



Fight against cerebrovascular diseases takes team approach

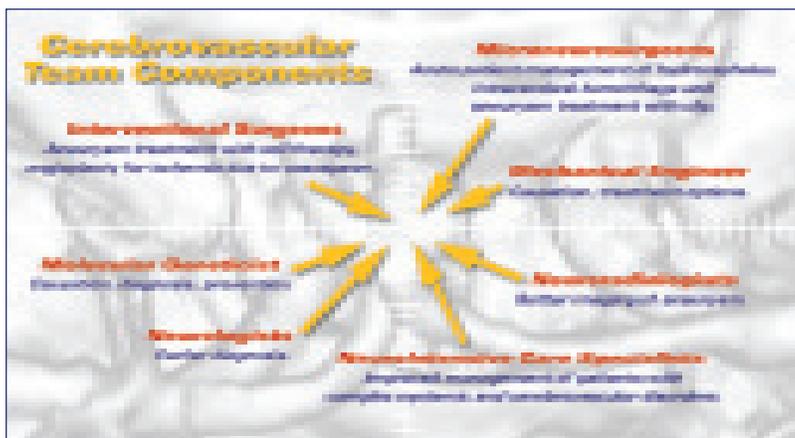
by Howard Yonas, M.D.



▲ **Dr. Yonas**
Director,
Cerebrovascular
Surgery

Because our knowledge regarding cerebrovascular diseases and our capacity to treat these disorders is rapidly evolving, delivering the best of care demands the integration of different specialists into a focused management team. The goal of the team is to deliver the best care irrespective of which member of the team the patient first encounters.

Today's cerebrovascular team at UPMC includes members of the Stroke Institute, the endovascular service, and the cerebrovascular surgical services of both the neurosurgical and vascular surgical services. Research efforts also demand the expertise of many different fields: mechanical engineering, molecular genetics, as well as imaging via positron emission tomography, magnetic resonance and CT. Collaborative efforts also exist between governmental and industrial partners to develop and test new approaches. All of these avenues are being aggressively pursued by members of the cerebrovascular team at UPMC.



▲ **Taking aim at aneurysms.**

Although there are aggressive programs in place to treat acute ischemic stroke, stroke due to a chronic compromise of brain perfusion, and intracerebral hemorrhage, cerebral aneurysms provide a useful example of how teams of clinicians and scientists work together to improve outcomes due to this unpredictable and often disastrously disabling disorder.

Cerebral aneurysms are found in about 3% of the population with an increasing incidence later in life. Most occur without apparent cause but recent

studies have clearly defined an important role of smoking, especially in women, as a risk factor for aneurysm formation.

Recent studies by David Peters Ph.D., a member of the University of Pittsburgh Department of Human Genetics, working with members of the Departments of Mechanical Engineering and Neurological Surgery, have identified a gene in patients with cerebral aneurysms that is not working correctly. Their collaborative efforts have shown that a gene in charge of remodeling of arterial walls that is influenced by mechanical stress is overly active in patients with cerebral aneurysms. Thus an inappropriate and aggressive remodeling occurs at vessel branch points. This is exactly where cerebral aneurysms occur. Recent studies suggest that smoking may increase the activity of the same gene.

The importance of this finding is that a routine blood test may be able to identify individuals at increased risk for aneurysm formation with the eventual goal being to develop the means of correcting the dysfunctional gene in order to prevent aneurysm formation. This is the ultimate goal of our team.

For the patient that does have an aneurysm, treatment options are available. For smaller aneurysms found incidentally, perhaps the best treatment is reduction of risk factors such as hypertension and elimination of smoking. Larger unruptured aneurysms and ruptured aneurysms do need treatment due to a significant risk for bleeding and rebleeding. As detailed by Dr. Michael Horowitz in this issue of *Pittsburgh Neurosurgery News* (page 6), important strides are being made in the endovascular treatment of cerebral aneurysms. The fact that the diagnostic and microvascular surgical approaches to cerebral aneurysms are also evolving rapidly, means that the treating physician now has options for treatment that were not conceivable a few years ago.

Unfortunately, even after a ruptured aneurysm is isolated from the circulation, the blood still present around the arteries at the base of the brain creates a 20% risk for delayed ischemic stroke due to spasm of vessels. The diagnosis and treatment of "vasospasm" provides an other opportunity for multispecialty focus.

(see *Cerebrovascular disease fight* on page 7)

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New trends, treatments in lumbar disc disease

by William C. Welch, M.D.



Dr. Welch
Director, Neurosurgical
Spine Services

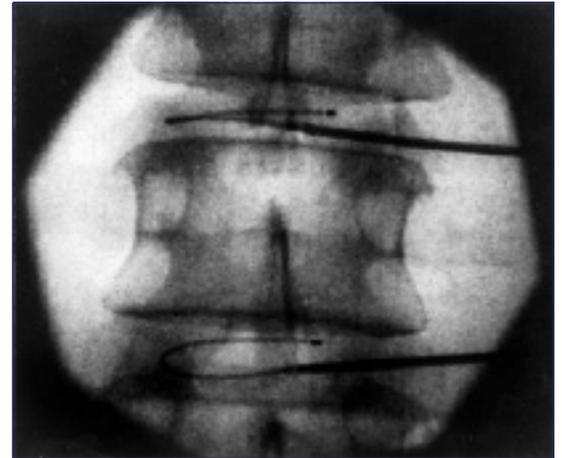
Lumbar disc disease may be defined as degeneration or rupture of intervertebral elements. This condition may be asymptomatic or symptomatic. The most common symptoms of lumbar disc disease is pain localized to the lower back or groin. With disc rupture, nerves may be compressed causing pain, numbness or tingling into the legs or groin.

In the past, the most common treatment for patients with lumbar disc degeneration or disc rupture was bed rest. Recent studies have shown that bed rest alone is not an effective treatment regimen. Other non-surgical therapies such as physical therapy and anti-inflammatory medicines or epidural steroids may have greater utility. Patients who have failed non-surgical treatment may be appropriate surgical candidates.

The decision to operate on patients with lumbar disc disease depends mostly on the patients presenting symptoms. Specifically, a determination must be made as to the level of disability experienced by the patient, the frequency and intensity of pain, as well as the location and radiation of pain. The presence of neurologic deficits, especially numbness, weakness bladder or bowel signs, more strongly suggests the need for surgical intervention.

Treatment for symptomatic lumbar disc disease in the past has typically relied on either microdiscectomy or fusion. Microdiscectomy involves a minimally invasive approach and removal of the ruptured disc component. This can be performed with magnifying loupes, microscopes, endoscopes, or arthroscopes, and is generally performed on an outpatient or overnight stay basis. Fusion is performed in cases of lumbar instability or painful degenerative disc disease (discogenic lower back pain). Fusion is typically performed with onlay bone grafting and pedicle screw instrumentation. This requires a 3-5 day hospitalization.

New developments in treatment techniques include intradiscal electrotherapy (IDET) and interbody fusion, both of which are undergoing prospective trials in the Department of Neurological Surgery. IDET is a percutaneous, outpatient procedure directed towards patients with degenerative disc disease. This technique involves the insertion of a small-bore needle into the involved disc segment. A catheter with a thermal tip is inserted through the needle and is coiled in the disc (Figure 1). The catheter tip is heated for 15 minutes. This has been shown to reduce the disc size through reorganization of collagen fibers. The technique also may create a thermal injury to the non-myelinated nerve fibers which innervate the disc end plates. This combination of collagen shrinkage and end-plate



(Figure 1, top)
Intradiscal
Electrotherapy
(IDET)
(Figure 2, bottom)
BAK Cage

rhizotomy has been shown to significantly reduce lower back pain in patients with discogenic disease.

Interbody fusion is a surgical technique by which the intervertebral disc is removed and replaced with a supporting structure, such as a titanium cage or bone (Figure 2). This provides reconstruction of intervertebral height, effects immediate stability, and promotes fusion across the intervertebral disc space. The surgery may be performed from an anterior, lateral or posterior direction. The approach depends on the patient's symptom complex, prior surgical treatment, and instability pattern. Minimally invasive, endoscopic access and fusion may also be considered in selected patients. The results of this treatment for degenerative disc disease has shown a statistically significant reduction in pre-operative pain and an increase in functional outcome scores.

Degenerative disc disease, radiculopathy from disc rupture and lumbar instability are common causes of disability. IDET and interbody fusion appear to be effective treatments for these conditions. To enroll your patients into these or any other ongoing spinal treatment and outcomes study, please call (412) 647-6773. ■

UPMC study encouraging in battle against stroke

Cell transplantation found safe, feasible in stroke patients



by Frank Raczekiewicz

Cell transplantation was found to be safe and feasible in stroke patients, according to University of Pittsburgh researchers in a study published in the journal *Neurology*. They also reported that half of the patients who underwent neuronal transplantation following stroke showed improvement in motor function. PET scan results also suggest cell viability as evidenced by increased metabolic activity in the area of the stroke as seen in six patients.

The phase I study evaluated the safety and clinical effects of an experimental treatment aimed at reversing neurological deficits from stroke through implantation of human neuronal cells in 12 stroke patients.

Principal investigators in the study were Douglas Kondziolka, M.D., professor of neurological surgery and radiation oncology at the University of Pittsburgh Department of Neurological Surgery, and Lawrence Wechsler, M.D., professor of neurology and neurosurgery at the University of Pittsburgh School of Medicine and director of the UPMC Health System Stroke Institute.

The nine men and three women in the study varied in age from 44 to 74 years. In eight patients, the stroke involved only the basal ganglia region of the brain and in four patients, both the basal ganglia and regional cortex were involved. All patients had stable neurologic deficits at least two months prior to implantation.

The first four patients were treated with two million neurons implanted at three sites along a single needle pass within the basal ganglia. The remaining eight patients were randomized to receive either two million neurons along one needle pass or a total of six million neurons implanted along three trajectories.

Assessment of safety and feasibility was performed using the NIH Stroke Scale (NIHSS), European Stroke Scale (ESS), Short Form 36 (SF36) and Barthel Index (BI).

"All outcomes measurements were consistent in identifying a trend toward improved scores in the group of patients who received six million neuronal cells," Dr. Kondziolka reported.

At the 24-week follow-up evaluation, six of the 12 patients had improved scores on the ESS, three patients were unchanged and three patients deteriorated compared to their baseline scores prior to neuron implantation. Motor elements of the ESS accounted for much of the change noted in patients, the study reported.

NIHSS scores reflected similar changes in functional performance. At the 24-week point, eight patients had improved scores, one patient was unchanged and three deteriorated compared with their baseline scores.

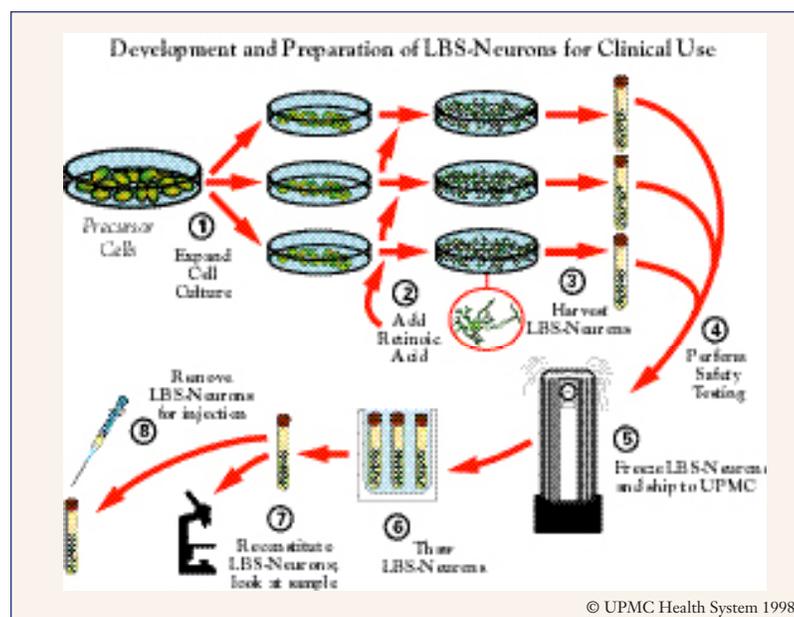
"These indications of efficacy must be tempered by the fact that signs of improvement were not consistent," Dr. Wechsler said. "Some patients had worse stroke scale and stroke disability scores at the end of six months than they had at the time of implantation."

An equal number of patients had no improvement or worsening in stroke or disability scales as had improvement. In several patients, inter-current events (including a new-onset seizure, a new stroke and worsening renal failure) affected functions, so that some signs of improvement could have been obscured, according to the study.

"In future studies, we plan to use additional instruments that will evaluate persistent neurologic deficits and their impact on function," Dr. Kondziolka said.

LBS-Neurons originated from a human teratocarcinoma, a tumor of the reproductive organs that is composed of embryonic-like cells, which was removed from a 22-year-old cancer patient over 20 years ago. Layton BioScience, Inc. has licensed a patented process that uses several chemicals to transform this cell line into fully differentiated non-dividing human neuronal cells (LBS-Neurons) that can be used in clinical applications. In extensive pre-clinical testing, implants of LBS-Neurons reversed cognitive and motor deficits in

(See *Cell Transplantation* on page 5)



Head injury: an overview of evaluation and care



▲
Dr. Marion
Director, Brain Trauma
Research Center

by Donald W. Marion, M.D., Patricia Carlier, R.N.,
and Leann Bullian, R.N.C., B.S.N., I.B.C.L.C.

Serious traumatic head injury is one of the most common causes of impaired brain function. Head injury can occur from impact to the head caused by automobile accidents, falls, and assaults. Head injury can also occur from lack of oxygen to the brain, as in near drowning, or lack of blood flow to the brain, as in a stroke. All individuals who have suffered a moderate-to-severe injury should be examined by a physician.

A patient with a mild-to-moderate head injury may only require observation for several days. Observation may be done at home with a mild head injury or in the hospital for a moderate head injury. These injuries may appear to be minor, but the patient may develop postconcussive syndrome. This can produce headaches, concentration difficulty, forgetfulness and memory problems, dizziness, irritability, anxiety and depression. These symptoms usually resolve with time but occasionally may require further intervention. A referral may be made to a neuropsychiatrist or physiatrist to formulate a plan of follow-up care for these individuals.

Patients who suffer severe injuries require immediate hospitalization and will spend some time in an intensive care unit. A neurosurgeon coordinates their care while hospitalized. Hopefully, a relationship will be established with the primary care physician, or PCP, at this point. The PCP or anyone on their office staff should feel free to call the neurosurgeon's office with any questions or concerns.



Interdisciplinary CIRCL works to help prevent, reduce injuries

The Center for Injury Research and Control (CIRCL) is an interdisciplinary, comprehensive component of the Department of Neurosurgery established in 1992 to help prevent and reduce injuries. Involving six schools and 18 departments of the University of Pittsburgh, the center conducts injury control research, gathers and disseminates information on injuries, provides training for health care professionals, and informs the public and community leaders on injury control measures. In September 1995 it became one of 10 centers in the country to receive official designation as an Injury Control Research Center by the Centers for Disease Control and Prevention (CDC). For more info about CIRCL, call (412) 648-2600. ■

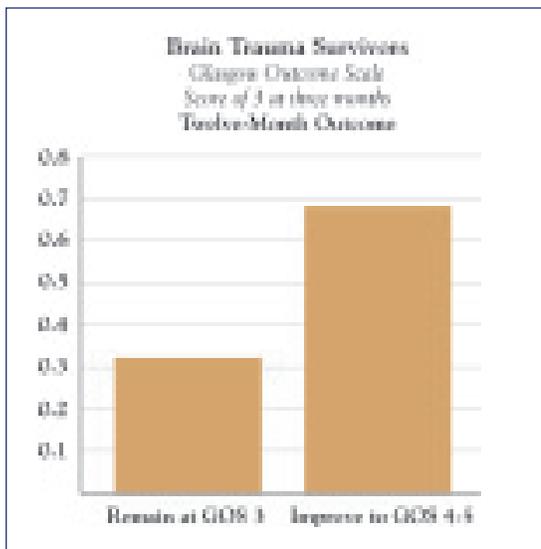
Many other physicians will be involved in their care and the patient will be evaluated by a physiatrist for determining their ability to participate in rehab. If accepted into a rehabilitation facility, the length of stay varies from a week to months. Discharge planning from rehab should begin on the first day of the patient's stay.

The rehab hospitals will make an effort to have a copy of the discharge from rehab summary sent to the PCP office. Some physiatrists attempt to reach the PCP by phone to give them a brief summary of the patient's progress and discuss any ongoing medical concerns and short term plans.

There are frequently medications that a patient is prescribed upon discharge from rehab. The physiatrist will write the prescriptions when discharged from the facility. Usually they will write prescriptions that should cover a one month period. The patient and their family will be encouraged to call the PCP's office upon discharge and arrange for an appointment within the first several weeks after they are home. This will enable the patient to have sufficient time to insure that they have enough medication until their appointment. Some medications that have been ordered may need to be continued for a period of time. The PCP may be comfortable managing the medication and ordering any necessary blood work. The neurosurgeon's office may also be contacted if there are questions related to medications. A joint effort that is most beneficial to the patient can be arranged for some medication management.

The physiatrist usually likes the patient to return for evaluation in one month. At that time a plan of care will be formulated once decisions are made about further rehab and therapy. This information will be passed along to the PCP. Follow-up with the neurosurgeon is also important. CT scans and perhaps even MRI scans will be done to follow-up on initial injuries and to monitor for complications that may arise such as post-traumatic hydrocephalus. The neurosurgeon will also play a role in recommendations for needs such as ongoing therapies, medication management and referrals that the patient may require. A clinic letter will be sent to the PCP regarding any subsequent appointments. The PCP or their office staff is encouraged to call with any questions or concerns.

Care does not end after hospitalization and rehabilitation for most persons with brain injury. A study conducted at the University of Pittsburgh's Brain Trauma Research Center found patients who survive a severe brain injury and rate as 3 on the Glasgow Outcome Scale at three months demonstrate an increased recovery potential, with 68% improving to moderate



disability or good functional status (GOS 4-5) at 12 months. Also, if an individual has a GOS of 4-5 at three months, they have a 95-99.9% chance of remaining at this functional level a year after the injury.

The post-acute environment has also experienced decreased lengths of treatment, some by 50%. Preliminary findings reveal limited access to comprehensive treatment compromise outcomes. Even post-rehab residential setting has been reduced to 1/5th the length of stay as compared to 1991. The implications: Individuals with severe brain injury move into the community successfully or unsuccessfully completing a rehabilitation program. But this move requires enormous effort. The demands of daily life can be a challenge to the individual, the family, the community and the health system. The primary health care provider is the keystone in facilitating this transition. Medical care and information are the basic needs to the brain traumatized individual and the family. A holistic approach bridges the gap between acute hospitals and reentry to the workplace, classroom or community. The health care provider must be knowledgeable of every aspect of care following a brain injury.

Some of the most common physical disorders that occur after injury are visual disturbances, balance, musculoskeletal injuries, sensory loss, seizures, hydrocephalus, encephalitis, dehydration, anorexia, dysphasia, and infections. A weekly to bimonthly exam may be necessary to identify these conditions for the first months following rehabilitation. A feeding/swallowing specialist, speech pathologist, audiologist, or physical therapist is necessary to aid in this evaluation. Management of spasticity, nutrition, seizures, pressure sores and urinary continence are specific concerns. The individual should receive an over all neurological assessment from his/her neurosurgeon three, six and twelve months from the date of injury.

Without the ability to monitor one's own performance through intellectual, emergent and anticipatory awareness, the individual has tremendous difficulty coping, performing tasks or achieving personal goals. The medical provider and staff can supply core information on agencies and programs available to support the family's medical, psychosocial, cognitive, financial, and environmental concerns. Difficulties focus around the cognitive, intellectual, behavioral and emotional problems, which may be supported through psychological and behavioral management. Cognitive retraining, vocational rehabilitation and reentry programs can provide the high functioning individual with skills to cope with the community. If more intense care is necessary, nurses and therapists can provide treatment and family education in the home.

Multiple studies demonstrate that close to 50% of individuals with a brain injury were intoxicated at the time of injury. These individuals were more likely to be intubated and have respiratory distress, have greater severity of injury, greater incidence of death, lower cognitive status at time of discharge, and suffer greater lengths of post-traumatic amnesia. If a post-trauma assessment determines the individual to be at risk, referral to a substance abuse rehabilitation center is necessary.

The head injured individual and family can be linked to support groups, financial planners, lawyers, and federal and state agencies for the disabled. The State Demonstration Grant Program is in place to improve access to health and other services for individuals with traumatic brain injury and their families. The Brain Injury Association, Inc. is an excellent source of information in regards to organizations involved in post-trauma management. This not only includes agencies, web sites, literature sources but also support groups and medical management. Families and medical professionals can find excellent resources at the National Resource Center for Traumatic Brain Injury through the Medical College of Virginia. ■

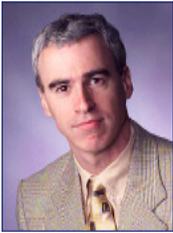
Cell transplantation

(from page 3)

animals in which stroke had been induced.

The cell transplantation procedure involves the use of a stereotactic frame and either a CT or MRI scan to determine the exact location of cell implantation. The surgeon injects the cells using a long-needled syringe through a small opening in the skull to multiple sites. The patient typically can leave the hospital the next day. ■

Endovascular therapy for intracranial vascular diseases showing considerable promise



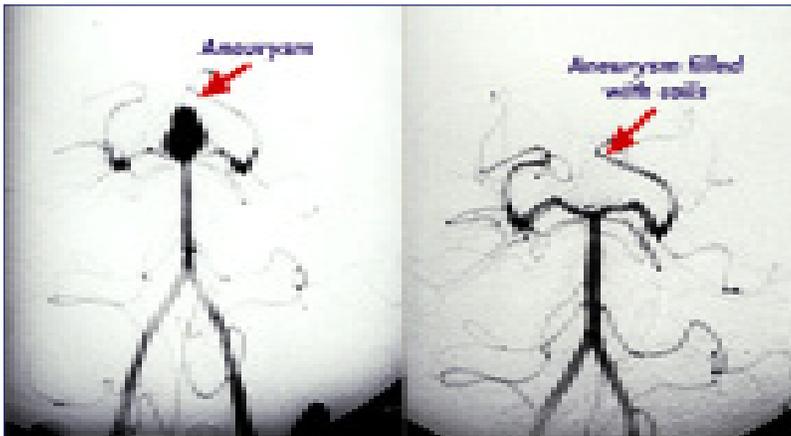
by Michael B. Horowitz, M.D.

Endovascular therapy for intracranial vascular disease is a developing field with considerable promise. The current endovascular options for the management of aneurysms, vascular occlusive disease, and ischemic stroke will be discussed below.

Aneurysms

The last few years have been exciting times for vascular neurosurgeons. Direct surgical clipping continues to remain the gold standard for aneurysm therapy although early follow-up studies relating to interventional radiologic management of aneurysms are beginning to be presented. Vinuela reported multicenter findings in 403 patients treated for ruptured aneurysms using first generation coils and catheters between 1990 and 1995. Complete aneurysm occlusion was achieved in 71% of small aneurysms, 35% of large aneurysms, and 50% of giant aneurysms. Procedural morbidity and mortality was 9% and 2%, respectively. Debrun reported results in 144 patients. This author divided his results into those achieved in a group treated when the procedure was first introduced and those treated later. In the second group a 72-80% complete occlusion rate was achieved when the dome-to-neck ratio was less than two. The

▲
Dr. Horowitz
Co-Director,
Center for Neurointer-
ventional
and
Neuroendovascular
Therapy (CNNET)



▲
Basilar tip aneurysm pre-embolization (left) and post embolization with GDC coils (right).

complete occlusion rate dropped to 53% when the ratio was less than two. Mortality and permanent morbidity in the latter group (119 patients) was 0% and 1%, respectively. The coming years should prove even more exciting as newer devices are released which improve the safety and efficacy of the interventional procedures. These include small balloons and stents which will aid in aneurysm occlusion.

In 1999 Johnston compared surgical and endovascular management of unruptured aneurysms at 60 university centers. Results in 2357 surgically treated lesions were compared to results in 255 coiled lesions. Adverse outcomes were recorded in 18.5% of surgical cases as compared to 10.6% of endovascular cases. In-hospital deaths occurred in 2.3% of surgical cases and 0.4% of endovascular cases. Length of stay was 9.6 days in surgical cases and 4.6 days in endovascular cases. Mean charges were \$43,000 in surgical cases and \$30,000 in endovascular cases. If the rebleed rate remains low for endovascularly treated lesions, the above findings should indicate that endovascular therapy may prove superior to surgical therapy for most lesions.

Extracranial Carotid Disease

In 1991 the North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated surgical benefit in the management of symptomatic internal carotid stenosis greater than 70% if perioperative stroke rates were less than 6%. At two years the risk of an ipsilateral stroke in medically managed patients (aspirin) was 26% vs 9% in the surgical arm. The Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS) study was published in 1995. This study demonstrated greater stroke reduction in surgically managed patients with greater than 60% stenosis. At five years the stroke rate in medically managed vs surgically managed patients was 11.1% and 5.1%, respectively. The most recent study on carotid ischemic disease was an analysis of the NASCET data for determination of the benefit of carotid endarterectomy in symptomatic patients with 50-69% stenosis. This review demonstrated a small but positive benefit of surgery over medical therapy with a surgical vs. medical five year ipsilateral stroke rate of 15.7% vs. 22.2%.

Angioplasty and Stenting for Extracranial Atherosclerotic Disease

Carotid endarterectomy remains the only well studied treatment for extracranial atherosclerotic disease and is the gold standard against which all other therapies will need to be compared. A number of investigators, however, have been looking into endovascular alternatives to surgery. Roubin, Dietrich, Theron, and Kellogg have each published series of carotid angioplasty with or without stenting. Technical success exceeded 95%, major stroke rates were less than 2%, minor stroke rates were less than 5% and mortality was less than 1%. Restenosis rates were less than 5%. In view of the procedure's promise and increased use, the National Institutes of Health has recently decided to support

a prospective trial comparing carotid endarterectomy with angioplasty and stenting.

Intracranial Cerebrovascular Ischemic Disease

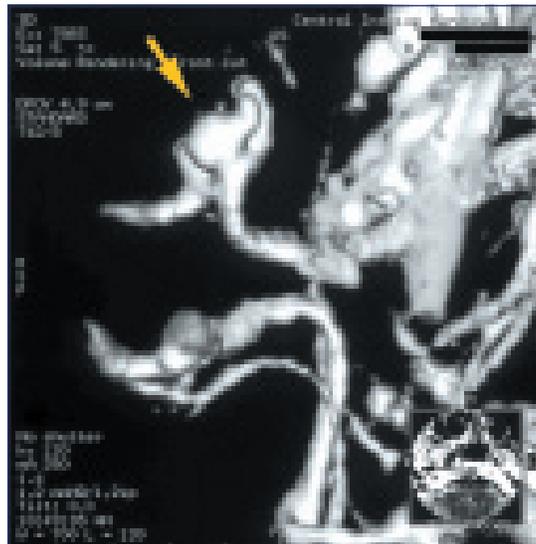
In 1985 the Extracranial/Intracranial bypass study demonstrated no efficacy to the use of EC/IC bypasses in individuals with ischemic cerebrovascular disease. Many have criticized this study on the basis that it failed to selectively study those patients with true hemodynamic insufficiency. Nevertheless, while EC/IC bypasses continue to be performed and be beneficial in select patients, no study has prospectively demonstrated its efficacy. Recently, new interest has developed in the field of intracranial percutaneous transluminal angioplasty/stenting of intracranial stenotic vessels.

For intracerebral thromboembolic disease recent advances in fibrinolytic therapy may allow neurologists, radiologists, and neurosurgeons trained in interventional radiologic techniques to limit or in some cases eliminate the devastating effects of acute vessel occlusions. The EMS Bridging Trial evaluated the safety of recombinant intravenous TPA or placebo followed by intra-arterial fibrinolytic infusion. The goal of this study was to see whether early treatment with intravenous infusions could improve outcomes. The National Institute of Neurological Disorders and Stroke rt-TPA study demonstrated improved clinical outcome in TPA treated patients at three months compared to placebo treated patients. The European TPA study, however, did not demonstrate a statistical difference in outcome between the two groups. Between 1987 and 1990 del Zoppo studied the effects of r-TPA in acute stroke. The overall frequency of extracranial carotid revascularization was 8% while the frequency of MCA recanalization was 26-38%. The Prolyse in Acute Cerebral Thromboembolism Trial (PROACT) tested the effect of super selective infusions of recombinant prourokinase (r-proUK) or placebo given within six hours of stroke secondary to middle cerebral artery occlusion. Recanalization was found in 58% of the r-proUK patients compared to only 14% of the placebo patients. The frequency of intracerebral hemorrhage with clinical deterioration was 15% in the pro-UK group and 14% in the placebo group.

Effectiveness of fibrinolytic therapy depends upon immediate referral of patients with TIAs and strokes to centers capable of performing arteriography, CT, diffusion MR, TPA administration, and super selective urokinase infusion. Because of the need to intervene quickly before irreversible ischemia sets in, there is no place for therapeutic nihilism when it comes to stroke management. Only when cerebral ischemia is treated with the same urgency and aggressiveness as cardiac ischemia will we begin to see improvements in outcome. ■

Cerebrovascular disease fight

(from page 1)



◀ CT Angiography provides non-invasive approach to high-resolution imaging to help detect aneurysms (arrow).

Studies of molecular genetics suggest that patients that develop vascular narrowing following aneurysm rupture may be predisposed due to an abnormal regulation of vascular tone. This new insight by Drs. Amin Kassam, associate professor of neurosurgery, and Peters may provide a route for identifying patients at increased risk as well as novel strategies for treatment. A funded study led by Mary Kerr, Ph.D. in the School of Nursing, is evaluating a multimodality approach to improving the diagnosis of patients developing symptoms due to vasospasm. This diagnostic study folds into a long-term effort of the team to base the diagnosis of delayed deficits that occur following subarachnoid hemorrhage upon the non-invasive measurement of blood flow rather than by the far less specific and invasive use of angiographic definition of large vessel anatomy.

Once a patient with delayed symptoms of ischemia following aneurysm rupture is identified, the team effort guided by members of the critical care division is shifted to emergently increasing blood flow to the brain. Raising the blood pressure, often to very high levels guided by the measurement of blood flow, is often acutely useful for reversing the neurological deficits. Our team has leaned toward the early use of angioplasty performed by the endovascular therapy team in order to lessen the duration and severity of the risk of ischemic stroke. These types of combined approaches have proven useful in improving our overall outcomes.

The only thing certain is change and by combining the knowledge and efforts of many basic scientists and physicians at UPMC, it is clear that change is occurring rapidly and that the beneficiary is the patient. ■



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Department of Neurological Surgery
University of Pittsburgh
UPMC Presbyterian/Suite B-400
200 Lothrop Street
Pittsburgh, PA 15213
(412) 647-3685

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