suitable for treating bilateral disorders (Fig 38).

These improvements lead directly to physicians pioneering new targets to treat other new neurological disorders.

Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease.
Benabid AL, Pollak P, Gross C, Hoffmann D, Benazzouz A, Gao DM, Laurent A, Gentil M, Perret J.
Stereotact Funct Neurosurg. 1994;62(1-4):76-84

Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder.
Nuttin B, Cosyns P, De r H, Gybels J, Meyerson B.
Lancet. 1999 Oct 30;35 .

Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression.
Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, Rauch SL, Rasmussen SA, Machado AG, Kubu CS, Tyrka AR, Price LH, Stypulkowski PH, Giftakis JE, Rise MT, Malloy PF, Salloway SP, Greenberg BD.
Biol Psychiatry. 2009 Feb 15;65(4

Deep brain stimulation for treatment-resistant depression.
Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy
Neuron. 2005 Mar 3;45(5):651-60.

Fig 39

Benabid (Grenoble) extended his work to stimulate the subthalamic nucleus (STN) to treat the cardinal symptoms of PD-tremor, rigidity, and bradykinesia (Fig 39, top).

Bart Nuttin (Leuven) pioneered stimulation for obsessive compulsive disorder (OCD) by stimulating the internal capsules, later the ventral capsule/ventral striatum with improved results (Fig 39, left).

Helen Mayberg (Atlanta) & Don Malone (Cleveland) reported favorable results of DBS in pathologically depressed patients (Fig 39, bottom & right). Mayberg stimulated the sub-genial cingulated gyrus and Malone the anterior nucleus of the thalamus.

DBS for depression remains investigational; DBS for OCD has CE Mark and is approved for humanitarian use in the US. DBS for both tremor and the symptoms of PD is fully approved in worldwide.

Meanwhile, Günther Deuschl, Kiel, and Yves Agid, Paris, collaborated to design and implement a prospective quality of life, randomized study, called Earlystim. Patients still early in the development of the disease were selected and randomized to DBS vs. OMT. The study was coordinated by Michael Schupbach, Bern Switzerland, who worked in Paris for the time of the study. The positive outcome of the study will show that the DBS patient group had a better quality of life than the control group who continued on medication. The paper has been accepted for publication in the New England Journal of Medicine.

Deuschl Schupbach Agid

Fig 40

Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus.
Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B.
Lancet. 2000 Jun 24;355(9222):2220-1.

Pallidal and thalamic neurostimulation in severe tardive dystonia.
Trottenberg T, Paul G, Meissner W, Maier-Hauff K, Taschner C, **Kupsch A**.
J Neurol Neurosurg Psychiatry. 2001 Apr;70(4):557-9.

Fig 41

The successful treatment of Parkinson's disease and tremor lead physicians to explore DBS for other movement disorders. Coubes, Montpellier, (Fig 41 top) reported on his results in generalized dystonia. Kupsch, Berlin, (Fig 41, bottom) reported favorable results in patients with tardive dystonia. Studies continue in patients with other dystonia types and other movement disorders.

A trio of physicians has led the exploration of DBS for epilepsy. Epilepsy involves major parts of the brain; hence, arresting the seizure may be considered at many sites. Fisher summarizes the many locations that have been explored (Fig 42-bottom).

Today, stimulation of the anterior nucleus (AN) of the thalamus has CE Mark in Europe; other targets are investigational.

Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report.
Velasco F, **Velasco** M, Ogarrio C, Fanghanel G.
Epilepsia. 1987 Jul-Aug;28(4):421-30.

Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy.
Vonck K, **Boon P**, Achten E, De Reuck J, Caemaert J.
Ann Neurol. 2002 Nov;52(5):556-65.

Brain stimulation for epilepsy.
Theodore WH, **Fisher RS**.
Lancet Neurol. 2004 Feb;3(2):111-8.

Deep brain stimulation…has been applied to the **cerebellum, caudate nucleus, centromedian thalamus, anterior thalamus, subthalamus, hippocampus,** and **neocortical seizure foci**

Fig 42

And so here we are in January 2013. Three stimulating systems, SCS, DBS, & SNS are commercially available. They are currently being used to treat 12 different medical disorders, either commercially, in clinical studies, or off-label at the initiation of individual physicians. The future of this area of medicine looks very bright indeed.

System	Disorder	Regulatory Status		Comment
		US	Europe	
SCS	Pain	Yes	CE	Continued growth forseen
SCS	PVD	No	CE	Limited patient benefit; no growth foreseen
SCS	Angina	No	CE	Medical referrals difficult
PNFS	Headache, Pain	No	CE	Promising, Investment needed
DBS	Pain	No	No	Continued off-label use at same low level
DBS	Tremor	Yes	CE	Continued growth
DBS	PD	Yes	CE	Continued rapid growth
DBS	Dystonia	Humanitarian	CE	Continued growth
DBS	OCD	Humanitarian	CE	Big opportunity – needs investment
DBS	Depression	Physician Studies	No	Pending clinical outcomes
DBS	Epilepsy	No	CE	Multitude of targets makes conclusions difficult
SNS	Incontinence	Yes	CE	Big opportunity with proper investment

Fig 43

This paper is an adaptation from a presentation given at an ECMT Training in Brussels Belgium on January 25, 2013.

Draft 2

Keith Mullett

ADDENDUM

Ten, twenty years later, people ask, “Where did that come from? Why did you do it that way? Here are a couple answers.

PISCES®

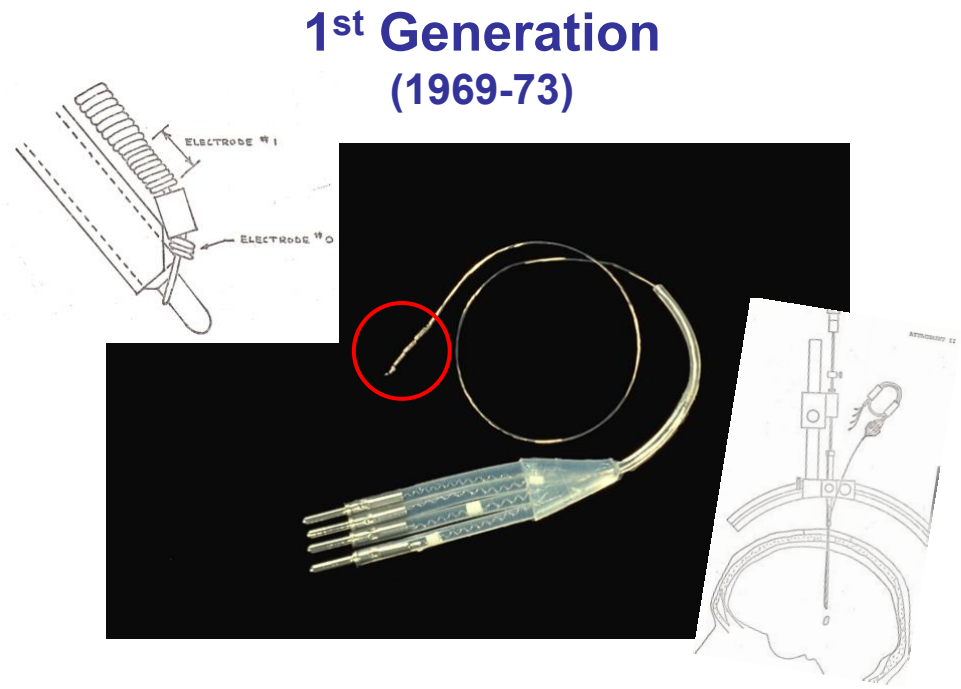
The PISCES® Family of SCS Leads was the first which could be inserted into the epidural space through a needle. Hence, a **Percutaneously Inserted Spinal Cord Epidural Stimulator (PISCES®).** It also reminds us that we really haven’t developed anything new. The ancient physician, Scribonius Largus, court physician to Roman Emperor Claudius, and his colleagues used the electrical fish to provide electrical stimulation to their pain patients, many of whom presented with painful gout.

ITREL®

In the early 70’s, Earl Bakken recruited Dr. Charles Ray, a neurosurgeon working for a pharmaceutical company in Basel, Switzerland to return to the US to become VP of Research for Medtronic. “Research” at that time included, in fact, was mainly Neuromodulation. This was in the time prior to the first implantable Neurostimulator. Systems used Radio Frequency coupled devices with an external transmitter and an implantable receiver. Charley conceived of a product line consisting of a family of transmitters, a family of receivers, a family of electrodes, and a family of leads (extensions). The physician could then select from among the choices in the “catalog of devices” to create an **Integrated Transmitter, Receiver, Electrode, Lead (ITREL®) System** for whatever therapy was needed for a particular patient. The name was copyrighted. However, before the concept was implemented the US Congress passed the Medical Device Act (1976) and the FDA quickly put a stop to the physician “pick and choose” approach. Companies were required to sell systems with clinically proven indications.

Marketing traditionally dislikes acronyms; that is an engineering thing. However, Marketing liked the Itrel name. When the first fully implantable Neurostimulator was developed, they named it the Itrel to emphasize to the physician that Medtronic fully implantable stimulators had IntegraTed RELiability (Itrel®).

0, 1, 2, 3 ???



The first DBS Leads were a copy of a lesioning electrode (above). It was necessary to inform the surgeon which of the 4 connector fingers was attached to which of the 4 electrode contacts at the distal end (red ring). We didn't have any implantable grade number tags available for those first leads. Hence, we chose to put white bands on the fingers to designate which was which electrode. 1 band, 2 bands, 3 bands, 4 bands, right ? Wrong! There was not enough room on the finger for the build technician to place 4 bands. OK, then 0 bands, 1 band, 2 bands, & 3 bands. Besides, the physician could remember that 0 was the distal (deepest) contact because that contact was shaped like a »0» (upper left).

A couple years later we were able to get bands with numbers printed on them so that only 1 band was needed per finger (above). However, the 0, 1, 2, 3 designation remained.