
BRAINLAB

Brain Storm

New techniques, agents, and technologies have sparked a revolution in neurosurgery

By Andrea Crawford

Photographs by John Abbott

The pons, as medical students learn, is the bridge-like part of the brainstem that connects the brain with the spinal cord. Tumors found there, called diffuse intrinsic pontine glioma (DIPG), strike children and grow aggressively among the key cranial nerve structures responsible for sensory and motor functions such as equilibrium, chewing, swallowing, and respiration. Upon diagnosis of DIPG, patients receive radiation as palliative care. There are no other options.

For years, Mark Souweidane, MD, director of the Weill Cornell Pediatric Brain and Spine Center, has seen the disease take its toll on patients and their families. "You watch a child succumb to a tumor the size of a walnut—you watch the angst, turmoil, and frustration it causes the family," he says. "You receive their continuous questions as to why there's nothing better. There's no stronger motivation than that to look for a better way."

Twelve years ago, Souweidane set out to look for that better way. He scoured the literature, collaborated with bench scientists, and assembled a team. They devised a treatment concept, found a promising therapeutic agent, and created a surgical procedure to administer it directly into the tumor, bypassing the blood-brain barrier. This past spring, with the opening of a clinical trial, Souweidane's team may have finally changed the par-

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Philip Stieg, MD, PhD

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adigm, offering hope where there had been none. "We had to start at ground zero, amid a lot of criticism that what we were doing was unfathomable," Souweidane says. "We wanted to infuse things into the brainstem that no one had ever tried before, and when we began there was no evidence that you could do this."

In May they operated on a four-year-old girl, the first attempt at surgical treatment for a patient with DIPG. In July they operated on a second child with the disease.

The current phase-one clinical trial is designed to look at safety and feasibility, and over the next one to two years the team plans to administer the treatment to a minimum of twelve patients between the ages of three and twenty-one. While it will be a long time before they can begin to assess efficacy, the surgery offers the first glimmer of hope for treating a disease long considered inoperable.

During the surgery, a radioimmunotherapeutic agent reaches the tumor through a method called convection-enhanced delivery (CED), a pressure-driven infusion through a surgically placed cannula. The agent, known as 124I-8H9, consists of an antibody produced by mice, which binds to the tumor to administer a radioactive substance to kill its cells. The technical feat alone is challenging because the tumors are small lesions, nine centimeters beneath the surface of the brain, which the team targets using interoperative MRI, a recently FDA-approved navigation system, and specially designed micro-catheters.

With its combination of innovative surgical technique—in which the team treated an area of the brain that had never before been accessed—and its novel application of an agent that uses antibodies to attack the tumors with radiation, the work on DIPG demonstrates some of the ways in which neurological surgery is in the midst of a revolution. Minimally invasive techniques have radically altered how neurosurgeons work, and the emerging field of molecular medicine—using surgery to deliver agents such as genes, cells, drugs, or antibodies to targets in the nervous system to treat a variety of diseases—is changing the way surgeons think about clinical care.

As the field redefines itself, the traditional role of the neurosurgeon is evolving as well. When Philip Stieg, MD, PhD, chairman of the Department of Neurological Surgery and of the Weill Cornell Brain and Spine Center, entered the field three decades ago, he says, "neurosurgeons were considered iconoclasts, unfriendly and inaccessible. Today neurosurgeons at NYP/Weill Cornell are part of a large team of physicians who take care of complex neurologic disorders." That approach extends from the operating room to the laboratory, as surgeons do their part not only in bringing scientific breakthroughs to their patients, but in taking ideas from the OR back to the lab—and helping to generate those breakthroughs.

Technology has driven much of the revolution. "When I started, I was operating with an incandescent light bulb," Stieg says, "and an advanced OR was one that had a microscope." Now he and his team of neurosurgeons use computer-guided instruments and three-dimensional technology. They get much better visualization of the brain's structures with bright illumination and magnification in extremely high resolution, advances that enable them to look around corners, around the brain stem, and at the complex relationships between compressive structures like blood vessels on nerves. "Our ability to visualize pathology has changed dramatically," Stieg says.

When Souweidane arrived at NYP/Weill Cornell in the mid-Nineties, no one had ever used an endoscope in the brain; today, 20 to 30 percent of the neurosurgeries they do are endoscopic. He points out that on a recent day he performed four operations: two tumor removals, one procedure to treat hydrocephalus (the overproduction of cerebral spinal fluid inside the brain's ventricles), and one biopsy of a tumor in the brain stem. In the not-too-distant past, each of those surgeries would have required traditional craniotomies, yet he had done each through a "burr hole," a quarter-inch opening in the skull. "These techniques

Michael Kaplitt, MD '95, PhD, with Dr. Stieg

have hugely impacted the field," Souweidane says. "Patients undergoing treatment today have no comparison to how it used to be—thank goodness. They're beneficiaries of an amazing amount of innovation." Stieg agrees, noting the improved speed and ease of recovery. "With less invasive surgeries," he says, "patients get better faster with the same outcomes."

In addition to making surgery easier on patients, endoscopic and minimally invasive techniques have also broadened what surgeons can do—changing the way they treat congenital malformations, brain tumors, and cystic structures such as colloid cysts, benign but potentially deadly tumors located deep in the central part of the brain. Weill Cornell neurosurgeons are removing tumors previously considered inoperable. For example, Theodore Schwartz, MD, a professor of neurological surgery who directs the center for epilepsy surgery and specializes in anterior skull base approaches for the treatment of pituitary tumors, uses endoscopes to take out types of tumors that very few surgeons would be able to remove, his colleagues say.

Spinal surgeons such as Roger Härtl, MD, the Leonard and Fleur Harlan Clinical Scholar and the neurosurgeon on call for the New York Giants, and Eric Elowitz, MD, assistant professor of neurological surgery, use computer navigation guides, resulting in much less destruction of muscle tissue, which is key to recovery and rehabilitation. Technological advances also allow interventional radiologists Pierre Gobin, MD, professor of radiology in neurological surgery, Athos Patsalides, MD, the Alvina and Willis Murphy Assistant Professor of Neurological Surgery, and Jared Knopman, MD, assistant professor of neurological surgery, to more safely, efficiently, and effectively treat intracranial vascular lesions such as aneurysms and arteriovenous malformations. Technology has reached the point where even noninvasive procedures are available. Susan Pannullo, MD '87, director of neurosurgical radiosurgery, delivers radiation to tumors and other targets through instruments that use beams and do not require incisions.

Perhaps the most surprising shift in neurosurgery has been in the emerging field of molecular techniques and treatments. In 2003 Michael Kaplitt, MD '95, PhD, associate professor of neurological surgery and vice chairman for research, was the first person in the world to administer gene therapy to the brain. Last year, he concluded a phase-two study of that work in treating Parkinson's disease—the first time that a randomized, double-blind study showed positive results for any type of biological therapy in a neurological disease. In 2009 John Boockvar, MD, associate professor of neurological surgery, in collaboration with Gobin and Patsalides, was the first to infuse the chemotherapeutic agent Avastin directly into a glioblastoma tumor, bypassing the blood-brain barrier—work featured in the *New York Times*.

"If you had asked about the future of neurosurgery twenty years

RENE PEREZ

Jeffrey Greenfield, MD '02, PhD

ago, almost everybody would have said it was in new types of devices and hardware," says Kaplitt. "Our current approaches would have been unthinkable then. Yet now there's not a field of neurosurgery where there aren't people actively taking leadership roles in both basic and translational research to apply molecular therapies or molecular techniques to novel problems." Jeffrey Greenfield, MD '02, PhD, assistant professor of neurological surgery in pediatrics and the Victor and Tara Menezes Clinical Scholar in Neuroscience, agrees. "Molecular medicine may not have changed our day-to-day practice of neurosurgery, but it's starting to make inroads in how we think about our patients, how we plan our surgeries, and how we think about their postoperative care," says Greenfield.

In an effort to allow clinicians and scientists at Weill Cornell to conduct more research into ways to attack rare tumors, last year Souweidane and Greenfield launched the Children's Brain Tumor Project. It grew out of conversations Greenfield had had with a patient, who was a college sophomore in 2010 when she learned she had gliomatosis cerebri—an inoperable, diffuse, and highly aggressive tumor—in almost every lobe of her brain. The patient died in May 2012, and that summer, using her tumor, Greenfield's team finished the first complete DNA mapping of gliomatosis cerebri, a vital step in finding potential therapies.

Over the eighteen months of treatment, Greenfield had to tell his patient and her family that physicians know virtually nothing about gliomatosis cerebri. "It was quite frustrating to be forced to admit that there's not a lot of research on rare diseases because there's no NIH funding impetus to take care of a disease that affects 200 people a year," he says. A foundation established by the patient's family helped to launch the Children's Brain Tumor Project. "We're going to figure out what we can do to offer hope to those patients," Greenfield says. "That's what the patient wanted."

Recently, we have seen the first surgery to attempt to treat DIPG, the first genomic analysis of gliomatosis cerebri, and now the first attempt to treat addiction through neurosurgery. This past summer, Kaplitt received FDA approval for a phase-one trial to treat cocaine addiction by stimulating the reward center of the brain. His work demonstrates how research in neurological surgery is further revolutionizing the field by changing the definition of what constitutes a neurosurgical case. His long-standing research on Parkinson's—and in treating its non-motor symptoms such as depression, addictive behaviors, and memory problems—has led to advances that could

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benefit millions who suffer from major depression, drug addiction, and metabolic diseases.

A few years ago, working with the Rockefeller University's Paul Greengard, PhD, the 2000 Nobel laureate in medicine, Kaplitt found that a protein known as P11 acts as a shuttle to bring neurotransmitter receptors to the surface of the cell, thus influencing its response to serotonin and dopamine. In a paper published in *Science* two years ago, they showed that when P11 is knocked out with gene therapy in the nucleus accumbens, a reward center in the brain, depression-like behavior occurred in animals; when they overproduced P11, normal behavior returned. The findings were corroborated in human samples from the brain bank of collaborator Carol Tamminga, MD, of Southwestern Medical Center. "So there's a human proof of principle that suggests that low P11 levels in this area of the brain may be one of the causative factors that define human depression, which we can potentially reverse genetically," Kaplitt says.

More recently, he has determined that P11 also has a profound influence in a second region of the brain, the subgenual cingulate cortex—an area currently being closely studied in relation to depression—and that its effects there may be opposite from what it does in the nucleus accumbens. "It seems to do very different things in these two regions, which highlights the value of focal neurosurgical interventions because drugs would influence the pathway only in one direction or another," says Kaplitt, who is preparing to publish his findings. "It's interesting in a way that fits nicely with what's known about depression through brain imaging technology."

Kaplitt has similar data showing how parts of the brain may influence metabolism, which Stieg notes could have application for treating eating disorders. That's just one example, Stieg says, where "we're waiting for the molecular biology, whether it be the creation of viral or genetic or chemotherapeutic agents, to catch up with the surgical technique." Neurosurgeons have therefore become important participants, even leaders, in helping to push the molecular biology. "We believe that neurosurgeons have a lot to offer in the scientific realm, and that the historical biases about neurosurgeons—that they may be smart but they operate and that's it—are fundamentally flawed," says Kaplitt, noting that almost half of the department's current residents have PhDs. "We believe that neurosurgery is completely compatible with quality science."

Each member of the department has numerous patient-centered trials where they're not only operating but also attempting to push the envelope for the entire field. "Our department on the whole is incredibly translational, and everyone, top to bottom, is running basic science labs that are taking things from the operating room into the lab and vice versa," says Greenfield. Kaplitt cites Souweidane as a prime example. With no formal background in research science, he simply had a strong desire to help his patients with intractable brain tumors. "So of his own volition he started a research effort," Kaplitt says. "He focused on a problem that was a strong unmet need in his field, and that evolved from an idea to the point where, now, he's treating patients."

His fellow surgeons give credit to Stieg, under whose leadership the department has supported its members' efforts to bring new therapies to patients. Even as its traditional surgical volume has grown dramatically in the last decade, the department had been structured to support research to an unusual degree, creating an environment where ideas flourish, says Kaplitt.

A prime example of Stieg's leadership and focus on mentoring his faculty was the department's launch of a Brain Summit in June 2011. Under the direction of Boockvar—working with Stieg, WCMC Dean Laurie Glimcher, MD, and NYP President Steven Corwin, MD—the Brain Summit brought together top neuroscientists from across the country and representatives of biotech firms to help drive scientific collaboration to accelerate cures. In addition, the forum provided an opportunity to expose promising research approaches to potential funders.

Stieg's drive for scientific collaboration also resulted in taking his whole department to Ithaca to meet with biomedical engineers, sparking several collaborations that continue to bear fruit. Weill Cornell's Härtl and Cornell's Larry Bonassar, PhD, associate director of the Department of Biomedical Engineering, for example, are working to bioengineer artificial spinal disks. These could offer treatment for patients with degenerative spinal disease with a substance that, unlike plastic or metal, mimics the qualities of human disks. Similarly, they are working to create tissue to repair annular defects, which currently have no treatment. "There are so many opportunities now, so much interest," Kaplitt says. "Smart, creative, energetic people with the right institutional backing and the right idea can start pushing these things into the clinic."

Stieg's mission to share his team's expertise globally and build a world-class collaborative teaching facility led to the launch in 2010 of the Surgical Innovations Lab, the only one of its kind in the world. Demonstrations of advanced neurosurgical techniques pioneered by Stieg and his team are shared in real time with other medical professionals via multimedia technology. Recently, Chinese, Arab, and Italian neurosurgeons watched and commented as Stieg taught residents how to perform complex surgical approaches to the skull base.

Recent scientific and technical advances are greatly broadening the range of what neurosurgeons are able to treat, even as an aging population increases the frequency with which surgeons see the conditions they have long treated, such as back pain, stroke, and movement disorders. But as vast as neurosurgery's scope may be today, Stieg says, its mission lies at the historic foundation of medicine: "We're always thinking about how to alleviate pain and suffering." ●