Translating Surgical Research to Clinical Practice

M. Sean Grady, M.D.

The field of neurosurgery is remarkable for the innovation generated by its practitioners.

There is a long tradition of neurosurgeons innovating at the bedside to improve surgical outcome. At the same time, neurosurgeons also have a tradition of working in the laboratory to test ideas and then bring them to the clinic. The establishment of the Hunterian Laboratory at Johns Hopkins University by Harvey Cushing clearly exemplifies this practice. In the present era, it can be difficult to translate research activities into clinical practice for a wide variety of reasons, including complexities and bureaucracy of clinical trials paper work, inadequate funding, barriers placed by the hospital controlling expenditures, and others. It is the hope that the information that follows will be useful to neurosurgeons whose creativity has always been remarkable regarding how to channel that creativity into meaningful changes in clinical practice.

BACKGROUND

In preparing this manuscript, I reviewed technologies available to me when I began my residency training at the University of Virginia in 1981. At that point, spine instrumentation was extremely rudimentary. Pedicle screws, cervical plates, artificial discs, or minimally invasive techniques were all far off in the future. The majority of instrumentation involved use of wire, hooks, rods, and external orthoses. Computed tomographic (CT) scanning had just recently been introduced and scan times for a study of the brain typically took 5 to 10 minutes. Magnetic resonance imaging (MRI) scanning had not been introduced. Radiation therapy consisted of conventional modalities with very little precision compared with today's stereological and intensity-modulated techniques. The pterional craniotomy was the mainstay for cranial base surgery. Parkinson's disease was exclusively treated with pharmacological agents, although it was becoming increasingly recognized that these drugs had substantial side effects with time. Brain tumors were diagnosed through routine simplistic histochemical stains; there were no molecular markers at that point. Finally, the pinnacle of vascular neurosurgery was achieved by the use of small clips to occlude aneurysms through microsurgery, introduced in the 1960s. These advances in the field certainly made surgery much safer that it was 30 years before, but when one compares them with today's techniques, it is readily apparent that there has been a huge advance in our field in this 25-year interval.

Today, spine surgeons are using minimally invasive techniques to perform decompression and fusion, leading to shortened hospital times, reduction of blood loss, and substantial decreases in the amount of pain after surgery. The introduction of MRI scanning has totally changed the perspective on diagnosis and treatment of problems of the nervous system. MRI scanning, angiography, and CT scanning are increasingly brought into the operating room to provide real-time imaging during surgical procedures. The gamma knife and other stereotactic radiosurgical technologies have substantially improved the ability to target and treat tumors and vascular malformations of the nervous system, with minimal morbidity. This has certainly changed the approach for vestibular schwannomas in the hands of many neurosurgeons. The development of endoscopic approaches for pituitary surgery as well as other techniques continues to evolve and has lessened some of the morbidity of the surgical approaches, while achieving similar clinical outcomes. Cranial base approaches enable surgeons to safely resect lesions previously thought to be untreatable.

Of course, deep brain stimulation has completely reenergized the field of functional neurosurgery, with its application in Parkinson's disease and other movement disorders. For the first time, it seems that molecular techniques applied in identification of human brain tumors have meaningful benefits with respect to length of survival, including techniques such as chromosomal deletion analysis (1p–19q) and staining of cell surface receptors, such as of the epidermal growth factor receptor v3. Finally, no one would dispute the influence that endovascular neurosurgery has had on treating aneurysms and arteriovenous malformations.

These advances simply point out that the training received by a neurosurgeon today is substantially different from what it was 25 years ago, and that residency really represents a foundation for learning as opposed to developing a set of learned skills that will not vary in the subsequent career of the practitioner. This opens the door for today's neurosurgeon to

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0148-703/07/5401-0106

perform research that directly changes how practice is conducted. There are a number of challenges for surgeons who wish to perform this work. These include working with other disciplines, including those outside of medicine, developing new skills, and finding ways to obtain hospital support and enthusiasm. The following are several examples.

MAGNETIC STEREOTAXY

Magnetic stereotaxy is a technique by which catheters are manipulated using external magnets combined with image guidance so that catheter position is controlled very precisely. When Matthew Howard and others originally conceived of the technology, the notion was that catheters would be placed into the brain, pulled through brain tissue, and directed to targets using image-guidance techniques. The ability of a magnet to both pull and direct an object proved to be a substantial problem based on laws of physics and magnetism. However, the directionality component seemed much more manageable and, in fact, this is how the system evolved. As prototypes of the system were developed, the device underwent a patent process and commercialization of the technology. Although experiments were performed in both animals as well as humans with respect to catheter navigation through brain tissue, ultimately, the device has been applied in cardiovascular work, where catheters are directed to areas of the heart wall for electrophysiological ablation of abnormal areas of endocardium.[3,4] Presently, the technique involves attachment of a very small magnet to the tip of the catheter and then using external magnets and fluoroscopes, the catheters are advanced through the arteries into the heart, where the heart wall is mapped and treated for abnormal electrical activity (*Fig. 18.1*). It is obvious that this same kind of technology could be applied in endovascular neurosurgery, and there has been some interest by Stereotaxis (the company manufacturing the device) in moving in this direction. The process of taking magnet manipulation of a catheter from an idea to a laboratory setting and then to commercialized technology has taken longer than 20 years. It involved collaboration and working relationships with engineers, physicists, venture capitalists, and business professionals to achieve this end. This kind of collaboration in today's era is absolutely essential to successfully take a research project and put it into clinical practice. Flexibility is also necessary because what one starts with as an idea can and often will change based on factors in the environment.

FIGURE 18.1. Magnetic stereotaxy device in operation for directional navigation of cardiac catheter.

DEEP BRAIN STIMULATION

There is no doubt that restorative neurosurgery has come to represent a major future opportunity for neurosurgery. The best and most common example today is deep brain stimulation for Parkinson's disease. For the properly selected patient, this technology is life changing and restores individuals to a state that was impossible to achieve with medication. Similar kinds of results can occur with epilepsy surgery and very recently, intervention for psychiatric disorders, including depression and obsessive-compulsive disorders, has been investigated. The surgical technique for deep brain stimulation requires extraordinary precision to position the stimulator on the exact target. Although much of this can be performed in advance through MRI scanning, it is common to use electrophysiological techniques to record neurons to ascertain that the stimulator is in the correct position. When placing stimulators into the subthalamic nucleus, this region has a specific neuronal "signature" that is apparent both audibly and on the oscilloscope. However, it does take a significant amount of training and additional personnel to correctly identify these signals as the probe is advanced through overlying brain tissue. Dr. Shabbar Danish and colleagues questioned whether computer averaging techniques might eliminate some of the human variable in detecting the neuronal signals.[1] They developed a signal intensity algorithm that used dual thresholding to identify specific spikes. Using this modality, the team of physiologists and neurosurgeons were able to compare a computer prediction of electrode entrance and exit from the subthalamic nucleus, compared with an expert physiologist (*Fig. 18.2*). There was a high degree of precision between the two systems and further work has shown this process to be reliable and robust in the operating room setting. As a result, some of the surgical techniques for deep brain stimulation are simplified and automated, making this technology available for surgical practitioners who do not have the benefit of a large surgical team including physiologists.

ENDOSCOPIC TRANSNASAL SURGERY

As endoscopic equipment has improved in general and in otorhinolaryngology surgery, these have now been adapted to treating intracranial tumors. Image guidance has played a special role in the use of these techniques. This is a natural

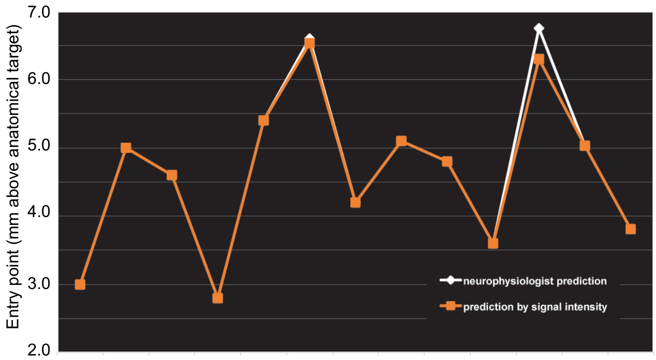

FIGURE 18.2. Computer signal averaging of electrophysiological recording for deep brain stimulation implantation. This illustrates a comparison between the neurophysiologist and the computer prediction regarding entry site of the subthalamic nucleus.

evolution for pituitary surgery, where less invasive techniques, working through the nasal cavity, can achieve surgical results equivalent to traditional sublabial approaches, which have a higher morbidity. As neurosurgeons have become more experienced in the use of endoscopes in this region, new drills and instruments have been developed that enable surgeons to approach intracranial tumors, including tuberculum sellae meningiomas, craniopharyngiomas, and, as illustrated in *Figure 18.3*, chordomas of the cranial base.[2] The next obvious evolution is robotic endoscopic surgery. Presently, systems such as the DiVinci Surgical System have been approved for urological and gynecological procedures. Its development in otolaryngology and head and neck procedures is underway, and a combination of image guidance associated with four remote control arms may provide better clinical precision with decreased morbidity in neurosurgical procedures. Residency training today must necessarily consist of such surgical techniques because they lend themselves well to surgical simulators.

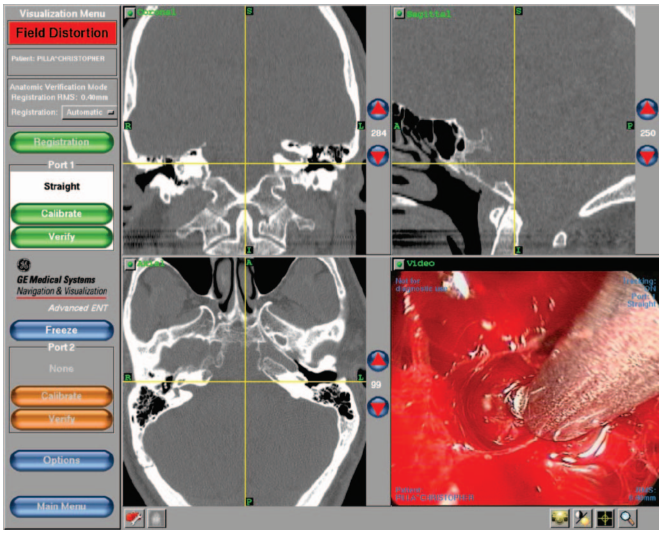
Patient: PILLA^CHRISTOPHER

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FIGURE 18.3. Endoscopic resection of a clivus chordoma with frameless simultaneous navigation.

NORMAL PRESSURE HYDROCEPHALUS

Even a clinical problem as straightforward as normal pressure hydrocephalus may lend itself to investigation. Recently, programmable valves have been promoted for use in such patients to enable flow rates to be changed through the use of an external device. This avoids repeated surgery to change valves and subsequent flow rates of cerebrospinal fluid. Further, such devices may reduce complications associated with over drainage. Although the technical aspect of placing a ventriculoperitoneal shunt, whether it has a programmable valve or not, is very straightforward, the access the neurosurgeon has to the nervous system for further investigation is unique. Many of these patients' diagnoses may be confused with Alzheimer's disease or other neurodegenerative disorders. As the numbers of patients being evaluated for this diagnosis at The University of Pennsylvania increased substantially with recent industry marketing of the programmable valve, an opportunity was identified to perform clinical research to help understand neurodegenerative disorders. This includes cooperative efforts between the Memory Disorder Center, The Alzheimer's Disease Center, and The Department of Neurosurgery at The University of Pennsylvania. In an Institutional Review Board-approved process, cerebrospinal fluid and frontal cortex is sampled and sent for analysis, including measurement of Aβ protein, tau, and isoprostanes. Within the cortex, immunocytochemical labeling for neurodegenerative disease proteins is performed, along with biochemical analysis and electron microscopy. Results are then correlated to surgical outcomes of patients with a clinical diagnosis of normal pressure hydrocephalus. In the initial data analysis, it is apparent that patients may have some features of Alzheimer's disease yet improve after placement of a ventriculoperitoneal shunt in the areas of gait and cognition. Memory does not improve, but the patient's level of attentiveness does, enabling them to better focus on their environment. Further work is pending. This represents an example in which a straightforward surgical procedure can enable a neurosurgeon to make substantial contributions into a much broader body of literature.

HOSPITAL MARGIN

Introducing surgical innovation into the hospital requires working with hospital administrators who are closely focused on a hospital's margin. Recognition by the neurosurgeon that case volume provides a substantial contribution profit is important but not sufficient.[5] Technology can be so expensive that it can take a profitable neurosurgical case and rapidly turn it into a major money loss for an institution. Examples include the use of the artificial disc as well as broad application of biologics, such as bone morphogenetic protein. Similarly, endovascular approaches for aneurysms can either improve or negatively impact a hospital's bottom line on the basis of the number of coils used. Consequently, it is important for the surgical innovator to understand the effect that technology has on a hospital's profit margin and work to ensure that technology makes sense from a financial perspective. Introduction of technology that causes substantial loss for an institution is extremely difficult and, in fact, will pose a major barrier except for diseases that have no satisfactory treatment today.

CONCLUSIONS

Collaboration has become absolutely essential in carrying out a research program that can be translated to clinical practice. This occurs at the investigator level, where surgeons must work with other physicians, engineers, and scientists as a research team. It is every bit as important to work with a hospital when introducing new technology to demonstrate to hospital administrators that such practice may have direct financial benefits for the institution. To advance the field of neurosurgery, the status quo must be challenged, but, at the same time, a critical evaluation of outcomes has been the mainstay of improving practice for longer than 100 years. The rewards achieved by translating research into clinical practice can provide enormous intellectual stimulus and contribute to a fulfilling career.

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