

# NEW YORK-PRESBYTERIAN Neuroscience

Affiliated with COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS & SURGEONS and WEILL MEDICAL COLLEGE OF CORNELL UNIVERSITY

August 2003

## Deep Brain Stimulation Surgery for Parkinson's Disease

**D**eep brain stimulation, the powerful new modality for treating the disabling motor symptoms of Parkinson's disease and other movement disorders, has become the procedure of choice at the Center for Movement Disorders Surgery at Columbia Presbyterian Medical Center, and at the Center for Stereotactic and Functional Neurosurgery at NewYork-Weill Cornell Medical Center. It has largely supplanted tissue ablation procedures, which had been the standard as recently as the 1990s.

"We have converted, almost totally, from doing lesions to stimulator

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## Endovascular Surgery Shows Promising Results

**D**iseases and malformations of the brain's endovascular system—once treatable only by invasive and complicated surgical procedures—are increasingly being treated essentially from within using a procedure known as endovascular surgical neuroradiology.

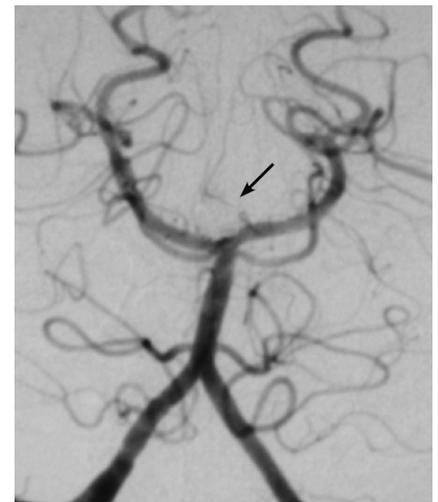
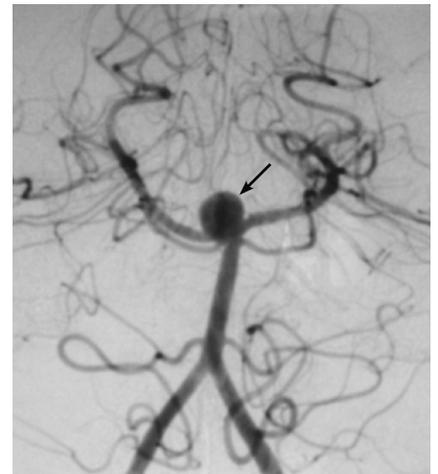
"We're brain plumbers," noted Philip Meyers, MD. "If the pipes are leaking, we plug the leak; if the pipes are clogged, we unclog them. All joking aside, endovascular surgical neuroradiology is a very important and rapidly growing specialty in major medical centers across the United States."

With an array of high-tech tools—glues, coils, tubes, balloons, and even tiny "umbrellas"—researchers at NewYork-Presbyterian Hospital are, as Dr. Meyers would say, "plumbing" the depths of the brain's blood vessels. Along the way, their innovations and studies have made them recognized world leaders in the treatment of stroke, aneurysms, arteriovenous malformations, and carotid stenting for opening the neck's plaque-choked artery.

"One of the biggest and most dramatic things we do is to take care of intracranial aneurysms, ruptured or unruptured," said Howard A. Riina, MD. "The endovascular way of treating aneurysms is by coiling them."

Developed in 1990 by Guido Guglielmi, MD, the Guglielmi Detachable Coil is a tiny, flexible platinum coil placed into an aneurysm via catheter. By packing the aneurysmal sac, it induces clotting and

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**Aneurysm, before and after:** The endovascular way of treating aneurysms involves the Guglielmi Detachable Coil. By packing the aneurysmal sac, the coil induces clotting and scarring to remove the aneurysm from circulation.

## Computed Tomography Perfusion: Improving Stroke Diagnosis and Treatment

Stroke's status as the third leading cause of death in the United States has served to spur researchers to find safe and effective tools for its diagnosis and treatment. To some, computed tomography (CT) scans have often been seen as somewhat of a "down and dirty" radiologic tool when compared to positron emission tomography (PET) scans, single-photon-emission CT scans, and magnetic resonance imaging (MRI).

Thanks to engineering advances and continued research, much of which is being done at NewYork-Presbyterian Hospital, CT perfusion scanners now show numerous advantages over other diagnostic tools, particularly in the diagnosis and safer treatment of emergency room and intensive care unit patients already in stroke or facing cerebral hemorrhage.

According to Pina C. Sanelli, MD, while PET scans have remained the gold standard for the evaluation of cerebral blood flow and brain metabolism for many years, they have often been a nonviable option for analyzing the stroke patient in the emergency room or intensive care unit after hours or on the weekend because of their limited availability and the need for prior preparation of the radioactive tracer. Therefore, she said, other modalities such as CT and magnetic resonance perfusion have emerged as promising tools for physicians. "When you're dealing with someone connected to multiple lines and/or



**A CT angiogram shows right middle cerebral artery occlusion with large parietal collaterals.**

on very aggressive drips that can't be interrupted, the enclosed MRI tube can present a major obstacle," added Igor Ougorets, MD. "By comparison, CT perfusion makes it easier to prepare the patient and the exam takes about 30 seconds—versus 10 minutes in MRI—to perform. You also have full access to the patient, so if something happens, the doctor or the technician can jump in to treat the patient, fix a line, etc. CT perfusion is definitely more user-friendly for the critically ill patient."

### Monitoring Vasospasm

Led by Robert DeLa Paz, MD, neurologists at Columbia Presbyterian Medical Center have discovered 2 increasingly

valuable uses for CT perfusion—acute stroke evaluation in the ER and treatment of the post-stroke patient in the intensive care unit.

"CT perfusion changes can be seen sooner after stroke onset than CT low-density changes, allowing earlier diagnosis and treatment," said Dr. DeLa Paz. He added that the technology is also useful in monitoring the reduction of blood flow to the brain that may be produced by progressive vasospasm, which can result from subarachnoid hemorrhage.

Dr. Sanelli believes that CT perfusion helps physicians to better "estimate the risk of developing vasospasm and stroke" by providing actual numbers for such parameters as cerebral blood flow and mean transit time. She admits that catheter angiography is the gold standard for vasospasm evaluations, but it is also an invasive procedure, which presents increased risks for patients. As a result, NewYork Weill Cornell Medical Center has been involved for more than a year in a new institutional review board-approved protocol to use CT perfusion to "provide us with information as to when patients are developing vasospasm and need an angio," noted Dr. Sanelli. "We feel that with CT perfusion we can image areas of the brain that may be undergoing end-vessel vasospasm." Historically, this has been difficult information to obtain, even with catheter angiography.

### The All-in-One Debate

A critical question facing doctors who treat stroke patients is how much of the brain has been infarcted and how much is still treatable ischemic penumbra. "If the diffusion-weighted imaging lesion is smaller than the perfusion-weighted imaging abnormality, there is a potentially treatable stroke penumbra," said Dr. DeLa

*"CT perfusion changes can be seen sooner after stroke onset than computed tomography low-density changes, allowing earlier diagnosis and treatment."*

—Robert DeLa Paz, MD

*Clinical debate has centered around whether it is possible for CT perfusion to provide both diffusion-weighted imaging and perfusion-weighted imaging data.*

Paz. “If diffusion-weighted imaging versus perfusion-weighted imaging is the same or larger, we conclude the tissue’s blood supply has been reduced too long or that the body has reperfused that tissue and we’re too late to do anything.”

Clinical debate in this area has centered around whether it is possible for CT perfusion to provide both diffusion-weighted imaging and perfusion-weighted imaging data alone (as postulated by Wintermark et al in Switzerland [*Adv Neurol* 2003;92:389-400]). According to Dr. DeLa Paz, researchers at Columbia Presbyterian Medical Center have used Dr. Wintermark’s methods and failed to obtain “a reliable discrimination between the two.” But at NewYork Weill Cornell Medical Center, according to Dr. Sanelli, preliminary data in this area have “demonstrated the reliability and reproducibility of CT perfusion” alone for delineating the cerebral infarct core, making it a useful tool in analyzing stroke patients in emergency situations.

It should be noted that the more limited brain coverage provided by CT perfusion is another consideration for making it reliable in diffusion-weighted imaging and/or perfusion-weighted imaging differentiation. “Would I like to have an 8-slice image of the brain as I do with MRI? Yes,” said Dr. Ougorets. “But I now have 4 slices with the CT perfusion where I used to have 1.” That said, Dr. Ougorets added that he has no reason to believe that in a few years CT perfusion won’t give him those 8 slices.

### **Risking t-PA**

Using CT perfusion to determine the viability of intra-arterial delivery of tissue plasminogen activator (t-PA) is another area researchers at Columbia Presbyterian Medical Center have been exploring. The suggested timeline for safe and effective stroke treatment using t-PA is within the first 3 hours after onset.

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**NewYork-Presbyterian Neuroscience** is a publication of the Neuroscience Centers of NewYork-Presbyterian Hospital. The Neuroscience Centers are at the forefront of research and practice in the diagnosis, treatment, and rehabilitation of neurologic disease. NewYork-Presbyterian Hospital is located at Columbia Presbyterian Medical Center and NewYork Weill Cornell Medical Center. The Neuroscience Centers include the Neurological Institute at Columbia Presbyterian Medical Center and the NewYork Weill Cornell Neuroscience Institute, which are respectively affiliated with Columbia University College of Physicians & Surgeons and the Weill Medical College of Cornell University.

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## Studying Gene Therapy in the Treatment of Neurologic Disorders

Researchers at NewYork-Presbyterian Hospital have launched the first clinical study investigating the safety and efficacy of gene therapy in the treatment of neurologic disorders in human patients. The Phase I trials, which involve surgical insertion of viral vectors into cells of the subthalamic nucleus, are targeting patients suffering from the major motor symptoms of Parkinson's disease. If successful, the therapy has broader implications for other neurologic and brain-related disorders.

For Michael Kaplitt, MD, PhD, co-principal investigator on the study, the trials open a new chapter in his personal research efforts in the area, which date from the late 1980s. "The concept of using gene therapy for Parkinson's disease evolved over the course of more than a decade," said Dr. Kaplitt.

When he began looking into the concept at Rockefeller University in 1989, Dr. Kaplitt and his team—and several other groups—were seeking to develop workable viral delivery systems that targeted the brain. All exploited the natural infectivity of viruses together with recently developed tools of recombinant DNA research. They found that genes that produce specific enzymes could be inserted into viruses disposed by nature to integrate cellular DNA.

Adeno-associated virus, which Dr. Kaplitt also studied, was one of a number of candidate vectors in the early 1990s. Researchers found it had several advantages for gene therapy. A harmless virus, adeno-associated virus does not provoke antibodies or stimulate inflammation, and it is able to enter nondividing cells such as neurons. After several years of work, Dr. Kaplitt and colleagues reported the first use of adeno-associated virus in the mammalian brain in

*Nature Genetics* (1994;8:148-154). Adeno-associated virus subsequently became and remains widely used in gene therapy experiments.

The disabling motor symptoms of Parkinson's disease arise, it is believed, from excessive neuronal firing in consequence of a chemical disturbance in the brain due, in the last analysis, to loss of dopaminergic neurons. One of dopamine's functions is to regulate output of the inhibitory neurotransmitter known as gamma-aminobutyric acid. Dr. Kaplitt and others believed that restoring gamma-aminobutyric acid to

procedures, bioengineered cells will renormalize neurochemical circuits without damage to tissue or insertion of an electronic device. A patient undergoes a stereotactic procedure after extensive imaging and preparation, which leaves within the brain only the modified adeno-associated virus.

Dr. Kaplitt and his colleagues planned the surgical intervention in detail and undertook animal studies, the success of which led to efforts to gain approval for human trials. The proposal advanced through the National Institutes of Health's

*"The concept of using gene therapy for Parkinson's disease evolved over the course of more than a decade."*

*—Michael Kaplitt, MD, PhD*

specific areas of the basal ganglia could, in principle, reduce the motor symptoms of Parkinson's disease, and that this plausible long-term solution might be implemented by introducing modified recombinant viruses equipped with the gene that expresses the gamma-aminobutyric acid-producing enzyme glutamic acid decarboxylase.

With this concept firmly in mind, Dr. Kaplitt and colleagues worked to develop a stereotactic procedure that would deliver these viral vectors specifically to the basal ganglia cells that could normalize the gamma-aminobutyric acid circuitry. Since the 1980s, neurosurgeons had enjoyed new success both in targeting highly specific areas of the brain and in treating symptoms by ablating tissue or, more recently, by employing deep brain stimulation. Now, it is hoped that in place of these

Recombinant DNA Advisory Commission, where it gained enthusiastic support, and the FDA approved it in August 2002. Matthew J. During, MD, co-principal investigator with Dr. Kaplitt and Professor of Molecular Medicine at the University of Auckland, in New Zealand, emphasized that these Phase I trials are still experimental. "Our primary objective has been to stress patient safety above all else," he said. "It is our hope that, with this approach, our trial will help demonstrate that gene therapy in the brain can be both safe and effective."

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## Deep Brain Stimulation

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implants,” according to Robert Goodman, MD.

Michael Kaplitt, MD, PhD, who performs the procedure at the Center for Stereotactic and Functional Neurosurgery, added, that “all of our experience over the past few years indicates that stimulators are better tolerated than lesions and have longer-lasting effects.”

Fully approved by the Food and Drug Administration (FDA) in 2002 after considerable media coverage in the lay press, deep brain stimulation has rapidly defined a new standard of care among Parkinson’s disease patients for whom medication has ceased to provide significant relief. Deep brain stimulation is not a cure, but for the right patients the procedure can substantially reduce motor symptoms and improve quality of life. A procedure that can be postoperatively programmed and adjusted to individual patients, deep brain stimulation has quietly and rapidly supplanted thalamotomy and pallidotomy, 2 sophisticated lesion-based techniques that for the past 2 decades represented state-of-the-art surgery for advanced Parkinson’s disease. These procedures, although quite frequently effective, carry various degrees of risk that deep brain stimulation largely avoids.



**Blair Ford, MD, consults with a Parkinson’s disease patient: “The care for these patients needs to be comprehensive, and optimally carried out in a context where there’s an accumulation of expertise, clinical experience, and institutional resources.”**

Crucial to the success of deep brain stimulation are comprehensive patient screening, preparation, education, and preoperative and postoperative care. Candidates for deep brain stimulation usually suffer from the advanced motor symptoms of Parkinson’s disease that arise in most patients within 5 to 10 years of initial diagnosis. Although these patients are invariably helped at first by levodopa—still the standard medication for Parkinson’s disease—their response to the drug eventually becomes problematic or unpredictable, and other medications fail to help. Sometimes a dose of levodopa will fail to control symptoms or work only intermittently, with spells of “wearing off” as levodopa ceases to work, during which patients become stiff or unable to move. Other patients suffer from rapid motor fluctuations or from dyskinesias, the most disabling of motor symptoms, that involves involuntary muscle contractions in the extremities, head, or trunk. Patients at this stage of the disease, according to



**A patient undergoing deep brain stimulation surgery: The surgeon inserts electrodes into the brain through burr holes in the skull. The electrodes reach their targets with the help of magnetic resonance imaging and brain mapping with microelectrodes.**

done by Shaik Ubaid, MD. Seth Pullman, MD, handles the same duties at the Center for Movement Disorders Surgery. The surgical procedure itself is

*Candidates for deep brain stimulation usually suffer from the advanced motor symptoms of Parkinson’s disease that arise in most patients within 5 to 10 years of initial diagnosis.*

Blair Ford, MD, can almost always benefit from deep brain stimulation if they are in good general health. Although younger patients tend to have the best results, advanced age alone is not a contraindication to surgery.

Like the lesion-based procedures that it has largely replaced, deep brain stimulation is a stereotactic operation in which a coordinate system enables the surgeon to target a specific location in the brain with millimeter-by-millimeter accuracy. However, instead of tissue ablation to create lesions that reduce motor symptoms, the surgeon inserts electrodes into the brain through burr holes in the skull. Brain mapping procedures to ensure proper placement of the stimulators are performed by neurologists with expertise in this technique. At the Center for Stereotactic and Functional Neurosurgery, this work is

performed by Dr. Goodman or Guy McKhann, MD, at Columbia Presbyterian Medical Center, and by Dr. Kaplitt at NewYork Weill Cornell Medical Center.

During deep brain stimulation, the patient remains awake and helps the surgical team guide electrode placement by answering various questions concerning symptoms and sensations. For patients with bilateral symptoms, electrode insertion is performed on both sides of the brain.

Once the electrode is anchored in the brain, its lead is attached to the inside of the skull, and a connecting wire is laid in behind the ear and neck, leading to the chest, where a battery-operated implantable pulse generator is placed in a surgically created pocket beneath the clavicle. (This can be done on the same

see [Deep Brain Stimulation](#), page 12

## Investigating Noninvasive Radiotherapy in Temporal Lobe Epilepsy

Researchers at NewYork-Presbyterian Hospital's Center for Movement Disorders Surgery believe painless, noninvasive radiotherapy can become a viable alternative to neurosurgery for patients with intractable temporal lobe epilepsy.

"This treatment may prove just as effective as surgery for at least some of the patients that we treat," says Robert Goodman, MD. Dr. Goodman and his surgical team are currently participating in a multicenter study to determine the effectiveness of gamma knife radiosurgery in temporal lobe epilepsy, with preliminary results expected within a year. The research is supported by the National Institutes of Health.

Surgery remains the accepted treatment for patients with refractory temporal lobe epilepsy. Dr. Goodman's study offers patients the radiologic option as an alternative to conventional surgery. The larger aim is to discover whether and to what extent the gamma knife can effectively eliminate symptoms while reducing or avoiding the risks of functional impairment that come with invasive neurosurgery.

"We might learn we can eliminate the seizure potential without eliminating all of the function in the part of the brain operated on," noted Dr. Goodman.

Gamma knife radiosurgery involves use of a multi-million-dollar system (it weighs 20 tons) that delivers highly focused beams of cobalt-60 radiation to 3-dimensional pinpoint targets within the brain. Therapeutic benefits accrue over time, presumably due to radiation-induced changes in cell function and metabolism. Developed in Sweden in the 1960s, the instrument has been employed for years by neurosurgeons—sometimes with outstanding success—to



**A CT scan of a patient with temporal lobe epilepsy—induced left medial temporal sclerosis.**

treat vascular abnormalities and brain tumors for which resection is not an option. With improved understanding of brain structure and neurochemical interactions, the gamma knife is currently on track to treat several movement disorders, including Parkinson's disease. To date, the procedure has been used to treat temporal lobe epilepsy in a small number of cases in Europe and the United States.

Epilepsy affects about 1 million people in the United States, an estimated 100,000 of whom become candidates for surgery when medication fails to adequately control seizures. Lesionectomy and other operations, ranging from curative to palliative, aim to reduce or eliminate seizures. Aided by advances in brain imaging, surgical procedures currently enjoy high rates of success overall. But with an estimated 1% mortality rate and postoperative complications as high as 10% to 20%, a noninvasive alternative would be welcome.

Although painless and bloodless, gamma knife radiosurgery is not without risk. While the procedure has proved safe in other uses, concern for complications—including radiation necrosis and edema, neurologic deficits,

and eventual neoplasms—remains. In addition, for reasons that are still unclear, patients only gradually become free of seizures. While the effects of neurosurgery are immediate, benefits from the gamma knife in epilepsy appear over several months.

Temporal lobe epilepsy patients in the current study, when offered the gamma knife option, still decided on invasive surgery approximately half the time. "By the time they're being recommended for surgery, they want to have it yesterday," said Dr. Goodman. "So if we suggest treatment with radiation, which takes 9 to 10 months, they don't want that delay." In addition, he added, these patients are often relatively young and may also have concerns about long-term adverse effects of radiation.

Use of the gamma knife for temporal lobe epilepsy does not rule out subsequent neurosurgery if the patient does not become seizure-free. As with other forms of surgery, if successful, the gamma knife may have other advantages. A current hypothesis holds that surgery may confer a neuroprotective benefit, and some evidence suggests that patients who become seizure-free at a young age avoid a variety of associated psychological and psychosocial problems. If the gamma knife provides these benefits without the risks of invasive procedures, it may become a widely used alternative in a rapidly advancing field.

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# Expanding t-PA's Use in Stroke Treatment

Neurosurgeons and interventional neuroradiologists at NewYork-Presbyterian Hospital are at the forefront of efforts to widen the window of opportunity for treating stroke patients. The medical treatment currently approved by the FDA for hemorrhagic stroke—intravenous tissue plasminogen activator, or t-PA—can be given only within the first 3 hours after the onset of symptoms. As a result, only 2% to 3% of patients who can benefit from the treatment actually receive it.

“If we get to them within those first 3 hours with intravenous t-PA, there’s a 30% improvement in morbidity and mortality,” said Sean Lavine, MD. Beyond 3 hours, he added, the risk of the drug’s causing a devastating hemorrhage in the brain outweighs any possible benefit.

The need to find effective interventions beyond those first 3 hours couldn’t be greater. Intracranial hemorrhage is the third leading cause of death and the primary cause of adult disability in the United States, making it the leading diagnosis for patients moving from hospitals to nursing homes. The standard strategy now used at NewYork-Presbyterian Hospital’s advanced treatment centers when patients show up within 3 to 6 hours after the onset of symptoms is the application of t-PA

“There have also been some preliminary studies on using intra-arterial urokinase,” said Dr. Lavine. The drug, approved by the FDA in October 2002 for treating clots in the heart, is already

where it deploys a self-expanding conical coil. The coil becomes so enmeshed in the clot that it can be dragged away when the catheter is removed.

The MERCI I trial, involving 50

*“There have also been some preliminary studies on using intra-arterial urokinase [in stroke treatment.] We’re hoping to improve the chances of a good outcome by 30% to 50% when it’s used in that 6-hour time frame.”*

—Sean Lavine, MD

showing results comparable to those with intra-arterial t-PA when used in the brain, he said. “We’re hoping to improve the chances of a good outcome by 30% to 50% when it’s used in that 6-hour time frame,” he added.

Ultimately, though, “you would prefer to not give any thrombolytic at all, because even when delivered intra-arterially, it still raises the risk of bleeding,” said Y. Pierre Gobin, MD.

To find a better way to clear neurologic emboli, Dr. Gobin invented a device, the Concentric Retriever, that is being examined in the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial at NewYork-Presbyterian Hospital.

patients at 7 centers across the United States, established that the device could be safely used up to 8 hours after the onset of symptoms. In 52% of the cases, the clot was successfully retrieved with the device. Just 2% of patients had a major complication during the procedure. Now in a Phase II trial at 20 centers across the United States, the MERCI device has been used on 80 patients.

“We are reporting a 55% recanalization rate of cerebral arteries,” Dr. Gobin said. “Half of the patients that were recanalized have a great recovery and are able to live independently.”

Dr. Lavine, who has been using the MERCI device, added, “I think it’s a promising, excellent idea. This device is one of the very few tools we have.” One challenge with using the device, he said, is that the coil needs to be stiff enough to hang onto the clot yet flexible enough to negotiate the twists and turns of the neurovasculature. “To be effective, the device has to have some stiffness,” Dr. Lavine explained. “But that comes at the expense of having more difficulty navigating to get it where you want it to go.”

As a result, the MERCI device has evolved as neurosurgeons such as Dr. Lavine, Dr. Gobin, and others have gained experience with it. In the latest incarnation, Dr. Gobin said, “we are using a nitinol coil, a special metal made of super-elastic material, to snare and remove the thrombus that is occluding the artery in the brain.” Nitinol, an alloy of nickel and titanium, is in a unique

*Y. Pierre Gobin, MD, has developed the Concentric Retriever to clear neurologic emboli. To use the system, neuroendovascular therapists guide a microcatheter beyond the site of the clot, where it deploys a self-expanding conical coil. The coil becomes so enmeshed in the clot that it can be dragged away when the catheter is removed. Says Dr. Gobin, “When you reopen the artery this way, there’s almost no risk of hemorrhage.”*

directly to the site of the clot, via a radiologically guided catheter. Intra-arterial t-PA has the added benefit of allowing the physician to pump higher concentrations of the drug into the confines of the blockage than could ever be safely delivered to the entire body intravenously.

“It’s much better to open the artery with a MERCI device,” Dr. Gobin said. “When you reopen the artery with MERCI, there’s almost no risk of hemorrhage.”

To use the mechanical system, neuroendovascular therapists guide a microcatheter beyond the site of the clot,

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# Brain Attack AND Cerebrovascular Disease Update



Friday • November 21, 2003  
8:00AM-6:00PM

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#### OVERVIEW

This conference will review new approaches to the diagnosis and prevention of stroke as well as a review of the most advanced treatments for cerebrovascular disease.

This course meets the 8 hour annual CME requirement for Stroke Center Certification.

#### TARGET AUDIENCE

Neurologists, neurosurgeons, interventional neuroradiologists, cardiologists, primary care physicians and emergency room physicians, nationally and regionally.

#### EDUCATIONAL OBJECTIVES

This course is intended to update the clinician on the latest advances in the diagnosis, treatment and prevention of brain attack and stroke.

1. To understand the rapid critical and radiological diagnosis of stroke and to apply rapid treatment, to learn evaluation techniques for stroke outcome, and to learn about stroke rehabilitation protocols.
2. To apply the latest developments on diagnostic imaging and ultrasound for ischemic and hemorrhagic stroke patients.
3. To learn about the use of tPA and other drugs in the treatment of acute ischemic stroke.
4. To learn about neuroendovascular approaches to intracranial hemorrhagic stroke, AVMs, and aneurysms.
5. To review the latest data on medical and surgical treatments for primary and secondary stroke prevention.

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# Emergency Treatments for Cerebral Hemorrhage

Intracerebral hemorrhage represents 15% of all strokes in the United States. It is also among the deadliest and most disabling forms of stroke. More than 40% of intracerebral hemorrhage patients die within 6 months or suffer devastating impairment.

Unfortunately, there are still no effective treatments—including surgery—for intracerebral hemorrhage or other forms of cerebral hemorrhage. Nevertheless, researchers at NewYork-Presbyterian Hospital say, studies are revealing opportunities for physicians to provide their patients with more than just supportive care.

“It’s about pushing the envelope, finding better ways to treat the patients,” said Stephan A. Mayer, MD. “We’re looking for the cutting-edge protocols.”

Dr. Mayer points to 2 ongoing trials exploring therapies to help patients cope with hemorrhage. Physicians at Columbia Presbyterian Medical Center are looking at recombinant factor VIIa as a possibility for arresting ongoing bleeding in intracerebral hemorrhage emergency room patients. In fact, Columbia Presbyterian Medical Center is part of a worldwide, multicenter trial testing the potential efficacy of recombinant human coagulation factor VIIa as an ultra-early hemostatic therapy for brain hemorrhage.

The preliminary dose escalation safety study, which treated 86 patients, offered “some indication of efficacy,” said Dr. Mayer. Because of those results, the department has initiated a proof-of-concept trial with a target enrollment of 240 (it now has 186). That trial started in January.

Researchers at Columbia Presbyterian Medical Center are also exploring options for treating a subset of intracerebral hemorrhage patients: patients with intraventricular hemorrhage. Current procedure calls for inserting a ventricular catheter, noted Dr. Mayer, but physicians in the Neurological Intensive Care Unit recognize that “simply placing a catheter may be life-saving, but otherwise doesn’t appear to substantially benefit patients.”

That’s why, in conjunction with other

centers, Dr. Mayer and his colleagues have been involved in a Phase II study enrolling 46 patients. The study’s purpose is to evaluate the risks and benefits of a combination therapy: placing the catheter and “examining the potential efficacy of direct intraventricular thrombolytic therapy using tissue plasminogen activator.” Because there is overwhelming evidence that clotted blood can be toxic, he added, “the hope is that by effectively lysing the clot and promoting its clearance, patients will suffer less damage due to reduced duration of contact with potential toxic blood elements (e.g., hemoglobin and thrombin).”

## Only Preliminary Results

At NewYork Weill Cornell Medical Center, Igor Ougorets, MD, is currently using a treatment method that involves controlling hyperglycemia in his patients. “Some animal studies have indicated that hyperglycemia produces more neuro-injury in ischemic tissue,” he explained. “The problem is that in all these areas all we have is preliminary data. We don’t yet have the study that takes neuro-injured patients on a tightly controlled glucose level and compares them with a group that was not controlled to see if the glucose control changes the neurological outcome.”

To date, according to Dr. Ougorets, treatment protocols for hemorrhage have not been based on the results of randomized trials but on the personal experience of neurologists in the field. All the researchers hope to change that, however, with their recent efforts.

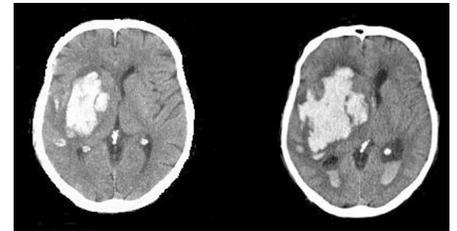
## Looking at Body Temperature

“Everyone agrees that overall temperature control has to be done,” said Dr. Ougorets. “The problem is that we don’t have clear-cut trials showing that it actually makes a difference in the outcome of our patients.”

Another critical issue is the treatment of fever in patients with hemorrhagic stroke, according to Dr. Mayer. “Body temperature elevations are independently correlated with death and poor functional outcomes after both intracerebral hemor-

rhage and subarachnoid hemorrhage,” he said, adding that conventional cooling blankets have been shown to be ineffective in reducing fever for these patients.

Dr. Mayer and his colleagues are currently conducting a clinical trial of the Medivance Arctic Sun Cooling System. The device seems to normalize body temperature more effectively than conventional cooling blankets. A hydrogel polymer provides enhanced contact with the patient’s skin, allowing the water-circulating blankets to stick to the body and thus maintaining the cooling process more effectively than conventional means.



A head CT scan demonstrating a left-sided basal ganglia hemorrhage (left). A follow-up CT obtained after the patient further deteriorated (right) shows significant enlargement of the hematoma.

“Using regular cooling blankets, patients’ body temperature remains over 101°F,” said Dr. Mayer. “With this system, they go right down to normal, and stay there.” The unexpected benefit of the system, he added, seems to be that “effective treatment of fever can produce clear and dramatic improvements in intracranial pressure levels, and in patients’ levels of consciousness.”

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# NEW YORK - PRESBYTERIAN Neuroscience

## t-PA

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class of materials known as shape memory alloys. After being heat treated while in a particular position, it can be bent and distorted, then reheated to regain its original shape. Thus, the device can be advanced within a microcatheter inside the cerebral artery occluded by the clot.

*Current work at NewYork-Presbyterian Hospital could one day mean a revolution in the treatment of cerebral infarction. That day can't come soon enough for the estimated 750,000 people in the United States who suffer a stroke each year.*

"On the engineering side, it can be very exciting to work with smart materials like that," Dr. Lavine said.

Both he and Dr. Gobin emphasized that the procedure remains experimental. But Dr. Gobin predicted that it will eventually become the treatment of choice at hospitals specializing in the treatment of stroke. "Most treatments for stroke will be mechanical, with a MERCI device," he said. If this is true,

the result will one day mean a revolution in the treatment of cerebral infarction. That day can't come soon enough for the estimated 750,000 people in the United States who suffer a stroke each year.

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## CT Perfusion

*continued from page 3*

Delivery even 5 or 6 hours out escalates the risk of hemorrhage dramatically, from 5% to as much as 30% or 40%.

Having served on some of the safety committees analyzing the 3-hour "deadline," Dr. DeLa Paz believes this to be an artificial timeline that can be expanded. The key is using intra-arterial administration of t-PA versus intravenous delivery. Using an intra-arterial catheter, he explained, "the lysis of occluding thrombus in the cerebral vessels and reconstitution of blood flow to the ischemic brain" may be achieved in only 20 or 30 minutes. That, he says, means that intra-arterial delivery of t-PA could begin as much as 4 or 5 hours after onset and still provide effective results with a low risk of hemorrhage.

However, intra-arterial delivery of t-PA carries a much higher risk of hemorrhage than intravenous delivery if it is

not correlated with a measure of potentially salvageable tissue. Using CT perfusion to determine how much viable brain exists and to generate constructive maps of cerebral blood flow, blood volume, and mean transit time is a boon to doctors treating stroke patients.

"Clinical science will only get you so far," said Dr. Ougorets. "You need additional information to appreciate what's happening to the brain tissue."

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*"Would I like to have an 8-slice image of the brain as I do with MRI? Yes. But I now have 4 slices with the computed tomography where I used to have 1."*

*—Igor Ougorets, MD*

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## Endovascular

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scarring to remove the aneurysm from circulation. Research has shown that, compared with surgery, the Guglielmi Detachable Coil treatment significantly lowers the risk of subsequent severe disability or death from a ruptured aneurysm.

“The study was so overwhelmingly in favor of coiling that the safety committee of the trial stopped enrolling new patients,” said Y. Pierre Gobin, MD.

Dr. Gobin, who worked for 10 years with Dr. Guglielmi at the University of California at Los Angeles, noted that new designs and materials for the coil are constantly being tested—including, most recently, special coatings designed to speed the development of an aneurysm-shutting clot.

Another new technique for treating aneurysms involves the use of the Neuroform stent. “With certain complex aneurysms, the Guglielmi Detachable Coil alone may not be ade-

quate,” said Dr. Meyers. “The Neuroform stent is a self-expanding tube designed specifically for use in the brain to treat complex aneurysms in a way that was never possible before. Aneurysm coils can then be safely placed into the aneurysm without jeopardizing the integrity of the main blood vessels.”

NewYork-Presbyterian Hospital can either cauterize the abnormal tangle of blood vessels, or deploy the new glue Neuracryl M that hardens slowly and smoothly. One of the hottest areas of research is the endoscopic widening of a plaque-clogged carotid artery, with the use of a stent to keep the artery clear. Until recently, the endovascular method was used only for patients too sick to undergo surgery, because when performed from within, the procedure can dislodge plaque that would then travel up the bloodstream into the brain, where it could cause a stroke. But a new invention offers the possibility of revolutionary new safety: a tiny filter that opens like an umbrella downstream from the stent to safely block any debris before it reaches the brain, while allowing blood to flow normally.

“It’s like a coffee filter for the blood, flowing into the brain when you’re reopening an artery in the neck,” Dr. Meyers said. “The filter catches any debris generated during revascularization of the brain’s arteries. The early

investigator. Those numbers, he added, “look as good as surgery, maybe even better, without having to perform surgery.” Other studies of similar debris-catching devices include the Acculink for Revascularization of Carotids in High-Risk patients (ARCHeR) and the Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH).

According to Sean Lavine, MD, it’s still too early to tell which of the devices will eventually be most effective—or even whether any of them will ultimately prove safer than surgery. There are “data on both sides,” Dr. Lavine said. “Some say using the devices increases the risk of embolic events; others say that it has dramatically reduced morbidity. We are currently investigating the benefit of these devices with active participation in trials such as ARCHeR, BEACH, and CREST.”

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*“The Neuroform stent is a self-expanding tube designed specifically for use in the brain to treat complex aneurysms in a way that was never possible before. Aneurysm coils can then be safely placed into the aneurysm without jeopardizing the integrity of the main blood vessels.”*

*—Philip Meyers, MD*

quate,” said Dr. Meyers. “The Neuroform stent is a self-expanding tube designed specifically for use in the brain to treat complex aneurysms in a way never possible before. Aneurysm coils can then be safely placed into the aneurysm without jeopardizing the integrity of the main blood vessels.”

For the treatment of arteriovenous malformations, Dr. Meyers added, NewYork-Presbyterian Hospital is “one of the largest treatment centers in the United States. It’s been one of the hospital’s strengths for many years.”

Neuroendovascular specialists at

evidence suggests that stent-supported angioplasty with filter protection of the brain’s blood supply may become a preferred method of treatment over standard surgical endarterectomy.”

Researchers at NewYork-Presbyterian Hospital are among the lead investigators in a multicenter trial of the procedure, called Carotid Revascularization: Endarterectomy versus Stent Trial (CREST). In the early phases of the study, “the complication rate with protection is 2% for asymptomatic patients, and 6% for patients with symptomatic stenosis,” said Dr. Gobin, the principal

## Deep Brain Stimulation

*continued from page 5*

day as the electrode surgery, or somewhat later.) For bilateral operations, 2 implantable pulse generators are installed. Three types of deep brain stimulation can be performed: thalamic stimulation, subthalamic nucleus stimulation, and globus pallidus stimulation. Each type corresponds to a different area in the brain where the stimulator is placed, and each tends to alleviate specific symptom formations. Beginning in April 2003, Medicare agreed to cover each of the 3 deep brain stimulation procedures for patients who fulfill diagnostic conditions.

Postoperative care after deep brain stimulation forms a crucial part of the entire procedure because it involves

turning on and adjusting the deep brain stimulator. Frequency, polarity, pulse width, and voltage may all be adjusted. This process may take several visits over weeks or even months. It is another reason why Dr. Ford comes out strongly in favor of a comprehensive program like that at Columbia Presbyterian Medical Center. "The care for these patients needs to be comprehensive," he maintained, "and optimally carried out in a context where there's an accumulation of expertise, clinical experience, and institutional resources."

Dr. Kaplitt, MD, PhD, agreed with Dr. Ford on the importance of comprehensive expertise and training for deep brain stimulation. He emphasized the time and teamwork expended on each patient in deciding whether a candidate is suitable for surgery and in planning the procedure. "Collectively, it takes an enormous amount of experience in order to get it right," said Dr. Kaplitt.

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