COMMERCIALIZING NEUROPROSTHESES:
THE BUSINESS OF PUTTING THE BRAIN BACK IN BUSINESS

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(Samuel W. Hall)

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ABSTRACT

Neuroprostheses are the set of physical devices that interact with the brain, or with other neural tissue to restore, augment, or otherwise influence function. The 1984 FDA approval of the cochlear implant, which uses an implanted electrode array to restore hearing to the deaf, revolutionized the neurological devices market, and catalyzed further research interest in neuroprosthesis. Subsequent commercialization efforts have sought to make the profound clinical benefits of neuroprosthetic technologies widely available to patients with neurological disorders ranging from epilepsy, Parkinson's disease, and depression to tetraplegia and blindness. Despite compelling scientific and technological advances over the past three decades, the clinical benefits of existing neuroprostheses have been only minimally realized. This study attempts to quantify the bottlenecks that have led to this disparity through a broad review of sensory, motor, and central nervous system prostheses, and an in-depth examination of three illustrative case studies. While a number of factors have contributed to the commercial non-viability of neuroprostheses, the burdens of FDA regulation and of securing adequate federal reimbursement through Medicare stand out as the single greatest challenges faced by technology developers. A century of Congressional oversight has produced FDA policies that are daunting even to the best funded of developers, and recent measures designed to expedite the review of breakthrough technologies have been underutilized to date. The exuberant medical spending of the late 1970s and early 1980s has led to Medicare coverage and payment policies that are profoundly biased against emerging technologies, and have diminished neuroprosthesis markets to the verge of extinction. Expeditious FDA review and more health economically sound Medicare policies are prerequisites for the commercialization of neuroprosthetic technologies that promise to change the lives of millions worldwide.

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INTRODUCTION

On June 13, 2002, before a captivated audience at the 48th annual meeting of the American Society of Artificial Internal Organs (ASAIO) in New York, William Dobelle showed video footage of a 39-year-old blind man, Jens Smith, driving a blue Mustang convertible cautiously around the Dobelle Institute's Long Island parking lot (Kotler, 2002). Dobelle, an enigmatic pioneer in the field of functional brain stimulation, had been working towards an artificial vision system for over 30 years, and just hours after the implant in Jens' occipital cortex was activated many of his dreams and expectations became reality. Early experiments on a World War II veteran who was blinded in a 1945 battle demonstrated promising results, but the computer technology available in the late 1970s limited Dobelle's ability to develop a portable, functional system. However, despite early innovations and successes, Dobelle had become a pariah in the field of neuroprosthesis research by the mid-1980s, and because most of his work on visual prosthesis had been conducted in private, outside of academia, many in the race to restore sight viewed his results with skepticism.

In late 1994, Dobelle ended more than a decade of virtual silence with the claim that the "summit" in visual prosthesis was closer than many in the field believed (Dobelle, 1994). Five years later, on the dawn of the new millennium, Dobelle submitted a paper to the ASAIO journal giving an outline of his system and presenting clinical results from a 62-year-old patient who had been blind for over 26 years (Dobelle, 2000). Images recorded by a miniature camera mounted on a pair of sunglasses were relayed to a Toshiba sub-laptop computer for processing, and the output stimuli were sent to an array of 57 platinum electrodes implanted in the patient's visual cortex. Jens and the seven other patients who have been implanted with the Dobelle Institute's Artificial Vision System to date perceive only crude images, resembling those displayed on athletics score boards, through their

implants. However, image quality matters little to patients who have been living in total darkness for decades. In a June 2002 interview, Jens quipped, "they've restored my fifth sense—it doesn't matter how crude it is (Kotler, 2002)."

Despite such enthusiasm, the visual prosthesis will not be widely available for years. In response to the rigors of securing FDA approval for a formal clinical investigation of his system in the United States, Dobelle has moved his operations overseas, and is currently collaborating with a neurosurgeon in Portugal to implant the prosthesis at a cost of over $100,000 (Kotler, 2002). This study is an attempt to understand and quantify the factors that drive innovators like Dobelle outside the United States and that render even revolutionary neuroprosthetic technologies commercially non-viable.

Neuroprostheses are the set of physical devices that interact with the brain or other neural tissue to augment, restore, or otherwise impact function. Such assistive devices range from intramuscular stimulation systems designed to limit limb atrophy in paralysis, to implanted bladder voiding systems and more complex implanted neuromuscular control systems intended to restore locomotion and limb function, to cochlear and retinal implants for the restoration of audition and vision. The overall research effort in neuroprosthetic technologies can be broken down into several major approaches—direct muscle stimulation, peripheral nerve stimulation, spinal cord stimulation, and cortical stimulation—each with its strengths and subset of potential applications. While the earliest attempts at neural prosthesis as a general concept were based largely in direct muscle stimulation (Liberson, Holmquest et al., 1961), peripheral nerve stimulation, spinal cord stimulation, and direct brain interfaces have become the focus of most current neuroprosthetic research.

Neuroprosthetics has evolved into a diverse and at times highly fragmented field, and a major objective of this project is to offer a broad and coherent perspective on current trends in neuroprosthetic research, in particular as such trends relate to the clinical utility

and commercialization of new neuroprosthetic devices. A number of broad reviews of the field exist—recent efforts by Prochazka and coworkers, and Grill and Kirsch (Grill and Kirsch, 2000; Prochazka, Mushahwar et al., 2001) stand out as noteworthy examples. However, strong bias towards the authors' own research interests are common to most reviews of neuroprosthetic technologies. Whether this slant is towards motor prostheses, as is the case with Prochazka et al., towards the use of penetrating microelectrode arrays, or in favor of any other emerging technology, such biases significantly limit the scope of neuroprosthesis reviews. Certainly, from the standpoint of fundamental research, narrow perspectives are not a significant shortcoming—while those researching visual prostheses rely on many of the same techniques and theoretical notions as groups focused on spinal cord stimulation for restoration of limb control, reviews focused within a single arm of neuroprosthesis are often more manageable and more pertinent. From the perspective of this project, however, a narrowly focused review is insufficient. In terms of potential for commercialization, the theoretical links between approaches in neuroprosthesis are more significant than the differences between them. It would be highly logical, for example, for a company developing penetrating microelectrode array technology for one indication to subsequently harness that same technology for broader uses.

The regulatory and financial barriers to successful neuroprosthesis commercialization are significant, as illustrated by the low number of new market entrants each year. To the extent that the development of new neuroprostheses is hampered by insufficient technology, there is a need for collaboration and free exchange of technological approaches among the field's various factions. Both of these observations support the assertion that unity and coherence in the field of neuroprosthetics are prerequisites for optimal innovation and clinical applications. A concise wide-angle review of neuroprosthetics is a daunting task, but the following attempt is intended as a step towards a

unified perspective that may be critical to the commercial success of neuroprosthetic technologies.

Over the past four decades, research in neuroprosthesis has generated a handful of clinical successes and has gained lasting acceptance in the scientific community—noteworthy advances have been made. However, research groups whose efforts have resulted in tangible clinical benefits are in the minority; cochlear implants, deep brain stimulators, and vagus nerve stimulation systems are the only devices that can accurately be portrayed as broadly available. The transfer of technologies from bench top to clinical practice has proceeded at a mere trickle, but the level of interest in neuroprosthetics research, the emergence of promising new technologies, and published accounts of limited clinical successes suggest that this slow rate of clinical and commercial progress is not the result of technological insufficiency.

Modern approaches to neural interfacing have their shortcomings, and the biocompatibility of implanted devices is, perhaps, the most significant issue in device design and implementation. However, these concerns confront the implantable medical devices industry as a whole, and the unsinkable commercial success of the cardiac pacemaker and other cardiac products has produced broadly applicable biocompatible materials. While the biocompatibility demands of intracortical devices are significantly greater than those of chest implants like pacemakers, materials currently used in penetrating microelectrodes and electrode arrays—namely silicon and platinum or iridium—have been shown to be sufficient in animal and limited human experience (Williams, Rennaker et al., 1999; McCreery, Yuen et al., 2000; Prochazka, Mushahwar et al., 2001; Weiland, Anderson et al., 2002). Furthermore, improved biomaterials are under development, and the use of neurotrophic factors and of highly biocompatible polymer coatings may offer promising strategies for the maintenance of an efficient chronic electrode-nerve interface. Effects such as tethering—

where neural tissue damage results from the forces exerted on microelectrodes and arrays by their leads—remain a significant concern, and provide a significant motivation for the development of fully-implanted leadless devices. Leads have proven to be a primary source of system failure and of resulting biocompatibility problems, and the minimization or elimination of leads may produce more robust, flexible systems. Because many facets of neural coding remain obscure, signal processing for sensory and other neuroprostheses remains a challenge. However, current signal processing technology has been adequate to provide profound clinical benefit to cochlear implant patients, and BCI processing algorithms have allowed limited communication with locked-in patients. The major technological hurdles that face neuroprosthetics research will not be easily or quickly overcome, but existing technology offers solutions sufficient for meaningful clinical applications.

Several important trends emerge from a broad review of neuroprosthetic technologies. Penetrating microelectrode arrays are rapidly becoming a core technology in ongoing neuroprosthesis development efforts, with applicability in virtually every device class. Microelectrode arrays are under investigation for applications in auditory prosthesis (Badi, Hillman et al., 2002), in visual prosthesis (Rousche and Normann, 1998; Maynard, Fernandez et al., 2000), as a mechanism of discrete spinal cord and peripheral nerve microstimulation in motor neuroprosthesis (Woodford, Carter et al., 1996; Mushahwar, Collins et al., 2000), and as the basis of brain-machine and brain-computer interfaces for both communication and control of motor neuroprostheses (Williams, Rennaker et al., 1999; Wessberg, Stambaugh et al., 2000). Companies founded to commercialize microelectrode array technologies, such as Cyberkinetics which now markets an array pioneered at the University of Utah, may find themselves very well placed as the clinical application of these technologies becomes more prevalent. The work of Iezzi and Fishman on implanted

epiretinal prostheses based on glutamate uncaging is a further example of the critical role microfabrication techniques have come to play in neuroprosthesis (Vastag, 2002).

The clinical deployment of the BION, a fully implanted microstimulator under development by Advanced Bionics Corporation, highlights the recent trend towards fully implanted leadless neuroprostheses. While the BION demonstrates the trend in motor neuroprosthesis, work based out of the University of Michigan on fully implanted cortical interfaces underscores the drive towards leadless devices in other arenas. Extrapolating from these growing interests, future generation neuroprostheses will incorporate penetrating microarrays or other micromanufactured components as the basis for closed-loop control of leadless neuroprostheses. Advances in telemetry and in microfabrication of electronics are among the critical prerequisites for the realization of these objectives, but progress will follow the demonstration of compelling clinical benefits. The recent founding of *Neurotech Reports*, the first publication devoted exclusively to the neuroprosthesis industry may prove instrumental in uniting venture capitalists with researchers, and in helping both groups to identify further broadly applicable trends in neurotechnology.

Technology is not the primary factor inhibiting clinical and commercial advances in neuroprosthesis. All current neuroprosthetic devices rely on the electrode-nerve interface as the sole means inducing neural response, and thus restored function. While recent research on techniques like neurotransmitter uncaging posit some exceptions to this rule, the electrode can be viewed as a persistent common denominator. Existing electrode systems, from microwires and platinum disc electrodes to penetrating microarrays, are capable of effectively and chronically interfacing with the human nervous system. Currently employed processing systems, as exemplified by cochlear implant processors and BCI algorithms, can both stimulate and record neural activity in meaningful ways. Some neuroprostheses are hampered by technological insufficiency—the insensitivity of microphotodiodes used in

subretinal prosthesis is a case in point. However, in general, currently deployed neuroprosthetic technologies are not being optimally employed towards clinical benefit. Neuroprostheses are being developed and tested faster than they are being accepted and commercialized, and federal policies are largely responsible for this fundamental disconnect.

The influences of FDA regulation and of Medicare reimbursement policy on the commercialization of the cochlear implant for the deaf, the NeuroControl Freehand System for the restoration of hand grasp in tetraplegia, and the NeuroCybernetic Prosthesis for the treatment of epilepsy tangibly demonstrate the stifling effect that federal policies can have on neuroprosthesis innovation. These case studies, presented in the following three chapters, point to several fundamental shortcomings in the way the FDA evaluates new medical devices, and in Medicare's procedures for determining both its coverage policies and payment rates for breakthrough technologies.

The FDA's legislative history has resulted in a regulatory paradigm where gaining approval for a new medical technology frequently costs tens of millions of dollars, and takes more than a decade. While the FDA has a statutory mandate to act in the interest of public health, the administration's policies are increasingly levying insurmountable burdens against the developers of neuroprostheses. A close examination of current FDA policy and practice in Chapter Four suggests that the administration must make a concerted effort to align its commitments to device safety and efficacy with the economic reality of neuroprosthesis markets and the ability of developers to demonstrate the clinical utility of their devices.

While the FDA's impositions on neuroprosthesis developers are often justified by its public health mandate, the burdens placed on commercialization efforts by the Centers for Medicare and Medicaid Services are unpredictable and frequently make questionable health-economic sense. Intricacies in the way Medicare determines the amount it is willing to pay for emerging technologies have resulted in profound disincentives for the clinical adoption

of neuroprosthetic devices, and have curbed neuroprosthesis markets to the point of commercial non-viability. As such, Medicare coverage and reimbursement policies constitute both the most pernicious and most easily changed hurdle faced by neuroprosthesis commercialization efforts. Chapter Five examines the specific flaws in Medicare policy that produce technology aversion, and suggests that Medicare should make fundamental changes to the way it views neurological devices.

Neuroprosthetic technologies hold the potential to revolutionize the treatment of virtually all neurological disorders, from blindness to Parkinson's disease, and may have even farther-reaching implications for society as cortical interfacing technologies mature. However, as high-technology breakthroughs, neuroprostheses have faced tremendous scientific, regulatory, and financial inertia. These barriers have become embedded in the regulatory policies of the FDA and in the coverage and payment policies of the Centers for Medicare and Medicaid Services, and expedient, intelligent policy reforms have the potential to bring life-altering clinical benefits to millions of individuals worldwide.