CHAPTER

1

What Is Neuromodulation?

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OUTLINE

DEFINING NEUROMODULATION

Neuromodulation is among the fastest-growing areas of medicine, involving many diverse specialties and impacting hundreds of thousands of patients with numerous disorders worldwide. In the past decade, neuromodulation has witnessed significant advances with regard to the science, mechanisms, clinical applications, and technology development. These advances have been coupled with the rapid growth of the neuromodulation device industry and improvements in current devices and development of next generation neuromodulation systems (Figure 1.1).

Neuromodulation is "technology impacting on the neural interface." It is the process of inhibition, stimulation, modification, regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral or autonomic nervous systems. It is the science of how electrical, chemical, and mechanical interventions can modulate the nervous system function. Neuromodulation is inherently non-destructive, reversible, and adjustable. The INS (the International Neuromodulation Society) (Sakas *et al.*, 2007) defines neuromodulation as a field of science, medicine, and bioengineering that encompasses implantable and non-implantable technologies, electrical or chemical, for the purpose of improving quality of life and functioning of humans. At the present time, neuromodulation implantable devices are either neural stimulators or microinfusion pumps. These devices are being utilized for the management of chronic pain, movement disorders, psychiatric disorders, epilepsy, dismotility disorders, disorders of pacing, spasticity, and others (Figure 1.2). Neuroprostheses such as cochlear implants and sacral root stimulators are also commonly included within the definition of neuromodulation.

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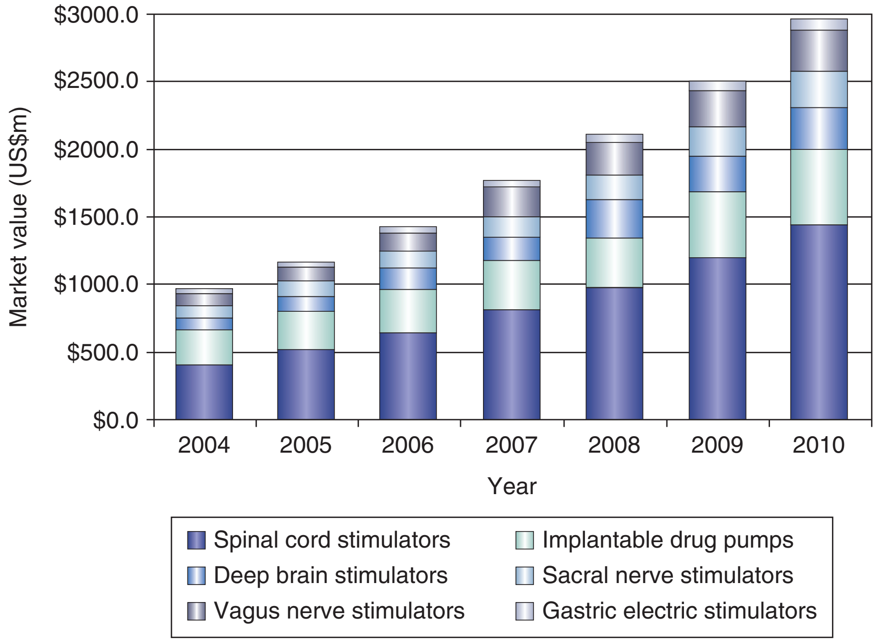

FIGURE 1.1 The growing neuromodulation market between 2004 and 2010. By the year 2010, the market is expected to reach $3bn (Source: Millennium Research Group, 2006)

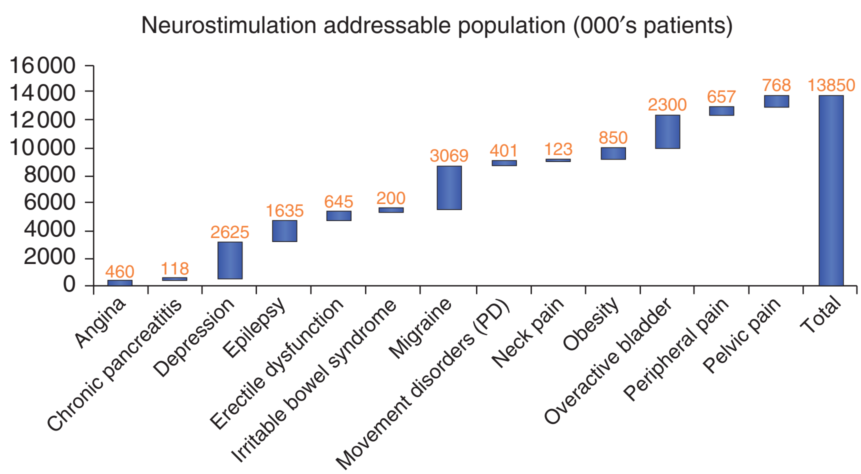

FIGURE 1.2 Some of the disorders and the numbers of persons affected by these disorders available to being treated by neurostimulation, a form of neuromodulation
(Source: US qualitative research with referrers and potential implanters, literature search, internal discussions, and data analysis)

Jan Holsheimer (2003) suggests that for a therapy to be considered neuromodulation, the therapy must consist of the following:

1. The therapy must be dynamic, ongoing (continuous or intermittent) intervention, and not a short and non-recurring procedure.
2. The activity of specific neural networks is affected by the ongoing electrical stimulation or by ongoing neuropharmacological stimulation.
3. The clinical effect is continuously controllable by varying one or more stimulation parameters to satisfy a patient's need.

Neuromodulation therefore is either electrical or chemical. Electrical neuromodulation is electrical stimulation of the brain, spinal cord, peripheral nerves, plexuses of nerves, the autonomic system, and functional electrical stimulation of the muscles, while chemical neuromodulation uses direct placement of chemical agents to neural tissues through utilization of technology of implantation such as epidural or intrathecal delivery systems.

Other Definitions and Terms

The term neuromodulation can be defined as a technology that impacts upon neural interfaces and is the science of how electrical, chemical, and mechanical interventions can modulate or change central and peripheral nervous system functioning. It is a form of therapy in which neurophysiological signals are initiated or influenced with the intention of achieving therapeutic effects by altering the function and performance of the nervous system. The term neuromodulation, in the opinion of these authors, should replace other terms that are relevant to the field and are being used, including neuroaugmentation, neurostimulation, neuroprosthetics, functional electrical stimulation, assistive technologies, and neural engineering (Sakas *et al.*, 2007). These terms have much overlap and tend to confuse the uninitiated.

Neuroaugmentation is defined by the OnLine Medical Dictionary as the use of electrical stimulation to supplement the activity of the nervous system. Neurostimulation is the process or technology that applies electrical currents, in varying parameters, by means of implanted electrodes to achieve functional activation or inhibition of specific neuronal groups, pathways, or networks. Functional electrical stimulation, also known as FES, is defined as a technique that uses electrical currents to activate nerves innervating extremities affected by paralysis resulting from spinal cord injury (SCI), head injury, stroke, or other neurological disorders, restoring function in people with disabilities (Wikipedia: Functional Electrical Stimulation). FES is electrical stimulation of a muscle to provide normal control in order to produce a functional useful contraction, therefore, electrical stimulation that produces only sensory response generally would not be termed as FES and electrical stimulation that reduces pain is also not FES. Neuroprosthetics "is a discipline related to neuroscience and biomedical engineering concerned with developing neural prostheses, artificial devices to replace or improve the function of an impaired nervous system. The neuroprosthetic that has the most widespread use today is the cochlear implant with approximately 100 000 in worldwide use as of 2006" (Wikipedia: Neuroprosthetics). Neural engineering is an emerging interdisciplinary field of research that uses engineering techniques to investigate the function and manipulate the behavior of the central or peripheral nervous systems. The field draws heavily on the fields of computational neuroscience, experimental neuroscience, clinical neurobiology, electrical engineering and signal processing of living neural tissue, and encompasses elements from robotics, computer engineering, neural tissue engineering, materials science and nanotechnology (Answers.Com.).

THE FIELD OF NEUROMODULATION

Neuromodulation, paraphrasing Jan Holsheimer (2003), should be concerned with long-term treatment of chronic conditions. It is a rapidly evolving multidisciplinary biomedical and technical field and is among the fastest-growing fields of medicine today. Multiple specialties are now utilizing neuromodulatory techniques to benefit their patients. The field of neuromodulation covers a wide and heterogeneous range of conditions that include disorders of cardiac pacing, eyesight, gastric motility, epilepsy, headaches, hearing , limb and organ ischemia, movement disorders, occipital neuralgia, chronic pain, peripheral neuralgias, psychiatric and neurobehavioral disorders, spasticity, stroke, traumatic brain injury, urinary frequency, urinary urgency, urinary and fecal incontinence, and more (see Figure 1.3).

Because the nervous system controls body functions and because disorders of body functions are ubiquitous, many clinical specialists, including anesthesiologists, cardiologists, gastroenterologists, neurologists, neurosurgeons, ophthalmologists, otolaryngologists, pain physicians, psychiatrists, physical medicine and rehabilitation specialists, and urologists use the therapies of neuromodulation.

The goal of this book was to provide a comprehensive review and discussion pertaining to all aspects of the field of neuromodulation. Specific chapters will address the fundamentals of neuromodulation, including mechanisms of neuromodulation, neural networks, neuroscience, basics of device design, impact of technology at the neural interface, computational science, modeling, and others. This essential information benefits all those involved with neuromodulation. In addition to the fundamentals and general background topics, specific clinical applications of neuromodulation for various conditions will be provided with chapters pertaining to the following topics.

NEUROMODULATION FOR CHRONIC PAIN

An extensive and detailed discussion of neuromodulation for pain management will be provided in

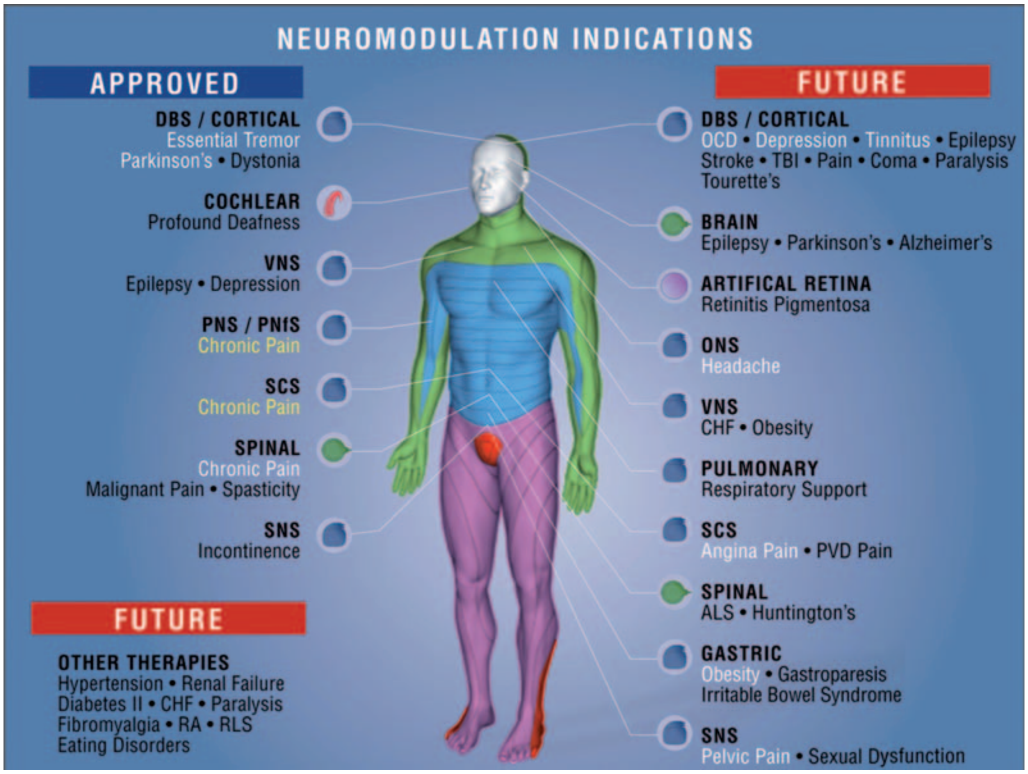

FIGURE 1.3 Uses of neuromodulatory devices, both electrical and chemical, to treat a myriad of disorders of the human body (Reproduced with permission of Advanced Neuromodulation Systems, Plano, TX)

multiple chapters. Chronic pain is estimated to be the third largest healthcare problem in the world, afflicting around 30% of the worldwide population (Latham and Davis, 1994). Chapters on micro-infusion therapy, spinal cord, peripheral nerve and brain stimulation will review the various methods and approaches used to treat chronic pain conditions. This includes chronic regional pain syndrome (CRPS), headaches, occipital neuralgia, failed back pain, neck pain, extremity pain, degenerative spinal disease pain, central pain, cancer pain, visceral pain, and other pain conditions.

Brain Neuromodulation

Brain neuromodulation involving cortical and sub-cortical neurostimulation has been growing significantly, with a number of emerging applications involving multiple disorders. The most visible among these has been the use of deep brain stimulation (DBS) for treatment of movement disorders (Parkinson's disease, dystonia, essential tremor). The success of DBS for movement disorders in over 55 000 patients worldwide has provided a platform for acceptance of the concept of a brain stimulator or a brain pacemaker. The use of DBS in Parkinson's disease and other movement disorders has ushered in a new ear of brain neuromodulation implants. In this context, the emerging use of brain stimulation for the treatment of neurobehavioral disorders such as obsessive–compulsive disorder and depression as well as epilepsy will be discussed. Additional applications of brain stimulation for eating disorders, addiction, obesity, tinnitus, blood pressure control, and traumatic brain injury will be discussed in the emerging application section. Additional brain neuromodulation chapters pertain to novel uses of brain infusion and neuromodulation approaches for Alzheimer's and other neurodegenerative disorders.

Neuromodulation for Spasticity

The use of intrathecal baclofen infusion pumps has provided significant relief for patients suffering from spasticity secondary to multiple sclerosis, stroke, and other conditions. This is one of the most common and successful uses of neuromodulation infusion devices.

Functional Electrical Stimulation (FES)

FES encompasses the control of movements that are compromised because of impairment. It enhances exercise of paralyzed extremities, and augments activity of afferent neural pathways (Popovic *et al.*, 2002). Applications to improve functional ability of patients include enhancing upper and lower extremity functions as well as increasing range of motion of affected joints. FES devices serve as neuro-orthoses or external controls for motor function. Other benefits of FES include increasing muscle mass, reducing venous pooling, increasing stroke volume and cardiac output, and improvement of cardiovascular fitness, especially for paralyzed patients, as in patients with spinal cord injury. Neuroprosthetics that employ FES are effective in providing functional enhancement in patients with severe neurological impairment as in patients with spinal cord injury or stroke. The goals of these devices are to provide independence of functions of daily living such as standing, walking, breathing, micturition, and defecation (Grill and Kirsch, 2000; Troyk and Donaldson, 2001; Chae *et al.*, 2002).

Neuromodulation and GI Disorders

The use of electrical gastric stimulation for the management of gastroparesis (Forster *et al.*, 2001) has proven to be an effective therapy for the problem. Gastric stimulation normalizes gastric dysrhythmias, entrains gastric slow waves, accelerates gastric emptying, and significantly reduces symptoms of nausea and vomiting in gastroparetic patients (Zhiyue *et al.*, 2003). A number of approaches using neurostimulation are being explored for the management of obesity (Cigaina, 2002, 2004). Additional stimulation of the enteric plexii and the endothelium, itself, has been used for motility disorders of the small and large intestines (Kenefick and Christiansen, 2004; Baeten, 2007; Dinning *et al.*, 2007; Sevcencu, 2007). We have provided chapters on gastric stimulation for obesity, dysmotility disorders and intestinal electrical stimulation are presented.

Neuromodulation for Urological Disorders

Sacral neuromodulation (Ganio and Masin, 2000; Hohenfellner *et al.*, 2001) has become a valid therapeutic option for patients with urological painful and dysmotility conditions such as interstitial cystitis, neurogenic bladder, and overactive bladder. There is an estimated 6% prevalence of classic interstitial cystitis (IC) in American women while an overactive bladder syndrome affects approximately 17% of the adult population of the USA with an estimated worldwide prevalence of 50 million. Additionally, neurogenic bladder (and bowel) is a complication of many common neurological disorders as in multiple sclerosis and spinal cord injury (Brookoff, 2000).

Treatment of refractory overactive bladder was first successfully performed using an implanted percutaneous tibial nerve stimulator (van der Pal *et al.*, 2006). Neurally augmented sexual function can be achieved by the application of electrical stimulation to spinal cord or peripheral nerves, including the sacral nerves (Meloy and Southern, 2006). Sacral nerve stimulation for IC, for overactive bladder, and urinary incontinence is mainstream therapy, today. These various neuromodulation approaches for treating urological disorders are covered in this specific section.

Neuromodulation for Cardiac Disorders

Cardiovascular diseases impose a heavy socioeconomic burden on any healthcare system. Today, pacemakers and defibrillators are common therapeutic tools for cardiac disorders which have improved and saved the lives of millions of patients worldwide. Cardiac pacing devices and neurostimulators have many similarities in evolution and development and significant knowledge can be learned from the story of cardiac pacemakers and defibrillators as applied to the future of neurostimulation. In addition, a number of neurostimulation approaches are being explored for treating cardiovascular disorders and these will be discussed in specific chapters.

In light of the fact that neuromodulation of the nervous system is capable of modulating all nervous system elements (brain, cranial nerves, peripheral nerves, spinal cord, and the autonomic nervous system), as well as body organs and the corresponding functions of the human body, the potential of this field is indeed enormous.

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