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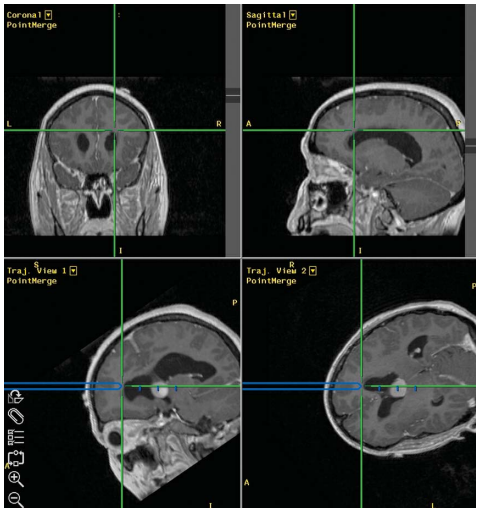
Minimally Invasive Approach Offers New Options in Neurosurgery

Seeking improved outcomes and shorter recovery times for patients, Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are pioneering the development of a number of innovative minimally invasive procedures specifically designed to address an array of neurologic problems, from brain tumors to spinal injuries.

At NewYork-Presbyterian Hospital/Weill Cornell Medical Center, much of the clinical practice and laboratory research of Mark M. Souweidane, MD, is dedicated to the treatment of childhood brain tumors, especially those found in the ventricular compartment of the brain. Minimally invasive techniques are a beneficial strategy for his patients because they require a smaller incision and less brain retraction, and they offer a shorter recovery time and better cosmetic results. "Most importantly," Dr. Souweidane commented, "it reduces the risk to the patient."



Neuroendoscopy, coupled with stereotactic navigational guidance, is used during minimally invasive surgical procedures to assist surgeons in the removal of a third ventricular brain tumor, as seen in the patient above.

Minimally invasive techniques incorporate endoscopy and guidance systems, used alone or in combination as tools for tumor biopsy or resection. Endoscopy offers a less invasive alternative to craniotomy, the conventional method used for

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Stenting Versus Endarterectomy: Outcomes Studied

Endovascular surgical neuroradiology provides physicians with an amazing array of treatment options for carotid artery disease and other brain diseases. However, this new technology is also presenting physicians with interesting challenges. Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are leading the way in studies that seek to address these issues.

Historically, surgeons have used endarterectomy to treat carotid stenosis. "In the hands of a skilled surgeon, endarterectomy is still an excellent procedure," noted Sean D. Lavine, MD. "But for patients who have radiation-induced stenosis, a high bifurcation of the carotid artery in the neck, or are otherwise medically challenging, endovascular treatment is now the preferred option."

Three years ago, Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital and other centers nationally initiated CREST (the Carotid Revascularization: Endarterectomy versus Stent Trial). Sponsored by the National Institute of Neurological Disorders and Stroke and the National Institutes of Health, CREST is a randomized clinical trial designed to evaluate the efficacy of carotid artery stenting as compared with carotid endarterectomy.

In carotid stenting, surgeons insert a

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Is Surgery the Best Option in the Treatment of AVMs?

Facing up to uncertainty about optimal treatment, Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital and more than 85 institutions worldwide are planning an extensive clinical trial that will assess the hazards of invasive intervention in patients with arteriovenous malformations (AVMs) that have not hemorrhaged. The results of this 5-year study—A Randomized Trial of Unruptured Brain AVMs (ARUBA)—may affect standards of treatment on an international scale.

Currently under review by the National Institutes of Health (NIH), the proposed study comes about in part because of surprising results from the ongoing New York Islands Arteriovenous Study, which developed prospective, population-based data on the incidence of AVMs (*Stroke*. 2003;34:29e). That study showed that asymptomatic individuals with AVMs are much more common than previously supposed. Whereas the substantial risk of morbidity after treatment is acceptable for those who have previously bled, it remains unclear whether invasive treatment is warranted for asymptomatic patients.

"We have the ethical equipoise that justifies the application for the trial," said ARUBA principal investigator Jay P. Mohr, MD, "and we hope it will be funded by NIH and we can get under way to finding the answer to this important problem."

Generally, AVMs are treatable with radiosurgery, microsurgery, and endovascular embolization. Fewer than half of all AVMs are discovered as a result of cerebral hemorrhage; they may also be detected in patients with seizures or headaches or, infrequently, with symptoms of focal neurologic deficit or pulsatile tinnitus. When the patient's age, the location of the AVM, or neurologic symptoms and deficits are factors, the decision to operate is generally not an issue. However, an increasing number of AVMs are being discovered without any perceived symptom and before any hemorrhage, as a consequence of improved and ever more sensitive imaging techniques. Neither plain skull films nor CAT scans can reliably indicate AVMs.

Photo courtesy of the Columbia University Medical Center Department of Neurology.

Hospital researchers are leading efforts to explore new treatment options for AVMs. The scan above shows an occipital lobe AVM.

"But MRI, particularly the T2, and magnetic resonance angiography," said Dr. Mohr, "have revealed a far larger number of them."

As a result, current treatment protocols are essentially based on studies of patients who have already experienced hemorrhage or other deficits. The mean age at diagnosis is 35 years, and the risk of surgery overall is estimated at 3%. When such patients present without deficits or AVM-related symptoms, surgeons must weigh whether surgical intervention is worth the risk.

The issue is in some measure controversial. According to Philip Stieg, PhD, MD, ARUBA will provide significant data. However, he expresses skepticism when it comes to forgoing treatment in favor of observation.

"From my perspective as a surgeon, if I think that it is a surgically accessible and straightforward lesion, I would prefer taking it out," he noted. He points to the highly individual nature of each case and also questions whether the study will last long enough to provide sufficient information.

The study plans to enroll 800 patients with unruptured AVMs. They will be offered the opportunity to participate by being randomly assigned either to a group that will receive invasive treatment or to a group that will be observed and not treated unless bleeding occurs. The results will be released after 5 years.

The current situation with AVMs may be compared, Dr. Mohr suggested, with recent concern about endarterectomy for carotid stenosis. Based on existing data, in cases where stenosis is extremely severe, operating on 8 patients will avoid at least 1 stroke, an excellent outcome for surgery. However, when obstruction is moderate, without impaired flow to the brain, the results of surgery are much less impressive. "We are probably going to find a cohort of patients with unruptured AVMs for whom intervention will be well worth the effort," said Dr. Mohr. "But at the moment, we don't know who they are or whether we will actually find them."

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mesh-like metal device in the carotid artery to restore blood flow to the brain. The insertion is performed via catheter and the patient is usually conscious. More than 1,000 participants have been enrolled in the lead-in phase of CREST, and more than 400 participants have been enrolled in the randomized phase.

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>
> —Sean D. Lavine, MD

"Initially, the study population was restricted to patients with symptomatic stenosis who had a stroke or transient ischemic attack," said Y. Pierre Gobin, MD, a lead investigator in the trial. Recently, CREST received approval to enroll asymptomatic patients to evaluate the procedure as a preventive measure.

However, in the fall of 2004, the FDA approved the first carotid stenting device; this has made enrollment challenging. According to Howard A. Riina, MD, researchers are finding that few patients "want to have surgery; they all want the stenting."

"Most doctors are performing stenting even when the data are not there," agreed Philip Meyers, MD, also a lead investigator in the CREST trial. "I tell patients the proven technique is surgery. Performed at expert centers by experts, it's very low-risk."

Still, coiling is fast becoming the method of choice (over surgery) in the treatment of aneurysms. According to Dr. Riina, success with coiling depends on the patient's age, how sick they are following the rupture, and the

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NewYork-Presbyterian Neuroscience

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Researchers Work Toward Development of Alzheimer's Vaccine

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are exploring new therapeutic options and trying to learn more about the origins of Alzheimer's disease (AD).

At NewYork-Presbyterian Hospital/Weill Cornell Medical Center, Norman Relkin, MD, PhD, is working with Marc Weksler, MD, to explore the potential of a vaccine designed to slow the onset of AD. The work was inspired by a 1999 study in mice that found that injections of a form of beta-amyloid, the protein core of the brain plaques seen in AD patients, cleared existing plaques from the brain and prevented new ones from forming.

"Shortly after that study was published," noted Dr. Relkin, "we began comparing the blood of AD patients with blood from normal elderly individuals, thinking that if mice could be induced to raise antibodies that fought off plaques, perhaps some people naturally produced such antibodies and were consequently less likely to develop AD. Virtually everyone has these antibodies, but the levels vary, and AD patients tend to have fewer than non-AD patients."

The researchers believed the results of this study could serve as the basis for developing a new vaccine treatment for AD based on the human blood product called intravenous immunoglobulin (IVIg). IVIg is obtained from thousands of healthy donors who as a group have higher levels of antibodies against beta-amyloid than AD patients. The results of the IVIg clinical trial are still being analyzed, but interim results are extremely encouraging, according to Dr. Relkin. Thus far, none of the patients treated with IVIg for 6 months have shown the typical signs of decline associated with AD, and several patients have improved measurably after treatment.

Since IVIg has been extensively tested for treatment of other diseases, it is expected to be safer than other vaccines under study for this purpose. The Weill Cornell investigators are extending these studies to check the long-term effects of treatment and are already planning a large-scale Phase III clinical trial at the national level.

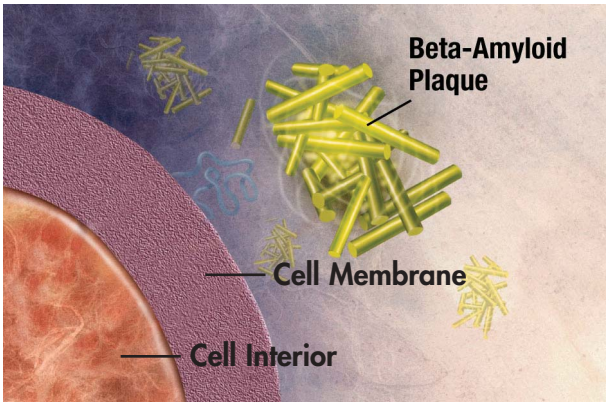

Image courtesy of the Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging.

An artist's rendering of beta-amyloid plaque, the protein core of the brain plaques seen in patients with AD. Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are using beta-amyloid plaque as the basis of a potential vaccine designed to slow the onset of the disease.

> None of the patients treated have shown the typical signs of decline associated with AD, and several patients have improved measurably after treatment.

Meanwhile, at NewYork-Presbyterian Hospital/Columbia University Medical Center, Richard Mayeux, MD, MSc, is studying the genetic epidemiology of AD. "We position ourselves to identify the important genes, and then look at how environmental factors interact with these genes," explained Dr. Mayeux.

Much of Dr. Mayeux's work has involved finding families with elevated rates of AD. In 6 years, Dr. Mayeux's research team has assembled around 500 families of Caribbean Hispanics with multiple cases of AD. The researchers have examined the genomes of these families for regions that turn up in AD patients but are absent for those without the disease.

"There seems to be an interaction between cerebrovascular disease and the APOE-e4 gene," Dr. Mayeux said, referring to the well-studied AD gene. Roughly 15% to 20% of the population carries the APOE-e4 gene, although only a fraction of them will get the disease. But that interaction "means that APOE-e4 carriers are more likely to develop AD if they have concomitant cerebrovascular disease, as compared with APOE-e4 carriers without cerebrovascular disease or those with cerebrovascular disease who lack the APOE-e4 allele," Dr. Mayeux explained. This theory implies that APOE-e4 carriers might be able to reduce their risk of AD by managing the risk factors for cerebrovascular disease, such as diet, exercise, blood pressure monitoring, and smoking avoidance.

Dr. Mayeux and his colleagues have also found a single AD gene in this population—presenilin 1. This gene is well known, but surprisingly, every member of the Caribbean Hispanic population with the gene has the same novel mutation, suggesting that a single founder brought the gene into the population.

Dr. Mayeux is leading a consortium of 18 Alzheimer's centers with the goal of creating a national repository of AD families in the United States. In 3 years, they have enlisted 600 families. One of

the biggest benefits of this data is that researchers will be able to confirm other genetic studies. Frequently, when a group finds a new gene, "no one can confirm [the finding] because they don't have enough other families to replicate [the work]," Dr. Mayeux remarked. "Confirmation is very important because false positives are very common in this kind of work."

Dr. Mayeux's epidemiology work could ultimately help determine which patients would be suitable for the vaccine currently being developed by Drs. Relkin and Weksler, assuming it proves effective.

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location of the rupture.

Endovascular coiling of an aneurysm is a minimally invasive procedure that uses fluoroscopic imaging to visualize the patient's vascular system and treat the disease from inside the blood vessel. Tiny platinum coils are inserted via catheter and deployed into the aneurysm, blocking blood flow into the aneurysm and preventing rupture. Data from the International Subarachnoid Aneurysm Trial, which compared endovascular coiling with open surgery for ruptured aneurysm, show 25% better outcomes in patients treated with the coiling procedure.

However, there is room for improvement. Dr. Gobin—who worked with the inventor of the Guglielmi Detachable Coil platinum coil back in the 1990s—and his team have worked to improve the platinum coils by coating them with a biodegradable polymer that induces a scar reaction within the aneurysm. The overall efficacy of the new coil has not been fully tested. Dr. Gobin's team hopes to begin recruiting patients for a clinical trial later this year.

One of the challenges in coiling aneurysms is that 10% to 20% of patients require additional coil placement because the coils compact. Coiled aneurysms often look filled, even with only 20% to 25% of their volume occupied and are thus prone to coil compaction, aneurysm regrowth, or both. Drs. Lavine and Meyers are awaiting Internal Review Board approval for 2 different trials—one using a platinum coil coated with an expanding polymer, and a second trial using a platinum coil filled with polylactic acid. Both procedures will, hopefully, create "more stable and complete occlusion of aneurysms," according to Dr. Lavine.

Another challenge in stenting is that a significant number of aneurysms have broad necks that allow the coil to fall out of the aneurysm and into the artery, potentially causing a stroke. Roughly 50% of aneurysms have a broad neck, meaning the stenting method cannot be used. Despite the prevalence of the problem, noted Dr. Gobin, "not that many physicians know how to treat it. The brain arteries are very challenging: very torturous, very thin, with lots of curves."

Until the recent development of a new, highly flexible stent, designed specifically for deployment in the brain, physicians were forced to use coronary stents. Because these stents are not self-expanding, there was an increased risk of injuring the artery during deployment. The new stent allows surgeons to navigate further into the vasculature of the brain, and because it is self-expanding, it is less traumatic to tissue. In addition to helping hold coils in the aneurysm, it is also designed to redirect blood flow away from the aneurysm, to promote healing.

Dr. Meyers, who is the principal investigator for a trial evaluating the use of the new stent, doesn't always use it. "The new stent is a great tool to have when there's no other solution for a patient with a wide brain aneurysm, because it lets us treat many patients for whom there is no other option," he said.

With all of these options currently under investigation, physicians at NewYork-Presbyterian Hospital expect to continue to see improved outcomes in the treatment of brain aneurysms and other injuries. "We can do so much more in the brain than we could just 5 years ago and the pace of progress is staggering. Our technical capabilities double every 5 years," said Dr. Lavine. "Now, we have new devices—and new choices—available to us almost on a monthly basis."

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Making Music: Research Into the Mystery of Musician's Dystonia

Steven J. Frucht, MD, refers to the diagnosis of focal-task specific dystonia (FTSD) as "a watershed event in a musician's life." Whether the embouchure is affected, as with brass and woodwind players, or the hand, as with violinists and pianists, the disorder can end a performance career, causing immense stress and psychological pain.

Dr. Frucht, who heads up research into FTSD in musicians (or "musician's dystonia") at the Center for Movement Disorders at NewYork-Presbyterian Hospital/Columbia University Medical Center, trained extensively as a pianist and violinist before turning to medicine. His work over the past 6 years has provoked greater awareness of performance-related dystonia among musicians nationwide and, in addition, laid the foundation for research that may lead to further insights into the fundamental mechanisms underlying all the focal dystonias, including spasmodic torticollis, oromandibular and orofacial dystonia, and writer's cramp.

Although reports of FTSD date to the 19th century, musician's dystonia was little more than a curiosity until the 1980s, when the affliction terminated the career of celebrated pianist Gary Graffman. Years earlier, in the 1960s, dystonia had also ended the concert career of pianist Leon Fleischer.

Dr. Frucht began work with the disorder after meeting Glen Estrin, a prominent French horn player who had developed embouchure dystonia in 1999. Their collaborative success in raising awareness of dystonia among union musicians in New York brought Dr. Frucht and his colleagues at the Center for Movement Disorders a deluge of new patients and led to the establishment of Musicians with Dystonia, subsequently allied to the Dystonia Medical Research Foundation. The organization aims to stimulate research and assist afflicted musicians in seeking help. Professional musicians represent a natural cohort for research purposes, and Dr. Frucht noted that his own projects currently include cortical and subcortical mapping studies of hands and mouths in musicians with dystonia and normal controls.

Dr. Frucht believes that the prevalence of FTSD among professional musicians today may be as high as 0.2%. The disorder normally arises during the fourth decade of life—often when a musician is reaching his or her professional peak. The DYT1 gene mutation, a marker for early-onset primary dystonia, is not implicated in musician's dystonia.

> "The sooner a person with dystonia... receives treatment the less likely [he is] to lose precious time.... Treatment allows [the patient] to enter the battlefield again. Otherwise, it's impossible."
>
> —Steven J. Frucht, MD

Indeed, the neuromuscular events that give rise to FTSD are not well understood. Musician's dystonia has been reported in connection with players of virtually every instrument, including woodwinds, brass, string instruments (viola and violin), and the plectrum instruments (guitar, banjo, and mandolin). Disruption of muscular control occurs in zones specific to mastery. Thus, the right hand is most often affected in pianists, while violinists are frequently afflicted in the left hand; in all cases, fingers or wrist develop an involuntary posture. With players of brass instruments, the embouchure is affected, with air leaks at the corners of the mouth, tremor, and puckering of the lips. Typically, no pain is involved. The affected musician may try to ignore the problem, attempt to compensate, or employ various strategies to overcome it before seeking help.

The introduction of a nerve-blocking drug, botulinum toxin type A, in the late 1980s led to a significant change in the treatment of all the dystonias. For musicians, it does not represent a complete cure because fine motor control remains a struggle even after treatment, and a variety of issues must be individualized to each patient. However, said Dr. Frucht, "it allows you to enter the battlefield again. Otherwise, it's impossible."

Botulinum did help pianist Leon Fleischer return to concert performance in 2004, 4 decades after his career was cut short by dystonia. Today, more than ever, timely and accurate diagnosis is indispensable. "The sooner a person with dystonia sees a specialist and receives treatment," said Dr. Frucht, "the less likely [he is] to lose precious time, as maestro Fleischer did."

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tumor excision, which requires the opening of a relatively large piece of the skull. Instead, intracranial endoscopy uses instruments no larger than several millimeters in diameter. These instruments are navigated through the fluid-filled chambers of the brain, offering high-resolution images with unsurpassed illumination.

Guidance systems include highly advanced imaging systems such as stereotaxy, computer-generated models of the brain, and intraoperative MRI. Stereotaxy used in conjunction with the endoscope offers a precise method for establishing the best trajectory to be used in reaching intraventricular tumors. The use of the MRI scan in the operating room, done at NewYork-Presbyterian Hospital and a few other centers nationally, allows surgeons to gauge the degree of tumor resection during the surgery and navigate the region. The integration of these technologies has revolutionized the minimally invasive approach toward certain brain tumors that have historically presented true surgical challenges.

"Minimally invasive surgery can be very beneficial in treating centrally located intraventricular brain tumors," noted Dr. Souweidane. "However, development of minimally invasive surgery at any institution requires substantial investment in technique, training, and equipment. The experienced doctor can recognize which patients are good candidates for minimally invasive surgery and implement rigid selection criteria. When these criteria are followed successfully, the results can be extremely beneficial for the patient."

Minimally invasive procedures are also being used to treat spinal cord injuries. At NewYork-Presbyterian Hospital/Columbia University Medical Center, Michael G. Kaiser, MD, treats patients with low-back pain, disk disease, spinal tumors, and spinal cord injuries. Depending on the patient's pathology, he often uses minimally invasive approaches that decrease the amount of soft-tissue trauma. "The typical patient I see has sciatica from a herniated disk in the lower back, or spinal cord dysfunction from a cervical disk within the neck that is compressing the spinal cord," he said. "Some patients have back pain that is related to a structural abnormality in the spine, where they've lost a certain degree of structural integrity so that motion produces pain. Or patients come with neurologic deficits, where the intrinsic problem involves the neural elements, like a spinal cord tumor. They have pain either in their back or extremities, or present with weakness, numbness, or loss of function. For lumbar disk herniations, we almost exclusively use [minimally invasive] approaches. With spine surgery, this decreases the amount of muscle and ligament injury of the surrounding tissues that help support the spine, reducing the patient's postoperative pain and allowing them to resume normal activities sooner."

> "Minimally invasive surgery can be very beneficial in treating centrally located intraventricular brain tumors. However, [it] requires substantial investment in technique, training.... When these criteria are followed successfully, the results can be extremely beneficial for the patient."
>
> —*Mark M. Souweidane, MD*

Photo courtesy of the NewYork-Presbyterian Hospital Spine Centers.

Navigational technologies such as MRIs assist surgeons in the use of minimally invasive techniques for spine surgery.

Minimally invasive techniques go hand in hand with the use of surgical navigation tools, according to Dr. Kaiser. "Because there is much less soft tissue exposure with these types of procedures, we need something to help us guide instruments and implants to the spine," he said. Advanced navigational tools create three-dimensional models of the patient's spine. Then, by means of a special algorithm, a computer incorporates the patient's anatomy at the time of surgery with prior imaging (X-ray) studies so that at the time of a procedure, surgeons know precisely where they are without actually seeing the spine.

At NewYork-Presbyterian/Weill Cornell, surgeons are using minimally invasive techniques to perform spinal fusions. Surgeons John Boockvar, MD, and Roger Hartl, MD, work with 2 newly released muscle retractor systems that spread apart tissue plains rather than cut them. "We are using state-of-the-art intraoperative navigation systems to assist in the placement of pedicle screws through these smaller incisions," said Dr. Boockvar. "Even simpler operations that have been routinely performed with the operating room microscope—such as lumbar and cervical discectomy—are now being performed through minimally invasive tubular retracting systems. We are using more percutaneous techniques that simply involve small holes in the skin to place pedicle screws and to restore vertebral body height after osteoporotic or metastatic fractures using kyphoplasty."

According to Dr. Hartl, surgeons also use nonmetal, bioabsorbable instrumentation for spinal fusion, particularly in the treatment of cervical spondylosis. "Patients find the option of undergoing fusion surgery without having permanent metallic instrumentation implanted less invasive and extremely attractive," he noted. In addition, Dr. Hartl is leading

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efforts at the Hospital to develop new, groundbreaking electromagnetic spinal navigation technology to further expand the application of minimally invasive spine surgery.

At NewYork-Presbyterian/Columbia, meanwhile, Christopher Winfree, MD, specializes in the treatment of complex peripheral nerve problems, including brachial plexus injuries, trigeminal neuralgia and other facial pain syndromes, regional pain syndromes, and failed back surgery syndrome. He works closely with the Comprehensive Pain Management Center at NewYork-Presbyterian/Columbia to treat chronic pain; a multidisciplinary team there includes anesthesiologists, physiatrists, psychologists, and therapists. Dr. Winfree uses minimally invasive techniques when he implants spinal cord stimulators through either a small incision, or no incision at all.

"We use a needle to place these electrodes in various parts of the body to treat chronic pain syndromes. Essentially, any pain that affects an extremity or a discrete nerve distribution can potentially be treated by spinal cord or peripheral nerve stimulation," he noted. "Typically, patients who have these stimulators go home either the same day or the following day. We are fortunate that because of technologic advances, we have the ability to do things more quickly and more easily—with less pain and less cost. We are also able to pick and choose the technique that is best suited for each individual patient."

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Important news from the NewYork-Presbyterian Neuroscience Centers—current research projects, clinical trials, and advances in the diagnosis, treatment, and rehabilitation of neurologic disease.