Special Report

Stroker: Early Pathophysiology and Treatment
Summary of the Fifth Annual DECADE OF THE BRAIN Symposium

Roberto C. Heros, MD, Moderator

The National Foundation for Brain Research convened a panel of leading basic and clinical research scientists from academia, government, and the private sector to present an overview of recent advances in the understanding of the early processes leading to stroke and of treatment options to prevent stroke or ameliorate the damage. The symposium, held on May 10, 1994, in Washington, DC, focused on (1) the significance and basic pathophysiology of stroke; (2) early recognition and diagnosis of stroke; and (3) early treatment of stroke.

Stroke is a medical emergency and requires the same immediate response that a heart attack receives. In fact, stroke is a "brain attack." Despite recent advances in basic and clinical neurosciences that have the potential to improve treatment of acute stroke, the general approach to treating such patients remains one of therapeutic nihilism. The lack of public knowledge about the symptoms and seriousness of stroke also contributes to the problem. In a 1989 survey conducted by the American Heart Association in San Francisco, almost two thirds of those surveyed were unable to identify correctly any of the early warning signs of stroke from a list of symptoms. Yet 90% could name at least one major sign of heart attack.

The distinguished panel of speakers at the Fifth Annual DECADE OF THE BRAIN Symposium sponsored by the National Foundation for Brain Research provided an overview of current and new concepts in stroke research and treatment strategies. The window of opportunity to ameliorate and prevent secondary damage from stroke may be widened through some of the maneuvers described by several speakers. In addition, educational efforts need to be enhanced to recognize stroke as a brain attack and a medical emergency requiring rapid transport of the patient to medical care and prompt initiation of treatment.

Dr Patricia Grady reviewed areas of research that have contributed to the understanding of stroke, much of it funded by the federal government through the National Institute of Neurological Disorders and Stroke (NINDS), a unit of the National Institutes of Health. She cited past research that delineated stroke risk factors including smoking, high blood pressure, age, previous stroke, race, and sex. Federally funded studies now under way are aimed at strategies to prevent secondary injury, to test anticoagulant agents, and to evaluate surgical interventions.

Significance and Basic Pathophysiology of Stroke

Significance of Stroke in Society: Dr Michael Walker

Stroke is the third leading cause of death in the United States, just after heart disease and cancer, but stroke is the leading cause of disability. Of the approximately 500,000 strokes that occur each year in this country, roughly one third of patients die, one third experience a second stroke, and most of the remaining stroke survivors live with some form of disability. The cost to the nation is estimated at $30 billion per year.

Society needs to know what to do to prevent stroke and to provide optimum care. Research funded by the federal government showed that increasing age heightens the risk of stroke and that more men than women and more blacks than whites have strokes. Although one cannot change one's age, biology, or race, one can modify behavior. Cessation of smoking, for example, reduces the risk of stroke by half for people of any age. Controlling high blood pressure and treating underlying conditions that may have caused a first stroke or transient ischemic attack can dramatically reduce the risk of stroke.

Mechanisms of Ischemic Cell Damage: Dr Dennis Choi

Processes of excitotoxicity can cause cell death and damage to neighboring cells. Identification of points at which these processes may be halted or slowed may benefit patients by averting or ameliorating secondary damage.

The central area of ischemia, the core, and the surrounding region, the penumbra, appear to be damaged by different processes. The core is damaged by a deprivation of blood that furnishes oxygen. The penumbra may experience secondary damage due to an overload of brain chemicals released in response to ischemic injury. Although there is no way to rescue dead tissue, intervention may protect neurons in the penumbra and may cancel out the cascade of brain chemicals that kill neurons.

This cascade begins when neighboring cells react to ischemia by sending out a flood of the neurotransmitter glutamate. Because brain energy has been lowered by ischemia, the normal pumping mechanisms that keep glutamate and other chemicals in balance fail. The cells absorb the glutamate, which is followed by an influx of...
large amounts of sodium and then an excess of calcium. This process results in cell death.

Related studies have shown that two types of excitotoxicity—rapid via \(\text{N-methyl-D-aspartate (NMDA)}\) receptors and slow via \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate (often grouped together as AMPA/K) receptors—cause cell death. By blocking NMDA and AMPA/K receptors, the glutamate-sodium-calcium cascade may be cancelled out and secondary damage limited. In animal models of ischemia the use of NMDA antagonists reduced the size of the infarct by half compared with controls. The penumbra is thought to be the area in which the NMDA antagonists can be most effective. Investigations are continuing in the search for other mechanisms that allow entry of the massive influx of calcium during hypoxia.

**Stroke Models and the Window of Therapeutic Opportunity: Dr William Pulsinelli**

There are two windows of opportunity—the reperfusion window and the treatment window—and they are limited by time. There is a time period during which the initiation of treatment may lessen the brain injury and improve neurological recovery and finally the point beyond which tissue is irreversibly damaged. The time limit, however, varies according to the type of cell.

Brain cells most vulnerable to ischemia are neurons, followed in decreasing sensitivity by oligodendroglia, astrocytes, and endothelial cells. Even within the population of neurons, there are thousands of different types that also vary in sensitivity to ischemia, and in some cases the vulnerability varies with the location of the cells. Using rat animal models, the investigators demonstrated vulnerability in different parts of the brain, from greater to lesser, with the hippocampus as most vulnerable, followed by the cerebellum, striatum, and neocortex.

In rat studies, the window of opportunity for reperfusion was within 3 hours after focal ischemia compared with 5 to 15 minutes for global ischemia caused by cardiac arrest. This work showed that the sooner reperfusion occurs the smaller the area of dead tissue and that cells could be saved if pharmaceutical treatment began within that time.

In applying this information to clinical trials of pharmaceutical interventions in human stroke, research physicians are merely observers, unable to exercise the same control of variables as they can in the laboratory. The lack of knowledge at present about the precise time of onset of ischemia and of reperfusion precludes accurate evaluation of the therapeutic window of opportunity.

Nevertheless, the premise is that such windows will be extended as knowledge of the pathogenesis of ischemic cells increases and as innovative therapies are developed to reverse these processes.

**Early Recognition and Diagnosis of Stroke**

**Logistics of Early Recognition and Transfer: Dr Thomas Brott**

Time is the enemy in treating a stroke patient. The first step in accomplishing urgent treatment is the recognition by the patient and those around him/her that a stroke has occurred. Second, emergency response teams need to recognize that prompt packaging and delivery of a stroke patient is vital. And third, at the hospital, speed is still important. Performing clinical evaluations of the patient in a parallel manner shortens assessment time and the time to therapy.

In communities where medical centers are participating in acute stroke treatment studies, efforts have been made to coordinate the existing prehospital care systems and achieve rapid evaluation and transport of stroke patients. A strategy of networking hospitals has been employed, with the patient being brought to the nearest hospital, not necessarily the academic center involved in the study. Transport time is kept to 10 to 15 minutes, and computed tomographic (CT) scanning and other necessary resources are usually available at most of the smaller hospitals. Parallel processing has allowed blood evaluation, CT scanning, and preparation of drug therapy to proceed simultaneously while the investigating physician talks with the patient and/or the family to obtain permission to include the patient in the study. Setting a target time for treatment, such as 1 hour, encourages all hospital departments to speed up activities.

**Clinical Diagnosis: Dr Louis Caplan**

The first consideration is to differentiate stroke from other conditions that can produce neurological symptoms and signs and then to separate hemorrhagic stroke from ischemic stroke. The distinction is vital because treatment for ischemia may be lethal for hemorrhage. Both hemorrhagic stroke and ischemic stroke have subtypes, and treatment again will depend on the location of the insult in the brain.

Procedures for differentiating types of stroke involve the following: (1) reviewing the neurological symptoms and signs, including the patient's medical history, activity at time of onset, course and development of symptoms, reports of prior episodes, and presence of deficits such as paraplegia, dysarthria, headache, vomiting, vision problems, and loss of consciousness; and (2) laboratory evaluation to pinpoint the site, type, and severity of the brain lesion and to learn if there is a cardiovascular problem and its severity. This includes brain imaging via CT and/or magnetic resonance imaging (MRI) scan; extracranial and intracranial ultrasound, magnetic resonance (MR) angiography, and sometimes standard catheter angiography; cardiac studies such as electrocardiography, echocardiography, and cardiac rhythm monitoring; and blood studies such as coagulation screening, platelet count, and hematocrit.

Finally, vital to the prompt diagnosis of stroke is increased education regarding the symptoms and emergency nature of stroke, not only for the general public but also for physicians and emergency medical crews.

**Neuroimaging of Early Ischemia: Dr Richard Latchaw**

Within the variety of imaging techniques used for evaluating the cerebral parenchyma and the blood vessels leading to the brain, some techniques are more useful than others to show changes in the brain. CT excludes hemorrhage but does not show parenchymal changes of stroke for at least 4 to 6 hours, beyond the window of opportunity. MRI shows an infarct sooner and is superior to CT at tissue differentiation but requires the impaired patient to be in the forbidding
MR environment. For example, MRI can indicate low blood flow at 1 to 2 hours. Cerebral angiography is an invasive technique and depends on the expertise of the radiologist. MR angiography can identify those who may benefit from standard angiography, but again the MR environment may be upsetting to the patient. Diffusion MRI can show cytotoxic edema, resulting from the sodium-calcium cascade, within the first hour after stroke, but the equipment is expensive and its reliability is yet to be proven.

Many sophisticated technologies for imaging are available that may be combined to aid in stroke diagnosis and therapy, but the basic need is for increased public awareness to get the patient to medical treatment as soon as possible.

**Hypothermia for Brain Protection:**

**Dr Myron Ginsberg**

Laboratory studies using the rat animal model have provided information about how cooling may protect the brain in stroke. Measurements made via a microdialysis probe showed that small degrees of cooling during ischemia virtually abolished the huge surge of brain glutamate described by Dr Choi. Cooling reduced the size of an infarct by 50% to 60% and reduced brain cell death by 75% to 100%. Moderate brain cooling instituted just after a period of cerebral ischemia also affects brain damage by retarding, although not completely preventing, the pace of nerve cell injury.

Studies are under way to treat early head injury with moderate brain cooling. Preliminary reports indicate that lowering the temperature even a few degrees, just 2°C to 3°C to a level of 33°C to 34°C, offers protection to the brain. Similar studies for stroke patients are hoped for soon.

Conversely, the rise of 2°C in body temperature can be harmful. Increased body temperature causes the blood-brain barrier to become more permeable, thus possibly allowing the leakage of damaging agents such as protein, which contributes to edema formation. Furthermore, oxygen free radical production is increased by hyperthermia.

Mild to moderate hypothermia may have a benefit during the 2 to 3 hours after stroke by widening the window of opportunity for administering therapeutic drugs. Although the technique may never protect all tissue, salvaging 50% tissue in an area responsible for movement, for example, could have a profound effect on the quality of life for stroke patients.

**Calcium Channel Blockade:**

**Dr James Grotta**

The role of calcium in stroke is a major area of study. Calcium channel blockers or calcium antagonists have been widely used in the treatment of heart disorders and stroke as neuronal protective therapy.

Calcium antagonists are a complex group of drugs, with their greatest activity on the peripheral and coronary circulations. Clinical trials testing the calcium blocker nimodipine in the treatment of subarachnoid hemorrhage demonstrated that the drug ameliorates damage from vasospasm possibly by protecting the nerve cells from calcium entry.

A potential problem is that calcium blockers dilate not only the brain vessels but also vessels throughout the body, a situation that can lead to hypotension, which in turn can lower cerebral blood flow. Additionally, side effects from calcium blockers may produce significant agitation and hallucinations in some patients if given in doses greater than 1.5 mg. Still, the benefits from the drug may outweigh the side effects, and these agents may be useful in buying time in treating stroke patients. Studies of some patients treated with calcium blockers showed that 80% to 100% were independent at 90 days after stroke, whereas only 48% of untreated patients were independent. Although the number of patients in the studies was small, the suggestion of benefit is there.

**Excitatory Amino Acid Inhibition:**

**Dr Choi**

Oxygen free radicals have been implicated in ischemic injury, and the understanding now is that an overload of radicals may result from the glutamate and calcium deluge. As oxygen free radicals assault the cell membrane, the membrane begins to disintegrate. The process resembles a chain reaction, with radicals multiplying rapidly as the cell membrane disintegrates.

Although always present in the human system, oxygen free radicals are kept in balance by natural antioxidants or scavengers. In ischemia, the balance is destroyed, and radicals form as a result of cells in the cortex reacting violently to the calcium overload by emitting nitric oxide synthase (NOS) that produces nitrous oxide, which can exacerbate the formation of oxygen free radicals. NOS may be an important link between NMDA and other receptors, the calcium overload, and oxygen free radicals leading to cell death.

Interference with the glutamate-calcium overload described earlier may be limited by side effects in humans. Some preventive benefit may come from providing patients at risk for stroke with antioxidant products to block the formation of excessive oxygen free radicals should stroke occur.

**Free Radical Scavengers:**

**Dr Edward Hall**

Recent biochemical, physiological, and pharmacological studies have strongly suggested a role for oxygen radicals in stroke. A free radical is a molecular species with an unpaired electron in its outer orbit. If an electron is unpaired, the molecule becomes highly reactive and tries to steal an electron from a neighboring molecule. This can set off a chain reaction in which damage to cells can occur as the radicals multiply.

Oxygen free radicals can arise from multiple sources, not only those mentioned by Dr Choi. Under hypoxic or ischemic conditions mitochondria will leak oxygen free radicals and form superoxide. Also, vascular events associated with reperfusion may play a role, and the enzymatic oxidation of some of the neurotransmitters, such as norepinephrine, serotonin, and dopamine, can form radicals.

Targets of free radicals include the cell membrane lipids (specifically the polyunsaturated fatty acids and cholesterol), proteins, and the nucleic acids DNA and RNA. The primary target during ischemic brain damage, at least during the initial phase, is polyunsaturated fatty acids in the cell membrane, which, when attacked by free radicals, undergo lipid peroxidation. The effect on the membrane structure is fragmentation. The membrane basically falls apart.

A further complication, even a paradox, is that post-ischemic reperfusion introduces more oxygen into tis-
sue, leading to more free radicals and more lipid peroxidation that can exacerbate neurological damage. Vulnerability of parts of the brain parallel their sensitivity to free radicals, with the hippocampus suffering more from reperfusion than the cortex.

The key is trying to stop lipid peroxidation. The discovery of a class of compounds called the 21-aminosteroids (lazaroids) led to the development of one type, tirilazad mesylate, identified as U-74006F. This compound has shown great promise as a neuroprotective agent through multiple mechanisms, including scavenging lipid peroxyl radicals, increasing membrane stability, and maintaining levels of the endogenous antioxidants vitamin E and ascorbate.

Animal models of ischemia and hemorrhage showed tirilazad to be effective by decreasing the size of infarction, peri-infarct edema, and vasospasm induced by subarachnoid hemorrhage. Tirilazad is currently being tested in clinical trials of subarachnoid hemorrhage and focal ischemia. Current information from phase III trials in Australia, New Zealand, and Europe shows that when tirilazad treatment for subarachnoid hemorrhage is initiated within 72 hours (allowing time for vasospasm to develop) and continued for 8 to 10 days, the outcome at 3 months is a 43% reduction in mortality, a 28% reduction in vasospasm, and improvement in the incidence of "good" recovery (Glasgow Outcome Score).

**Thrombolytic Therapy – Systemic: Dr Brett**

The primary lytic agent within the intravascular system is plasmin, which occurs when plasminogen is activated by a series of activators. In thrombolytic therapy, certain substances may be given to patients to promote lysis, usually through the activation of plasminogen.

Urokinase, a natural substance and a direct activator of plasminogen to plasmin, is used primarily for intravascular therapy. Streptokinase, probably the most commonly used thrombolytic agent worldwide, is not a direct activator but must combine with plasminogen in a streptokinase complex, which then is active in converting plasminogen to plasmin. Because streptokinase is not a natural substance, it may produce allergic reactions in 5% to 10% of patients receiving it. The allergic reactions can lead to the development of significant hypertension. Tissue plasminogen activator (TPA) is another substance recently used to lyse clots.

Pilot studies done in the late 1980s demonstrated that intravenous thrombolytic therapy could be administered early after the onset of stroke, and many of the patients treated within 3 hours. The studies also showed that the procedure was safe and effective in dissolving occlusive thrombi. Randomized efficacy trials of TPA and streptokinase are well under way or near completion in Europe, North America, Australia, and Japan. Preliminary data are encouraging, and results of one trial are expected early next year. The remainder should produce information in late 1995 and early 1996.

Although systemic side effects of the drugs are virtually nil, there are some dangers in intravenous delivery in that the patient may develop an excess of plasmin, leading to a state of anticoagulation, a bland infarct may be converted to a hemorrhagic infarct, or a gross hemorrhage may develop. In addition, the danger of distal embolism exists as the more proximal clot is fragmented in the process of being lysed. Yet it is through clinical trials that information will be accumulated on which is the best agent, what is the best dose, who is the best patient, and, more basically, whether or not these agents work at all.

**Thrombolytic Therapy – Intra-arterial: Dr Latchaw**

The intra-arterial method of administering thrombolytic agents has been effective in a small uncontrolled series of patients. Therapy needs to be done within 6 hours after the onset of stroke, and the techniques employed require a high level of expertise. An infusion of urokinase or TPA is sprayed or dripped into and around clot over minutes or hours via a microcatheter threaded through the artery up to and around or through the clot. Angioplasty may be done, if necessary, during the procedure to clear a stenosis.

Problems resulting from the procedure may be persisting neurological deficit from already infarcted tissue and the danger of hemorrhage due to increased pressure at the site of the infarcted tissue after clot lysis.

**Surgical Therapy of Stroke: Dr James Robertson**

One of the surgical therapies of proven benefit to stroke patients is carotid endarterectomy. Two trials are presently under way: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Endarterectomy Study. Early results from the NASCET demonstrated that for symptomatic patients with greater than 70% stenosis, carotid endarterectomy was effective in preventing stroke. The trial needs to continue to determine the benefit to patients with 30% to 69% blockages.

One new approach to standard carotid endarterectomy procedures is the placement in the carotid artery of a stent similar to those used to help prevent restenosis and reocclusion in coronary arteries. The benefit of interventional techniques, such as arterial angioplasty to open an occluded carotid artery, is unknown. The plaque is very friable and may break up, causing additional problems, and there may be a higher rate of induced stroke. Finally, it is not clear which patients would benefit from such techniques.

Surgery for hemorrhagic stroke depends greatly on the location and type of problem. Clipping aneurysms is far superior to medical treatment, and with the addition of tirilazad along with nimodipine for vasospasm, the outlook becomes even brighter. New approaches in this area include placement, via endovascular navigation, of small balloons or coils in small aneurysms with narrow necks.

Surgical treatment for stroke is undergoing change, with two disciplines—neurosurgery and neuroradiology—using different approaches to treat occlusive lesions as well as lesions capable of causing hemorrhage.

**Panel Discussion**

After the presentations, the panel responded to questions from the audience.

**Question:** Please comment on the concern that results from animal model studies may not be useful for human patients, who often have other medical conditions in addition to stroke symptoms.

**Panel:** Investigators use animal models because testing conditions may be rigidly controlled. Science is done by reduction, and animal studies finally do translate into...
useful information for humans. Furthermore, scientists cannot use human patients to understand pathophysiology until the safety and effectiveness of a procedure or therapy is assured through animal models.

**Question:** Why is there a greater incidence of stroke in the southeastern United States, often termed the Stroke Belt?

**Dr Walker:** The reasons are not clear but probably relate to a population that has greater risk for stroke and may not have as ready access to medical care as in other areas of the country. Increased public education may one day change the figures.

**Question:** Is the effect of parallel processing on the stroke patient harmful in terms of raising his/her anxiety level? Being surrounded by a number of busy medical personnel might increase the patient’s fears.

**Dr Brott:** The patient is usually able, at the time of entry into the study, to understand that all the activities are aimed at his/her benefit. Emergency teams recognize the possible anxiety and work together with other disciplines to reassure the patient during this period.

**Dr Latchaw:** Having an anesthesiologist on hand during the processing is helpful to monitor hyper/hypotension and to sedate the patient as necessary.

**Dr Grotta:** It is also important to have a neurologist in attendance.

**Question:** Please comment on the increased white blood cell count as a risk factor for stroke and myocardial infarction and the mechanism involved.

**Dr Hall:** Elevated white blood cell count is a marker for pathology and may exacerbate focal ischemia.

**Dr Grotta:** Possibly clot formation is affected by the elevated count.

**Dr Robertson:** There is no certainty that elevated white blood cell count is a risk factor for stroke. One study noted different normal counts for whites versus blacks and men versus women.

**Question:** In South Africa, whites have more strokes than blacks. Please comment.

**Dr Caplan:** That statement is probably not quite accurate. Black/white stroke rates in the metropolitan areas of South Africa are the same as in the United States. Also, there may be a difference in reported strokes because fewer blacks may seek or have access to medical treatment or be diagnosed. The issue is one of ascertainment.

**Question:** Can the theory of antioxidants really help in prevention?

**Dr Choi:** In attempting to produce ischemia in a certain group of cats in one of our studies, we were unable to do so. Investigation showed that the cats had been highly dosed with vitamin E before delivery to the laboratory. This is certainly anecdotal evidence, but all lab personnel began taking vitamin E.

**Dr Walker:** In today’s environment of concern about healthcare costs, showing that preventive therapies are effective is a major effort. This can only be done through controlled trials. For example, the carotid endarterectomy study has shown that this procedure can reduce the risk of second stroke by 60% within 4 years. This dramatically affects the taxpayer because those patients will not need caregivers, certainly a major factor that drives up healthcare costs.

**Dr Heros:** In conclusion, the recurring emphasis in the presentations on the need for increased public education about stroke symptoms and the need for immediate response by emergency medical teams and physicians underscores the seriousness of brain attacks. Clinicians and researchers must continue to work toward developing effective stroke therapies and demonstrating through well-designed controlled clinical trials whether or not these therapies are useful. Working together we can, during the DECade of the Brain, make a major contribution by reducing the morbidity of stroke and its staggering cost to society both financially and in terms of pain and suffering.

**Appendix**

**Moderator**

Roberto C. Heros, MD, Lyle A. French Professor and Department Chairman, Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, Minn.

**Participants**

Patricia A. Grady, PhD, Acting Director, NINDS, National Institutes of Health, Bethesda, Md.

Michael D. Walker, MD, Director, Division of Stroke and Trauma, NINDS, National Institutes of Health, Bethesda, Md.

Dennis W. Choi, MD, PhD, Professor and Head, Department of Neurology, Washington University School of Medicine, St Louis, Mo.

William A. Pulsinelli, MD, PhD, Semmes-Murphey Professor and Chairman, Department of Neurology, University of Tennessee Health Science Center, Memphis, Tenn.

Thomas Brott, MD, Professor of Neurology, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Louis R. Caplan, MD, Professor and Chairman, Department of Neurology, Tufts University School of Medicine, Boston, Mass.

Richard E. Latchaw, MD, Professor of Radiology and Neurosurgery, Margaret and H.O. Peterson Chair of Neuroradiology, University of Minnesota Medical School, Minneapolis, Minn.

Myron D. Ginsberg, MD, Professor and Vice-Chairman, Department of Neurology, University of Miami School of Medicine, Miami, Fla.

James C. Grotta, MD, Professor, Department of Neurology, University of Texas Health Science Center, Houston, Tex.

Edward D. Hall, PhD, Senior Scientist, CNS Diseases Research; Program Leader, Neurological Disorders Program; The Upjohn Company, Kalamazoo, Mich.

James T. Robertson, MD, Professor and Chairman, Department of Neurosurgery, University of Tennessee College of Medicine, Memphis, Tenn.

**Sponsor**

National Foundation for Brain Research, Lawrence S. Hoffheimer, Executive Director, 1250 24th St NW, Washington, DC 20037.

**Acknowledgment**

The symposium summary was prepared by editorial consultant Joan Z. Muller.

**Key Words** • cerebrovascular disorders • stroke assessment • stroke prevention
R C Heros

Stroke. 1994;25:1877-1881
doi: 10.1161/01.STR.25.9.1877

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/9/1877.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/