University of Pittsburgh
NEUROSURGERY NEWS
December 2018, Volume 19, Number 3

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The Future of Surgery for Epilepsy and Movement Disorders

by R. Mark Richardson, MD, PhD

Technology is driving the advancement of functional neurosurgery in foundational ways. On the practical side, robotics is well on its way to rendering stereotactic frames largely obsolete for many surgeries. Stereotactic surgeries also are moving out of operating rooms and into MRI scanners, taking advantage of our ability to image brain structures in real time and with incredibly high resolution. For instance, the recent development of direct intra-cerebral therapeutic delivery with real-time MRI feedback is enabling a new era of clinical trials that will bring gene therapy mainstream for Parkinson's disease and other brain disorders.

Importantly, the success of this technology in deep brain stimulation (DBS) surgery has led to the question of whether there is any benefit to performing DBS with patients awake using microelectrode recording. For this reason, much of our own work at the University of Pittsburgh is centered on understanding the extent to which using intraoperative intracranial neurophysiology in new ways could improve DBS outcomes.

We are motivated in these efforts by advances in computational neuroscience and engineering that are changing how humans will interact with their own brains. The field of brain-computer interfaces has evolved clinically to include closed-loop brain stimulation devices, with the advent of FDA-approved responsive neurostimulation for epilepsy.

Many clinical trials are underway that seek to apply this strategy to symptom control in both movement and psychiatric disorders, ushering in a new era where devices will sample brain activity from multiple locations and compute multiple simultaneous programs for modulating brain activity. As the computing power and energy use efficiency of devices increases, artificial intelligence strategies will be deployed for real-time device control and self-programming.

Lastly, data science will play a significant role in the future of functional neurosurgery, given the huge volumes of neurophysiology and imaging data collected, where active strategies for data management will be paramount for success.

UPMC Epilepsy and Movement Disorders Surgery Program Director, R. Mark Richardson, MD, PhD, preparing patient for deep brain stimulation (DBS) procedure.

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Editor's Message

"The best way to predict the future is to create it." — *Abraham Lincoln*

The field of neurological surgery has always been at the forefront in surgical innovations. Due to the incredible challenges of safely operating on the brain, spine, and peripheral nervous system, neurosurgeons have always relied upon the continuous development and adoption of newer and better technological advancements.

Many of the paradigm-shifting approaches in neurosurgery such as radiosurgery, endovascular neurosurgery, endoscopic endonasal surgery, and the surgical treatment of cranial disorders have largely been developed by faculty members of our own department.

Given that our faculty are intimately involved in the development of the latest technologies throughout the breadth of neurosurgery, we thought that they might want to share their visions for the direction of their subspecialties.

In this issue, **Mark Richardson** describes how robotics and other technologies are driving the future of surgery for epilepsy and movement disorders. **Paul Gardner** explains how we are developing the best methods to teach minimally invasive neurosurgical techniques that have been pioneered at UPMC.

Raymond Sekula describes how the future of cranial neuralgia treatment will involve a combination of microsurgical techniques and newly developed drugs.

L. Dade Lunsford describes the future of imaged-guided neurosurgery, which will include faster and more practical intraoperative imaging technologies. **Ian Pollack** explains how the future of pediatric neurosurgery will include the availability of molecular genetic techniques for brain tumors and an increased implementation of precision imaging of the brain. Finally, **Brian Jankowitz** predicts that the future of cerebrovascular neurosurgery will involve a more radical change than any other aspect of neurosurgery.

The members of our department are in an excellent position to accurately predict the future of neurosurgery because we indeed are the ones who are creating it.

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See One, Do One, Teach One

Staff and Former Grads Team Up to Teach Minimally Invasive Neurosurgical Techniques Pioneered at UPMC

by Melvin Field, MD, and Paul Gardner, MD

The path to becoming a UPMC trained neurosurgeon is a long, challenging journey requiring years of training after completion of medical school. Not only does such training require the surgeon to acquire excellent surgical technical skills and an in-depth knowledge regarding the physiological, anatomical, and pathological processes involving the central nervous system, it also requires a passion for neurosurgery and innovation to be successful after training is complete.

As one of the oldest and largest neurosurgical training programs in the country, the University of Pittsburgh has been a neurosurgical pacesetter for education. Although thousands of lessons, pearls, and standards are learned during the training of a neurosurgeon, a consistent and overriding theme since the department's inception in 1949 is that training does not end with graduation. This mantra lives as a foundation in virtually every neurosurgeon who has trained at UPMC. The result is a global footprint of innovations developed, advanced, and popularized at UPMC and spread throughout the neurosurgical world.

For more than three decades, UPMC neurosurgeons have been leading the way in developing less invasive ways to manage disorders of the brain and spinal cord. From Gamma Knife® radiosurgery to minimal-access spine surgery, educating current and future neurosurgeons about these "more civilized" approaches has been a priority.

Beginning in the early 1990s with courses in image-guided neurosurgery and Gamma Knife® radiosurgery, UPMC neurosurgeons started teaching neurosurgeons from outside the department the principles of neuronavigation and how to apply them to various regions of the brain in a less invasive manner. As neuronavigation became accepted as a standard of care in contemporary cranial neurosurgery, UPMC neurosurgeons also began to integrate lessons learned from other surgical disciplines to solve common neurosurgical dilemmas related to complex regions of the brain and skull base. Benefitting from the advances in optics and illumination applied in otolaryngology, UPMC neurosurgeons began using high-resolution endoscopes in conjunction with their otolaryngology peers to access skull-base tumors through the nose. Courses in endoscopic skull base surgery soon followed and revolutionized the field by demystifying and popularizing the techniques.

At the same time, UPMC neurosurgeons began to integrate the principles of thoracoscopic surgery to gain access to tumors and lesions deep within the brain substance itself. Using Thoracoport™ and endoscopes, UPMC neurosurgeons began removing tumors deep within the brain. Combining neuronavigation, neuro-endoscopy, and a "port," neurosurgeons were able to remove lesions while minimizing damage to nearby structures using very small openings and without removing tissue to access the problem

(Continued on Page 7)

The Future of Cranial Neuralgia Treatment

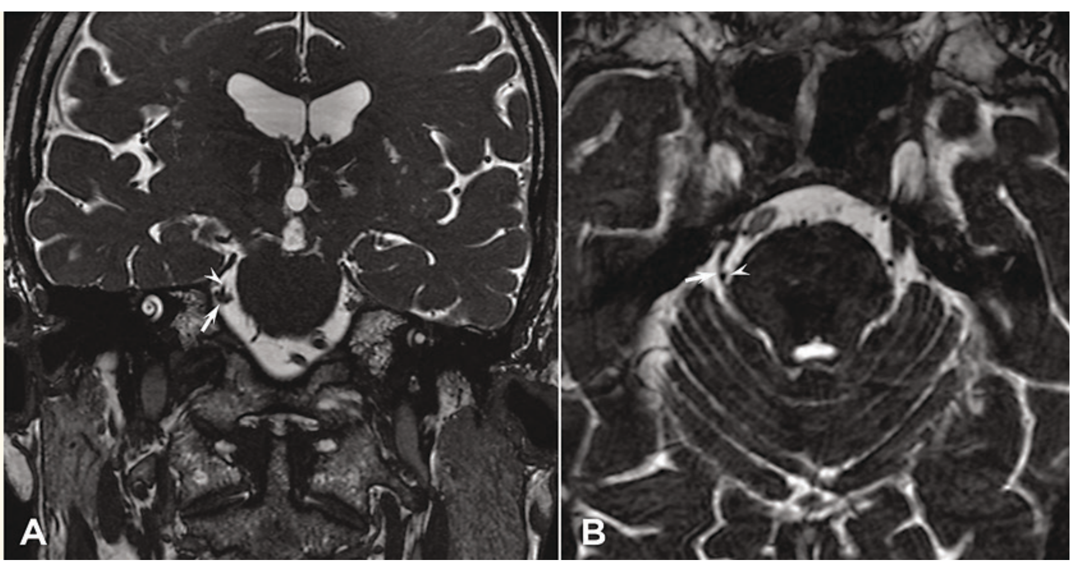
by Raymond F. Sekula Jr., MD, MBA

Cranial neuralgias (e.g., trigeminal neuralgia, hemifacial spasm, glossopharyngeal neuralgia) are among the most debilitating medical disorders known to man. Trigeminal neuralgia (TN) is the most widely recognized neuropathic cranial nerve disorder, marked by evoked and spontaneous attacks of pain in the distribution of the trigeminal nerve, with periods of complete remission and subsequent recurrence in most patients. Perhaps more than any other disorder, TN has long fascinated neurosurgeons because of the severity of pain associated with a single attack and the therapeutic challenges that the disorder presents. In my practice, men have told me that they would rather pass a kidney stone than experience another attack of TN. Often, a man will arrive with a half-shaven face, an effort to avoid a trigger of a TN attack. Although women generally harbor a higher pain threshold than men, women with TN uniformly share that the pain of childbirth does not compare to a single attack of TN. Until a half century ago, purposefully destructive procedures (e.g., trading pain for numbness) with mixed results were the mainstay of treatment for TN.

Hemifacial spasm (HFS) is a movement disorder characterized by involuntary spasms of the facial muscles with associated fatigue of the face. HFS is a debilitating condition leading to decreased quality of life (QOL). In a recent University of Pittsburgh study of more than 300 patients with HFS, we found that QOL in HFS patients is negatively affected by the disorder more than patients with malignant brain tumors. For centuries, HFS patients were thought to have a psychological disorder and many were even institutionalized.

In the 1970s, an operation was developed at the University of Pittsburgh known as microvascular decompression, a procedure that largely preserves the integrity of the cranial nerves and aims to relieve mechanical pressure of the respective nerve caused by a blood vessel. Over the past decade, we have worked to refine these procedures in a variety of ways. In one refinement, we have eliminated the use of rigid retractors to hold back the brain to expose the nerve in favor of working through an even smaller corridor. This has resulted in a reduction in complications and dramatically shorter lengths of hospital stays, which has allowed us to extend the operation to elderly patients, formerly considered to be unfit for such an operation. Additionally, we have worked to improve visualization of the cranial nerves by MRI so that we can better predict which patients truly have vascular compression of the trigeminal, facial, or glossopharyngeal nerves and might benefit from microvascular decompression surgery.

Still, in certain patients, relief of symptoms is elusive, and the fact is that some patients will experience pain or uncontrolled symptoms for the rest of their lives. This month, however, we are pleased to participate in a Phase 3 trial designed to investigate the efficacy and safety of the first drug specifically developed and targeted (i.e., a Nav 1.7 blocker) for trigeminal neuralgia. Results from the Phase 1 and 2 trials have been encouraging. Since January 2016, we have collected and carefully characterized hundreds of saliva samples from patients with cranial neuralgias to better understand the genetic underpinnings of these disorders. Finally, we have partnered with the University of Pittsburgh Pain Center, under the direction of Dr. Michael Gold, where we have recently discovered that GABA receptors are present in trigeminal nerves, which might represent a new pathway for future therapies.



Severe Neurovascular Contact: *(A) Coronal SSFP image demonstrates the right superior cerebellar artery (white arrowhead) indenting the cranial surface of the right trigeminal nerve (white arrow). (B) Axial SSFP image demonstrates the right superior cerebellar artery (white arrowhead) deviating the right trigeminal nerve (white arrow).*

The Future of Image-Guided Neurosurgery

by L. Dade Lunsford, MD

Lasting technology innovation must have two important ingredients: medical merit and fiscal benefit. The introduction of high-definition intraoperative imaging began in 1981 at UPMC when the first dedicated "therapeutic "CT scanner was installed in Operating Room 12 at Presbyterian University Hospital (Figure 1). Within a few years, almost all brain and spine surgery became image guided. In some patients, imaging was obtained during the procedure itself. Brain biopsy, placement of electrodes for seizure monitoring, resection of brain tumors, intracavitary radiation, and endoscopic evacuation of colloid cysts were examples of surgeries augmented by the need to pinpoint a brain or spine target and reach it safely. In other patients, high-definition imaging was obtained in advance and integrated with specially constructed platforms that were used during the surgery. We routinely use imaging adjuncts such as ultrasound, fluoroscopy, angiography, and magnetic resonance imaging.

Figure 1: *OR 12 at UPMC Presbyterian featuring third-generation dedicated "therapeutic" CT scanner.*

The use of advanced imaging technology must make the procedure more accurate, safer, and faster. Making the newest technology work cannot replace the original goal of the surgical procedure itself. It must augment, not replace, the focus of what we do. One of the advantages of intraoperative CT is that we don't have to change how we do surgery just to get the imaging. We can use the same tools in every patient. Intraoperative MRI has become an important adjunct in certain procedures since it can provide more graphic detail of targets in the brain. Combined with laser interstitial thermal therapy (LITT) and, at some medical centers, focused ultrasound, MRI can provide intraoperative thermal brain maps that track the development of heat-generated lesions to treat brain tumors, epilepsy, and movement disorders. Preoperative brain maps can be created using magnetoencephalography to define critical brain functions in cortical locations, allowing surgeons to avoid injury.

Stereotactic radiosurgery using Gamma Knife® represents another example of the critical codependence of modern brain surgery with image guidance. Since 1987, our center has pioneered the use of this surgical procedure to treat tumors, vascular malformations, chronic pain, and movement disorders. Depending on the patient, we use precision guiding devices coupled with MRI, CT, or angiography to target the brain or pathological structure and then cross fire up to 201 beams of radiation without the need for any scalp or skull incision. More than 15,400 patients have benefitted.

One of our center's goals over these 37 years has been to evaluate and then publish studies that define the medical merit and the fiscal benefit of image-guided surgery. The future introduction of dedicated surgical MRI will require a similar process. For what patient can we expect value? Do the required surgical MRI safety features augment or obstruct the surgical workflow and improve outcomes and reduce risks? New medical technology breakthroughs must follow a simple rule: to be a difference, it must make a difference. Intraoperative imaging reduces surgical morbidity, expands management options, and reduces hospital stays. These features define both medical merit and fiscal benefit.

The Future of Pediatric Neurosurgery

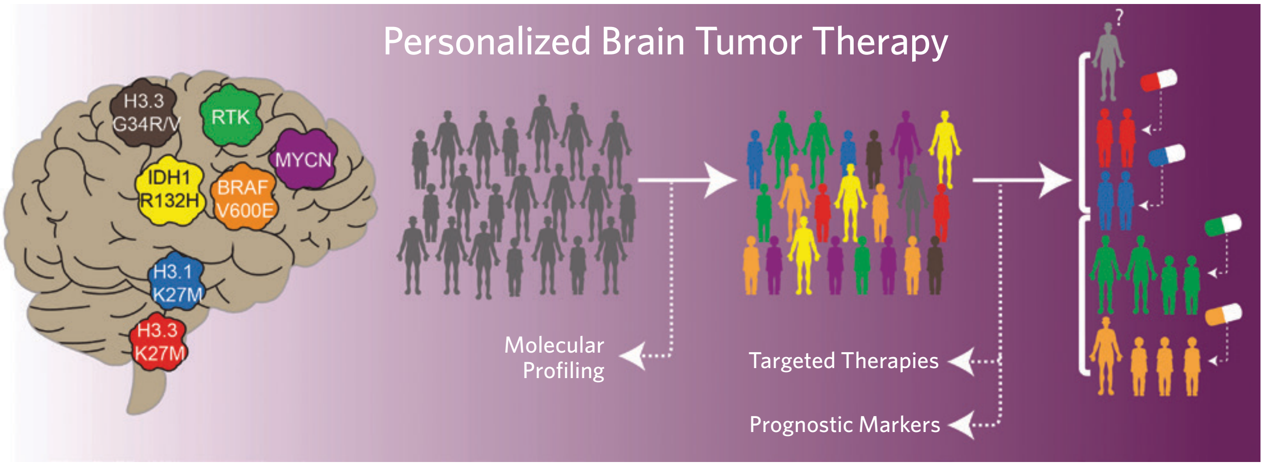
by Ian F. Pollack, MD

In the discipline of pediatric neurosurgery, there are a host of advances that will influence the future course of neurosurgery. These include, among many others: 1) the increased use of endoscopic techniques to treat pediatric hydrocephalus and reduced reliance on shunts; 2) the increased implementation of precision imaging and brain- and seizure-mapping technologies to make brain surgeries, such as tumor and epilepsy resections, safer and more reliable in targeting a lesion of interest; and 3) the widespread availability of molecular genetic techniques to classify pediatric brain tumors.

The first two advancements are well under way, but the third, which also applies to adult brain tumors, will likely engender the most dramatic changes in patient management in the years to come. The insights that have been gained in the last few years, and that continue to emerge regarding brain tumors, may fundamentally reshape treatment approaches going forward. Already, classification schemas for medulloblastoma, the most common malignant brain tumor of childhood, have evolved to incorporate four distinct subsets of tumors (i.e., the so-called SHH, WNT, Group 3, and Group 4 subsets) that differ in their gene expression profiles, demographic characteristics, and prognosis. Ongoing research will likely further divide these four groups into additional subsets. Rather than being strictly of academic interest, recognition of these risk-related subgroups has also led to distinct treatment pathways and application of molecularly targeted therapeutic agents. This stratification of therapy may lead to the reduction or avoidance of potentially neurotoxic therapies, such as high-dose craniospinal radiation, and influence the timing and extent of definitive tumor resection, which may improve not only quantity but also the quality of survival. Similar subdivisions of previously monolithic tumor types, such as malignant gliomas, have also occurred and will likely lead to distinct therapeutic pathways and more personalized pharmacological and immunotherapeutic strategies based upon the patterns of mutations expressed in a given tumor.

The frequent detection of recurring patterns of mutations in certain tumor types, such as diffuse brainstem glioma, have begun to provide a rationale for using biopsy-based rather than imaging-based criteria for diagnosis, provided that therapeutically active agents can be identified, which remains a work in progress. In contrast, for pediatric low-grade gliomas, it has been recognized that greater than 80% of tumors have alterations in the BRAF/MAP kinase signaling pathway. Most such tumors respond to one or more of a variety of pathway inhibitors that have been developed, which has had a major impact on post-biopsy or post-resection management.

These advances are not without their challenges. Gone are the days when pediatric brain tumors could be neatly categorized into a small number of diagnoses for treatment protocols. We are entering the era of molecularly stratified therapy, and soon post-surgical treatments may become even more personalized, using one of several molecularly targeted pharmacological or immunotherapeutic options. Leveraging this information will require a multidisciplinary management philosophy encompassing neurosurgery, pediatric oncology, radiation oncology, pathology, and molecular diagnostics, complemented with a robust laboratory-based effort to define promising new agents. We are fortunate to have all the pieces of this puzzle well represented at the UPMC Children's Hospital of Pittsburgh and are in a strong position to contribute to the exciting changes that will occur in the field.



A schematic illustrating the various molecular subtypes of pediatric high-grade gliomas, which differ as a function of age and tumor location. (Figure provided by Sameer Agnihotri, PhD.)

News & Notes

Maroon Named Humanitarian of the Year

Joseph Maroon, MD, renowned health and sports medicine expert and Heindl Scholar in Neuroscience at the University of Pittsburgh, was presented the Humanitarian of the Year Award by the Jerome Bettis Bus Stops Here Foundation at the group's 13th Annual Caring for Kids Gala, held September 27 at Pittsburgh's Heinz Field. Pittsburgh Steeler Ryan Shazier was also honored at the gala, receiving the Most Courageous Man of the Year Award for his remarkable recovery from a severe spinal cord injury suffered in a 2017 game against the Cincinnati Bengals.

A video featuring National Football League commissioner Roger Goodell was shown at the gala acknowledging Dr. Maroon and Shazier for their work and contributions. In 1982, Dan Rooney appointed Dr. Maroon as the Steelers' neurosurgeon — the first such role in the league — and he has served in that role ever since. He has also served on the NFL's Head, Neck and Spine Committee for 12 years and has written and published extensively on managing concussions and head and spine injuries in athletes of all ages, from youth football to the pros.

Agarwal Authors Neuro Fundamentals Book

Fifth-year resident **Nitin Agarwal, MD**, is the author of a book *Neurosurgery Fundamentals* from Thieme Publishers, a portable reference source for residents and medical students that offers readers a swift assimilation of neurosurgical care essentials.

The book includes comprehensive technical overviews on a wealth of topics including the neurological exam, neuroanatomy, neuroradiology, neurocritical care, traumatic brain and spinal cord injury, degenerative diseases and spinal deformity, neurovascular surgery, neurosurgical oncology, pediatric neurosurgery, functional neurosurgery, stereotactic radiosurgery, neurological infectious diseases, and interdisciplinary care. Socioeconomic topics on training, licensure, credentialing, and advocacy are also included.

Congratulations

A paper coauthored by **Nitin Agarwal, MD, Robert Friedlander, MD,** and **Daniel Wecht, MD**, entitled "Reducing Surgical Infections and Implant Costs via a Novel Paradigm of Enhanced Physician Awareness," was selected as the Socioeconomics, Health Policy, & Law Paper of the Year by the Congress of Neurological Surgeons. The paper, published in the May edition of *Neurosurgery*, investigated the effects of increased physician awareness on infection incidence and surgical device cost containment.

Raymond Sekula, MD, director of the department's Cranial Nerve and Brainstem Program, was named a recipient of UPMC's prestigious Award for Commitment and Excellence in Service (ACES). The ACES recognition honors staff who exemplify UPMC's five core values — Quality and Safety, Dignity and Respect, Caring and Listening, Responsibility and Integrity, Excellence and Innovation. Each year, fewer than one percent of UPMC staff from across the health system receive this honor.

Fifth-year resident **Ezequiel Goldschmidt, MD, PhD**, was awarded the Preuss Research Brain Tumor Award by the Congress of Neurological Surgeons for his abstract, "Cerebrospinal Fluid (CSF) Can Inhibit Wound Healing and Induce CSF Leaks by Inhibiting Angiogenesis."

Minimally Invasive Neurosurgical Techniques *(Continued from Page 3)*

at hand. Since being described and popularized by UPMC neurosurgeons, the field of port-based neurosurgery has grown rapidly and is now being used worldwide for various pathologies including brain tumors, brain hemorrhages, and brain cysts.

More recently, UPMC neurosurgeons have also been integrating endoscopic tools to assist with disorders of the posterior fossa, including acoustic neuromas and trigeminal neuralgia, and they have been integrating new robot-assisted navigation systems to more precisely remove blood clots from the brain. In addition, by working with oculoplastic surgeons, transorbital approaches have been advanced to provide novel corridors to the anterior and middle fossa for a variety of pathologies.

These minimal-access approaches developed and popularized at UPMC are now taught throughout the world. UPMC neurosurgeons and previous graduates routinely organize, teach, and lecture on these topics at virtually every major neurosurgical conference held in North America and the developed world.

A few years ago, UPMC neurosurgeons recognized a void in post-training neurosurgical education related to these very techniques for which UPMC was internationally recognized. Evaluation of past graduate and previous course participant surveys showed that many of these techniques were taught in isolation and that there was no singular resource available for learning them all in the same setting despite significant overlap between them. Drs. Paul Gardner and Brian Jankowitz began working with previous graduates Drs. Mel Field and Johnathan Engh to develop a more comprehensive course in minimally invasive brain surgery for both academic and private practice neurosurgeons. The course, taught by current and past UPMC neurosurgeons in collaboration with otolaryngologists and ocular surgeons, covers these minimally invasive techniques developed and popularized at the University of Pittsburgh. This course has had more than 1,400 participants and the cranial base center has hosted more than 475 observers to learn these techniques.

The next course, to be held this January in Orlando, Florida in conjunction with Florida Hospital, will include didactic and lab sessions on image-guided endoscopic skull base surgery, endoscopic posterior fossa surgery, image-guided port-based intraventricular neurosurgery, image-guided robot-assisted endoscopic and port-based intracerebral hemorrhage evacuation, and image-guided keyhole supraorbital and transorbital surgery. The vision of the course is to expand the field of minimally invasive brain surgery as it continues to grow and to provide a resource for neurosurgeons to learn the tools necessary to implement the full spectrum of minimal-access neurosurgical techniques within their daily neurosurgical practice.

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The Future of Cerebrovascular Neurosurgery

by Brian Jankowitz, MD

The future of cerebrovascular neurosurgery may involve a more radical change than any other subspecialty in the field of neurosurgery. Cerebrovascular neurosurgeons will evolve into stroke doctors, treating more ischemic disease than hemorrhagic disease of the brain. A typical day is more likely to involve opening a chronically occluded carotid artery with a direct endovascular bypass, or stenting a subclavian artery causing subclavian steal, as opposed to clipping an aneurysm in a traditional open fashion. No incision will exceed 2mm, nor will there ever be a need for an incision above the belly button to treat aneurysms and other vascular malformations of the brain and spinal cord. A combination of coils, adjunctive stents, flow diverting stents, liquid embolics, and radiosurgery will make an open craniotomy largely a thing of the past.

Learning from the wisdom of cardiologists, most patients will be able to roll up their sleeve and have most aneurysms and AVMs treated through the wrist via the radial artery. There will be no need for the patients to even disrobe. When the procedure is completed, a personalized snug-fitting watch or bracelet will be provided to tamponade the artery, allowing for immediate ambulation and early discharge. General anesthesia will also become a thing of the past as patients gain confidence in awake treatment, allowing immediate feedback, eye contact, and conversation with their cerebrovascular neurosurgeon, which also happens to facilitate same-day discharge after outpatient brain surgery.

Endovascular therapy will also facilitate implanting endovascular smart devices, such as cylindrical sensors within the carotid artery that can monitor blood pressure and compress the baroreceptors in the carotid bulb to eliminate hypertension. Electrode-laden stents, or "stentrodes," will be placed within intracranial arteries or veins to monitor brain activity, allowing such varied biofeedback mechanisms as detecting and treating seizures, warning of oncoming depressive episodes, or sensing drug cravings. To enable healing of a damaged brain or to treat neurodegenerative diseases, stem cells will be administered intra-arterially or even through tiny needles that puncture the inner blood vessel wall and allow migration of cells into the brain. Antibody-mediated targeted chemotherapy for brain tumors will also be administered in a similar fashion to avoid systemic toxicity and finally overcome the "blood brain barrier." For the treatment of intracranial hemorrhage, neurosurgeons will finally start to accept that blood in the brain is bad and should be removed as soon as possible. Patients with a suspected intracranial hemorrhage based on an ultrasound applied in the ambulance will be treated like an acute ischemic stroke patient, taken directly to the angiography suite for a combined CT scan, angiogram, and minimally invasive blood clot removal through a dime-size hole in the skull. Such radical changes should translate into far better patient outcomes than were achieved in the past.

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