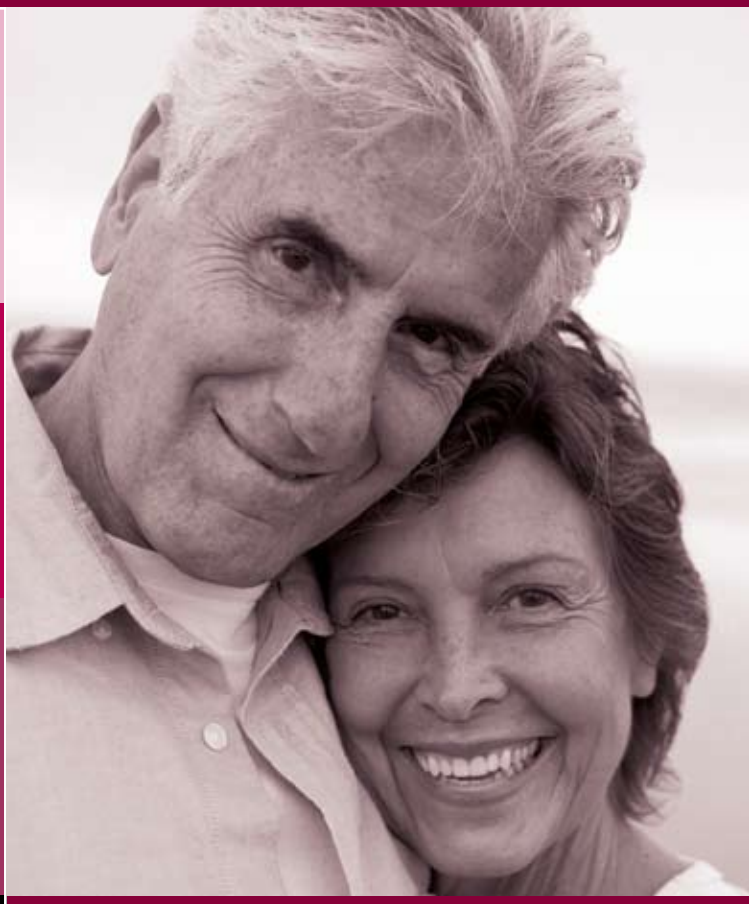
Stroke:



Challenges, Progress, and Promise

FEBRUARY 2009

National Institute of Neurological Disorders and Stroke

National Institutes of Health

Contents

Introduction

Chances are

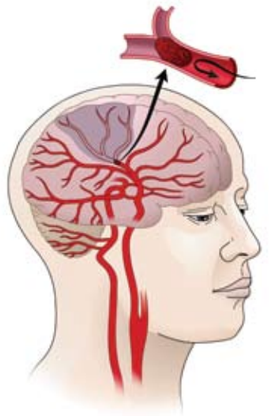
that nearly everyone...

...reading this has already had an unwelcome introduction to stroke, perhaps through firsthand experience or by witnessing its effects on a relative. Research sponsored by the National Institutes of Health (NIH) shows that about one in six Americans will experience a stroke at some point after age 65. Stroke is fatal in about 10 to 20 percent of cases and, among survivors, it can cause a host of disabilities, including loss of mobility, impaired speech, and cognitive problems. These trends have made stroke the third leading cause of death in the U.S. (behind heart disease and cancer) and a major cause of disability.

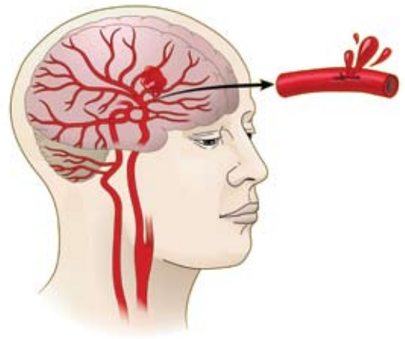
A stroke is a sudden event affecting the brain's blood supply. In an ischemic stroke, a blood vessel that supplies the brain becomes blocked. In a hemorrhagic stroke, a blood vessel in the brain bursts. Although stroke is most common in older people, it can occur in individuals of any age, including young adults, children, infants, and fetuses in the womb.

Fortunately, the prospects for preventing and treating stroke are far better than they were just a few decades ago, thanks in part to research supported by the NIH's National Institute of Neurological Disorders and Stroke (NINDS). NINDS-funded investigators have identified many risk factors for stroke, such as hypertension (high blood pressure), arming people with the ability to reduce their risk through lifestyle changes or medication. Clinical trials supported by NINDS also led to the only drug approved by the Food and Drug Administration specifically for treating acute ischemic stroke—the "clot-buster" tPA. When given within three hours of stroke onset, the drug significantly reduces the likelihood of long-term disability.

Current NINDS priorities in stroke research are set by its Stroke Progress Review Group (SPRG), an advisory body made up of scientists, clinicians, patient advocates, and industry representatives. One such priority is to develop new and more effective treatments for acute stroke. NINDS is supporting research on novel ways to restore blood flow to the ischemic brain, as well as treatments that would act directly on brain cells to protect them from the effects of stroke. Another priority is to improve post-stroke recovery by tapping into the brain's capacity to repair itself; for example, by using drugs to stimulate the growth of new brain cells or physical therapy regimens to stimulate the re-wiring of existing cells. Finally, stroke prevention and the identification of stroke risk factors remain important parts of the NINDS portfolio.



An ischemic stroke occurs when a blood ve sel supplying the brain becomes blocked, as by a clot.



A hemorrhagic stroke occurs when a blood vessel bursts, leaking blood into the brain.

NINDS supports several complementary networks of research centers aimed at improving treatment and care for individuals with acute stroke. The Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) helps move experimental therapies for acute stroke from the lab into early-phase clinical studies. SPOTRIAS sites are located at major academic medical centers across the country, where scientists studying the molecular and cellular mechanisms of stroke can work closely with clinicians who have expertise in acute stroke care. The Neurological Emergencies Treatment Trials (NETT) network creates a similar collaborative framework among neurologists, neurosurgeons, and emergency medicine physicians to facilitate clinical trials on stroke in the emergency room. Meanwhile, through the Stroke Preclinical Trials Consortia, NINDS is forging collaboration among investigators who are testing potential stroke treatments in animal models. Finally, NINDS outreach programs help bridge research and practice by educating individuals, their loved ones, and healthcare providers about the latest advances in treatment and prevention.

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1. Stroke Basics

The effects of stroke manifest themselves rapidly. The five most common symptoms of stroke are:

- Sudden weakness or numbness of the face or limbs, especially on one side of the body.
- Sudden confusion or difficulty speaking or understanding speech.
- Sudden trouble seeing in one or both eyes.
- Sudden trouble walking, dizziness, or loss of balance or coordination.
- Sudden severe headache with no known cause.

The exact symptoms depend on where in the brain's vascular system the blockage or rupture has occurred. Strokes that predominantly affect one hemisphere of the brain are common. Since each hemisphere controls the opposite side of the body, a stroke in the left hemisphere will cause motor and sensory deficits on the right side of the body, and vice versa.

The long-term outcomes after a stroke vary considerably and depend partly on the type of stroke and the age of the affected person. Although most stroke survivors regain their functional independence, 15 to 30 percent will have a permanent physical disability. Some will experience a permanent decline in cognitive function known as post-stroke or vascular dementia. Unfortunately, many stroke survivors face a danger of recurrent stroke in the future. About 20 percent of people who experience a first-ever stroke between ages 40 and 69 will have another stroke within five years. Finding treatments to help prevent stroke in this high-risk group is a major focus of NINDS-supported research.

Ischemic Stroke and Transient Ischemic Attack

Ischemic strokes make up about 80 percent of all strokes. Just as a heart attack occurs when there is insufficient blood flow to the heart, an ischemic stroke (sometimes called a "brain attack") occurs when there is a sudden interruption in blood flow to one or more regions of the brain. Like all cells in the body, neurons and other brain cells require oxygen and glucose delivered through the blood in order to function and survive. A few minutes of oxygen deprivation—called ischemia—is enough to kill millions of neurons. Moreover, ischemia can provoke inflammation, swelling (edema), and other processes that can continue to cause damage for hours to days after the initial insult.

Obstructive blood clots are the most common cause of ischemic stroke. Clotting (or coagulation) is a vital function that helps prevent bleeding when a blood vessel is damaged, but clots can also obstruct normal blood flow. When a clot forms in association with the wall of a blood

Medical Terms for Common Stroke Symptoms and Disabilities

Hemiplegia: paralysis on one side of the body.

Hemiparesis: weakness on one side of the body.

Hemineglect: lack of awareness of one side of the body or one side of the visual field.

Dysphagia: difficulty swallowing.

Dysarthria: difficulty talking, caused by facial weakness.

Aphasia: difficulty speaking or understanding speech, caused by damage to the brain's language centers.

vessel and grows large enough to impair blood flow, it is called a thrombus; a clot that breaks off the vessel wall and travels through the blood is an embolus. A cardioembolic stroke is caused by a clot that originates in the heart. Cardiac emboli are most likely to form in people with heart conditions such as atrial fibrillation (AF, an irregular heartbeat), heart failure, stenosis, or infections within the valves of the heart. They may also occur post-heart attack.

Another contributor to ischemic stroke is chronic atherosclerosis, which is a buildup of fatty deposits and cellular debris (plaque) on the inside of the blood vessel wall. As atherosclerotic plaques grow, they cause narrowing of the blood vessel (a condition called stenosis). Atherosclerosis can also activate cells involved in clotting.

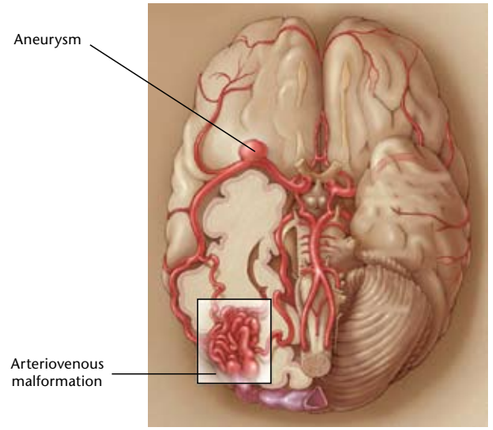
Immediately after an ischemic stroke, the brain usually contains an irreversibly damaged core of tissue and an area of viable but at-risk tissue called the ischemic penumbra. Restoring normal blood flow—a process known as reperfusion—is essential to rescuing the penumbra. The longer reperfusion is delayed, the more cells in the penumbra will die. The region of brain tissue that is finally damaged is called an infarct.

If a stroke were a storm, a transient ischemic attack (TIA), or "mini-stroke," would be an ominous thunderclap. Symptoms of a TIA are similar to those of a full-blown stroke but resolve within 24 hours, typically in less than one hour. Still, the short-lived nature of TIAs does not mean that they leave the brain unharmed. In about 40 to 50 percent of people who have experienced a TIA, a tiny dot of infarct can be seen by brain imaging.

Even when there is no sign of brain infarction, a TIA is both a warning and an opportunity for intervention. While someone who has experienced a full-blown stroke has a two to seven percent risk of having another stroke within the next 90 days; the 90-day risk of stroke following a TIA is 10 to 20 percent. In many cases, TIAs may be caused by an unstable clot that could create a more permanent blockage within the brain's blood supply at any moment. Fortunately, there are a variety of treatments that can reduce the risk of stroke following a TIA, including medications to lower blood pressure and inhibit blood clotting. If necessary, surgical procedures can clear away plaque in the arteries that supply the brain, or a procedure called stenting can be used to widen the arteries. Severe strokes could be avoided if more people sought medical attention after a TIA. (For more about these treatments, see the chart on p. 10 and "Current Stroke Treatment and Prevention" on p. 14.)

Hemorrhagic Stroke

An intracerebral hemorrhage occurs when a blood vessel ruptures within the brain. Several conditions can render blood vessels in the brain prone to rupture and bleeding. Chronic hypertension and a condition known as cerebral amyloid angiopathy can weaken the blood vessel wall. Poor blood clotting ability due to blood disorders or blood-thinning medications like warfarin further increase the risk of bleeding. Finally, structural abnormalities that can form in blood vessels during brain development also a play a role. For instance, an arteriovenous malformation (AVM) is a tangled mass of thin-walled cerebral blood vessels in the brain. AVMs are thought to be present from birth in one percent or less of the population.



An aneurysm is a bulge in a blood vessel and an arteriovenous malformation is a tangled mass of thin-walled vessels. Both of these structures are associated with a risk of hemorrhagic stroke.

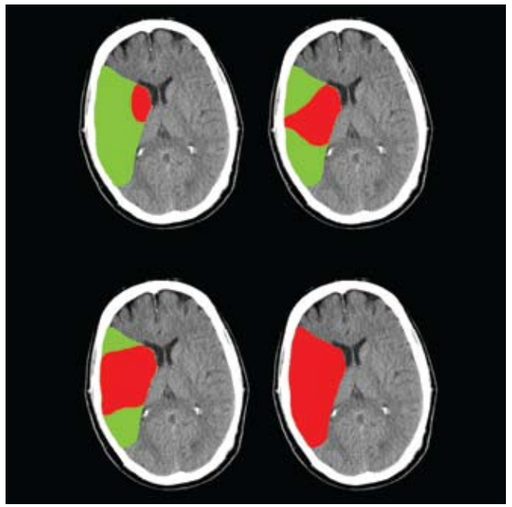
Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) refers to a buildup of protein deposits known as amyloid on the inside wall of blood vessels. It is a major contributing factor to intracerebral hemorrhage in older people and is sometimes associated with small ischemic infarctions and vascular cognitive impairment.

CAA is regarded as a disease of aging. It is rarely observed in individuals under age 50, but is seen in about 50 percent of individuals over age 90. The proportion of intracerebral hemorrhage cases in older people that are causally linked to CAA is unclear, but recent estimates place that number as high as 50 percent.

The buildup of amyloid inside blood vessels weakens the vessel wall and may lead to blood vessel rupture. In recent years, a poorly understood connection has emerged between CAA and Alzheimer's disease. Beta-amyloid—the toxic protein fragment that accumulates in clumps (called plaques) within the brain tissue of people with Alzheimer's disease—is a component of the amyloid deposits found in people with CAA. Moreover, Alzheimer's disease and CAA share similar genetic risk factors, such as the gene encoding apolipoprotein E (APOE). A variant of this gene known as e4 increases the risk of Alzheimer's disease and the risk of recurrent intracerebral hemorrhage.

A subarachnoid hemorrhage is the rupture of a blood vessel located within the subarachnoid space—a fluid-filled space between layers of connective tissue (meninges) that surround the brain. The first sign of a subarachnoid hemorrhage is typically a severe headache with a split-second onset and no known cause. Neurologists call this a thunderclap headache and it demands immediate medical attention. The rupture may occur in an AVM, but typically it occurs at a site where a blood vessel has weakened and bulged, called an aneurysm. Aneurysms affect as much as one percent of the population, and are sometimes hereditary. NINDS-funded studies have shown that the risk that an aneurysm will rupture is related to its size and shape, its location, and the person's age. The risk is increased by smoking. Information about these risks helps doctors advise individuals on whether an asymptomatic aneurysm should be treated.



Immediately after an ischemic stroke (top left), a core of irreversibly damaged brain tissue (red) is surrounded by an area of viable but at-risk tissue called the penumbra (green). Unless blood flow is restored quickly, the tissue within the penumbra will be lost (bottom right).

Unlike other tissues in the body, neural tissue normally is shielded from direct contact with blood by the blood-brain barrier, which is a tightly sealed network of cellular and extracellular components that lines blood vessels in the brain. The blood-brain barrier is permeable to oxygen and other nutrients in the blood, but generally impermeable to red and white blood cells, and large molecules. During a hemorrhagic stroke, these cells and molecules are released en masse into the delicate environment that surrounds neurons. Meanwhile, the accumulation of blood, known as a hematoma, can cause an increase in intracranial pressure that further impairs normal blood flow and damages the brain by compression.

Vascular Cognitive Impairment

Even in the absence of a clinically obvious stroke or TIA, impaired blood flow in the brain may eventually lead to vascular cognitive impairment (VCI). At one extreme, VCI includes vascular dementia, but it also refers to a gradual decline in mental function caused by multiple strokes, some silent, over time. It is often associated with a more diffuse small vessel disease, caused by narrowing of small-diameter blood vessels that supply limited territories within the brain. Clinically, VCI may resemble Alzheimer's disease (AD) and many older individuals with dementia meet the diagnostic criteria for both diseases. However, while AD primarily affects memory, VCI appears to primarily affect the brain's executive function—the ability to plan activities from getting dressed in the morning to negotiating a business deal.

2. Stroke Diagnostics and Brain Imaging

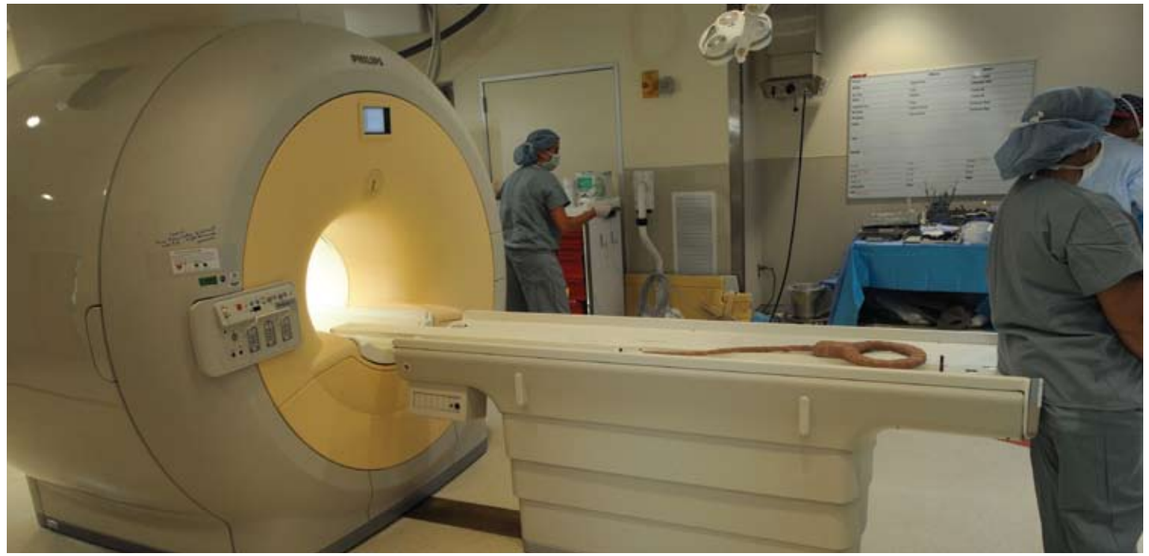
When a stroke is suspected, a physician will carry out a detailed assessment of the individual's signs and symptoms. One common assessment tool is the NIH Stroke Scale, developed by NINDS. This is a checklist of questions and tasks that scores an individual's level of alertness and ability to communicate and perform simple movements. Other common diagnostic procedures include blood tests and an electrocardiogram to check for cardiac abnormalities that might have contributed to the stroke.

Brain imaging techniques play an important role in stroke diagnosis, in the evaluation of individuals with stroke for clinical trials, and, to a growing extent, assessment of stroke risk. Several imaging techniques can be used to generate visual "slices" of the brain or even three-dimensional reconstructions. This in-depth look at the brain helps to: rule out other potential neurological conditions such as a brain tumor, differentiate ischemic from hemorrhagic stroke, identify which blood vessels have been damaged, and determine the extent and location of the infarct.

Computed tomography (CT) and magnetic resonance imaging (MRI) are the two most common imaging techniques used to identify infarctions caused by stroke. CT uses X-ray beams passed through the head at multiple angles to generate high-resolution brain images. It is faster, more widely available, and less expensive than MRI.

MRI, which does not involve X-rays, exposes the brain to a magnetic field in combination with a radio wave pulse. The brain's absorption of this pulse and the rate at which energy is released when the pulse ends varies in different brain tissues and yields an image. Diffusion-weighted imaging (DWI) is a highly sensitive type of MRI that measures the diffusion of water in brain tissue, which changes during an ischemic stroke. DWI is especially useful for detecting small infarcts and is superior to CT for diagnosing ischemic stroke. Research studies suggest that DWI in combination with a brain blood perfusion study can be used to help identify the ischemic penumbra—brain tissue that is blood-starved, but salvageable if blood flow can be restored quickly. In many individuals, the extent of ischemic penumbra is related to the degree of diffusion-perfusion mismatch, which is a DWI signal that occurs in brain tissue with normal water diffusion but abnormal blood flow.

Several imaging techniques are used to examine cerebral blood vessels. These techniques can reveal the site of blockage in an ischemic stroke or detect stenosis or vascular malformations (such as an aneurysm or AVM) that put a person at risk for stroke. Angiography of the brain involves



MRI scans are commonly used to check for damage to the brain and the brain's vasculature in people suspected of having a stroke.

Brain imaging

techniques play an important role in stroke diagnosis...and to a growing extent, in the assessment of stroke risk. Several imaging techniques can be used to generate visual "slices" of the brain or even three-dimensional reconstructions.

imaging after a contrast agent that shows up dark on a scan has been injected into a vein in the arm or leg, which yields a map of the brain's blood vessels.

A procedurally similar technique called perfusion imaging is sensitive for detecting abnormal blood flow in the brain. Doppler ultrasound involves passing high-frequency, inaudible sound waves into the neck or head. These sound waves bounce off of cells moving through the blood, producing an image and providing information on how fast the blood is traveling. In general, blood cells speed up as they move through a narrow vessel.

3. Stroke Risk Factors

Given that stroke is caused by blockage or rupture of a blood vessel, it should be no surprise that similar modifiable risk factors contribute to stroke and cardiovascular disease, including hypertension, smoking, diabetes, high cholesterol, and lack of physical activity. It is possible to dramatically reduce these risks through healthier lifestyle choices or medications (such as blood pressure-lowering drugs). In fact, since 1950, there has been about a 60 percent decline in the mortality rate from stroke and a smaller but significant decline in the age-adjusted annual incidence of stroke—the number of people who have a stroke each year, adjusted to account for the increasing age of the population. Many experts attribute these trends to increasing awareness and control of stroke risk factors. (For quick facts about the most potent modifiable stroke risk factors and ways to counteract them, see "Modifiable Risk Factors " on p. 10.)

Unmodifiable Risk Factors

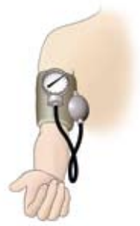
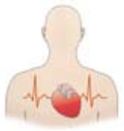
The risk of stroke varies by age, sex, race, and even where we live. Although these risk factors are considered unmodifiable, they help inform stroke prevention strategies at the individual and population levels.

Stroke and Age

The effects of age on the cardiovascular system, combined with the insidious nature of other types of risk over the life span, make it a key risk factor for stroke. A major source of information about stroke risk is the Framingham Heart Study, which began tracking the cardiovascular health of some 5,000 individuals from the Framingham, Massachusetts area in 1948 and has since expanded to include their children. The study, which receives primary support from NIH's National Heart, Lung, and Blood Institute (NHLBI) and support for its stroke component from NINDS, has shown that the risk of stroke doubles for each decade between the ages of 55 and 85.

Stroke in young adults is relatively infrequent, but it does happen. The Northern Manhattan Study, supported by NINDS, found that, among people living in that area in the mid-1990s, the annual incidence of stroke was about two per 10,000 among people age 20 to 44, and about 56 per 10,000 among people ages 45 and older. This study and others in the U.S. have found that hemorrhagic and ischemic strokes tend to occur in roughly equal proportion in young people. The increased risk of stroke that occurs with age therefore appears to be mostly an increased risk of ischemic stroke. (Also see "Stroke in Infants and Children" on p. 11.)

Modifiable Risk Factors

Risk factor	How much it affects stroke risk	Why it affects stroke risk	What you can do
Hypertension 	Hypertension causes a two- to four-fold increase in the risk of stroke before age 80. After age 80, the impact of hypertension declines and other risk factors become more important.	Hypertension promotes atherosclerosis and causes mechanical damage to the walls of blood vessels.	Blood pressure medications, such as thiazide diuretics and angiotensin-converting enzyme (ACE) inhibitors, can reduce the risk of stroke by 30 to 40 percent. Early treatment is essential. Among older people with normal blood pressure, prior mid-life hypertension increases stroke risk up to 92 percent. Guidelines from the Centers for Disease Control and Prevention recommend a target blood pressure of less than 140/90 mm Hg.
Cigarette smoking 	Smoking causes about a two-fold increase in the risk of ischemic stroke and up to a four-fold increase in the risk of hemorrhagic stroke.	Smoking promotes atherosclerosis and aneurysm formation, and stimulates blood clotting factors.	Stroke risk decreases significantly two years after quitting smoking and is at the level of nonsmokers by five years.
Diabetes 	In terms of stroke and cardiovascular disease risk, having diabetes is the equivalent of aging 15 years.	In diabetes, glucose is not efficiently taken up by the body's cells and accumulates in the blood instead, where it can damage the vascular system. Hypertension is common among diabetics and accounts for much of their increased stroke risk.	Blood pressure medications, dietary changes, and weight loss can lower stroke risk. Controlling blood sugar appears to reduce the risk of recurrent stroke.
Physical inactivity and obesity 	Waist-to-hip ratio equal to or above the median (mid-value for the population) increases the risk of ischemic stroke three-fold.	Obesity is associated with hypertension, diabetes, and heart disease.	While no clinical studies have tested the effects of exercise or weight loss on stroke risk, both tend to reduce hypertension and boost cardiovascular health.
Atrial fibrillation (AF) 	AF affects fewer than one percent of people under age 60, but is more prevalent in older people. It is responsible for one in four strokes after age 80, and is associated with high mortality and disability.	AF refers to irregular contraction of the atrium—the chamber where blood enters the heart. AF can lead to blood stagnation and increased clotting.	Warfarin, a blood-thinning medication, can reduce the risk of stroke in people with AF. People under age 60 with AF and no other stroke risk factors may benefit from aspirin. Importantly, pacemakers have no effect on the risk of stroke associated with AF.
Cholesterol imbalance 	High-density lipoprotein (HDL) cholesterol is generally considered protective against ischemic stroke. Low-density lipoprotein (LDL) cholesterol, when present in excess, is considered harmful.	LDL and HDL are needed to carry cholesterol (a fatty substance) through the blood (made up mostly of water), and deliver it to cells. Because LDL delivers cholesterol to cells throughout the body, excess LDL can cause cholesterol to build up in blood vessels, leading to atherosclerosis. HDL sends cholesterol to the liver to be eliminated.	Clinical trials have shown that cholesterol-lowering drugs known as statins reduce the risk of stroke. However, some studies point to only a weak association between stroke and cholesterol, and there is speculation that statins reduce stroke risk by acting through some unknown mechanism.

Stroke in Infants and Children

Compared to stroke in the adult brain, stroke in the young, growing brain is associated with unique symptoms, risk factors, and outcomes—and with more uncertainty in all three of these areas. Although stroke is often considered a disease of aging, the risk of stroke in childhood is actually highest during the perinatal period, which encompasses the last few months of fetal life and the first few weeks after birth.

As in adults, the symptoms of stroke in infants and children include headache, hemiplegia, and hemiparesis. But very young children with stroke are more likely than adults to experience other symptoms, such as seizures, breathing problems, or loss of consciousness. Because the incidence of childhood stroke is relatively low, parents and doctors often mistakenly attribute these symptoms to other causes, leading to delays in diagnosis. Moreover, the time of onset is usually unknown for strokes during the perinatal period.

Investigators know less about the risk of childhood stroke than they know about the risk of adult stroke. However, well-documented risk factors include congenital (inborn) heart

abnormalities, head trauma, and blood-clotting disorders. An important risk factor for African American children is sickle cell disease. Although sickle cell disease is known for its effect on red blood cells—causing them to take on a sickle shape—it can also cause a narrowing of cerebral arteries. A 1998 study of some 3,000 people with sickle cell disease found that 11 percent experienced a stroke before age 20. Fortunately, that same year, a study funded by NHLBI showed that repeated transfusions to replace sickled blood cells with normal blood cells reduced the risk of stroke by 92 percent. Yearly Doppler ultrasound imaging is recommended for young children with sickle cell disease and, if stenosis is found, repeated transfusions can be used as a means of stroke prevention.

Strokes during the perinatal period have been associated with premature birth, maternal infections, maternal drug abuse, prior infertility treatments, and maternal health conditions such as autoimmune disease and preeclampsia (a potentially serious combination of hypertension and kidney problems that affects about six percent of pregnant women).

The outcome of stroke in the very young is difficult to predict. A stroke during fetal development may lead to cerebral palsy—a permanent problem with body movement and muscle coordination that appears in infancy or early childhood. A stroke that occurs during infancy or childhood can also cause permanent disability. Generally, outcomes are worse in children under age one and in those who experience decreased consciousness or seizures. Fortunately, the developing brain is also known for its remarkable capacity to replace lost nerve cells and fix damaged connections between them. Healthy areas of the brain are often still pliable enough to compensate for damaged areas.

A child with serious deficits immediately after a stroke can make an impressive recovery.

Treatment of stroke in children presents unique challenges. Delays in diagnosis, which can be especially prolonged in cases of perinatal stroke, mean that valuable time is lost. Moreover, most treatments for acute stroke were developed based on studies in adults and the guidelines for their use in children are still being refined. To address some of these issues, NINDS and NIH's National Institute of Child Health and Human Development (NICHD) sponsored a workshop on perinatal stroke in August 2006 that brought together experts in pediatrics, neurology, cardiology, and public health. Goals set by this group include the development and testing of new therapies for perinatal stroke, a better understanding of the risk factors for it, and improved brain imaging methods to diagnose it.

Stroke in Adults

From ages 55 to 75, the annual incidence and short-term risk of stroke are higher in men than in women. However, because women generally live longer than men, their lifetime risk of stroke is higher and they account for a larger fraction (about 61 percent) of stroke deaths each year.

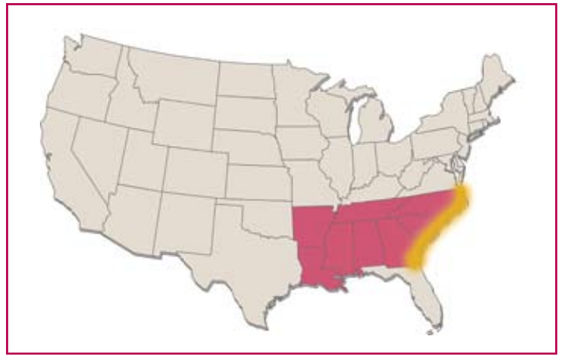
Women have unique stroke risks associated with pregnancy and menopause. In women of childbearing age, the risk of stroke is relatively low (with an annual incidence of one in 10,000), but a recent study estimates that pregnancy increases that risk three-fold.

Several factors contribute to the increased risk of stroke during pregnancy. The activity of blood clotting proteins is naturally amplified during pregnancy, increasing the chances of ischemic stroke for the mother (and perhaps contributing to perinatal stroke). Most maternal strokes occur during the first several weeks after delivery, suggesting that the drop in blood volume or the rapid hormonal changes following childbirth also play a role. Pregnancy-related stroke is more likely to occur in women who experience certain complications, such as infections or preeclampsia, or who have other risk factors for stroke, such as hypertension or diabetes.

Hormone replacement therapy (HRT) may ease the discomfort and the loss of bone density associated with menopause. It was once considered a possible means of stroke prevention in post-menopausal women. However, a series of placebo-controlled clinical trials sponsored by NINDS and NHLBI has shown that HRT increases the risk of stroke. NHLBI's Women's Health Initiative showed that treatment with the hormones estrogen and progestin increased the risk of stroke by 31 percent in women with an intact uterus. In women who had undergone a hysterectomy, treatment with estrogen alone increased the risk of stroke by 39 percent. The NINDS Women's Estrogen for Stroke Trial (WEST) found that women who had experienced a prior ischemic stroke and received estrogen were more likely to have a fatal recurrent stroke.

Stroke Across Races and Regions

People from certain ethnic groups have a higher risk of stroke. Many studies show that the age-adjusted incidence of stroke is about twice as high in African Americans and Hispanic Americans as in Caucasians. Moreover, several studies have found that, on average, African and Hispanic Americans tend to experience stroke at younger ages than Caucasians. The stroke mortality rate is higher in African Americans than in Caucasians or Hispanics. The incidence of the various stroke subtypes also varies considerably in different ethnic groups.



In the U.S., stroke mortality is unusually high in a cluster of Southeastern states known as the Stroke Belt. In the Belt's "buckle" (gold), stroke mortality may be double the national average.

Stroke is a global health problem. In some Eastern European countries and in the Far East, stroke rates are much higher than in the U.S. Within the U.S., stroke mortality is unusually high in people living in a cluster of Southeastern states—Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee—known as the "Stroke Belt." A recent study funded by NIH's National Institute on Aging suggests that the "belt" is worn from childhood. That is, people who lived in the Stroke Belt during grade school but later moved away had the elevated stroke risk characteristic of the area, while people who moved to the Stroke Belt as adults did not have an elevated stroke risk.

Although clearly influenced by differences in the prevalence of known stroke risk factors, the basis for these ethnic and geographic trends is not fully understood. For example, higher rates of hypertension and diabetes explain some, but not all, of the increased stroke risk among African Americans and residents of the Stroke Belt. Socioeconomic disadvantages in income and education level also appear to play a role. However, within a given geographic area, the most disadvantaged groups do not necessarily have the highest stroke risk. Finally, the relatively high percentage of African Americans living in Stroke Belt states does not explain the Stroke Belt's existence, since Caucasians living there also have an increased risk of stroke.

With an eye toward improving stroke prevention in high-risk communities, NINDS is supporting two studies to confront these issues: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS). Launched in 2003, REGARDS has enrolled more than 30,000 participants (including 12,000 African Americans), with half of the participants coming from the Stroke Belt and half from the 40 other mainland states. REGARDS investigators have found that, in individuals with hypertension, awareness and treatment of it is more common in African Americans, but that effective treatment—lowering blood pressure to the normal range—is more common in Caucasians. They have also found evidence that strokes are more likely to occur without diagnosis in African Americans than in Caucasians, and in Stroke Belt residents than in non-residents. Thus, a lack of awareness about stroke and a failure to intervene at the first signs of disease may explain the high stroke mortality of certain groups.

Launched in 1990, the NOMAS study has been tracking stroke incidence, risk factors, and outcomes in Northern Manhattan, where about 60 percent of residents now identify themselves as Hispanic and 15 percent identify as African American. NOMAS investigators have found that AF has an especially high impact on stroke risk in Caucasians, while a trend for hypertension and diabetes has a higher impact in Hispanics and African Americans. Physical inactivity appears to be a strong risk factor in all three ethnic groups.

4. Current Stroke Treatment and Prevention

Today, there is a small but growing arsenal of treatments that can markedly improve the chances of recovering from a stroke. There is also a wealth of knowledge about what causes stroke and how to reduce the chances of having one.

Medications

As described in the chart on p. 10 (Modifiable Risk Factors), medicines that lower blood pressure and cholesterol can protect against atherosclerosis and reduce a person's risk of stroke. Aspirin and other blood-thinning medications have been used for years to reduce the risk of ischemic stroke in individuals with AF or prior stroke. Recent studies have helped refine the use of these drugs to maximize safety and efficacy. This section, however, begins with a discussion of what happens when prevention fails and a person requires emergency treatment for an acute ischemic stroke.

Thrombolytic Drugs

In treating acute ischemic stroke (acute meaning that the stroke has occurred within the past few hours), the immediate goal is to break apart the offending clot, a process known as thrombolysis. The body produces its own thrombolytic proteins, and some of these have been engineered into drugs. One, called tissue plasminogen activator (tPA), had a proven track record for treating heart attacks. In the late 1980s, NINDS-funded investigators laid the plans for the first placebo-controlled trial of tPA to treat acute ischemic stroke. They knew from animal studies that irreversible brain injury is likely to occur if blood flow is not restored within the first few hours after ischemic stroke. Therefore, the NINDS tPA Study Group tested the drug within a three-hour time window. Compared to individuals given placebo, those given intravenous tPA were more likely to have minimal or no disability three months after treatment—a finding that persuaded the U.S. Food and Drug Administration to approve tPA for use against acute stroke. Trials in Europe and the U.S. subsequently confirmed those results. Recent studies attempt to identify individuals who may benefit even after three hours of stroke onset. In any case, more brain tissue will be saved the earlier the treatment is delivered.

A 1998 follow-up analysis of the NINDS trial found that, after their initial hospitalization, people who received tPA were less likely to require inpatient rehabilitation or nursing home care. The authors estimated that this lower dependency on long-term care would translate into a savings to the healthcare system of more than $4 million for every 1,000 individuals treated with tPA.

Because treatment with tPA interferes with blood clotting and has also been shown to increase leaking along the blood-brain barrier, it carries a risk of intracerebral hemorrhage. Therefore, it is not recommended for some people, such as those with a history of brain hemorrhage or significantly elevated blood pressure (greater than 185/110 mm Hg). The risk of tPA-induced hemorrhage increases over time from stroke onset, which has limited its use to the first three hours after stroke (where benefit was most clearly established in the U.S. trials).

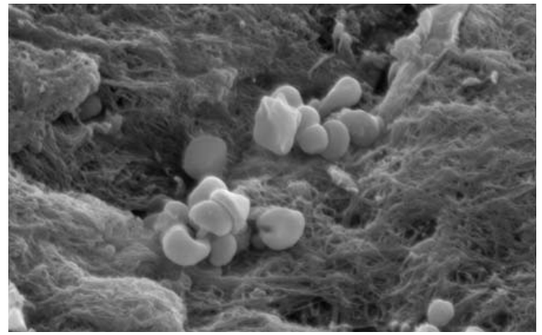
Antiplatelet Drugs and Anticoagulants

Blood-thinning medications fall into two classes: antiplatelet drugs and anticoagulants. Antiplatelet drugs inhibit the activity of cells called platelets, which stick to damaged areas inside blood vessels and lay the foundation for blood clots. The most common antiplatelet drug is aspirin. Anticoagulants, such as heparin (produced by inflammatory cells in the body) and warfarin (found in plants and also known by the trade name Coumadin©), inhibit proteins in the blood that stimulate clotting.

Antiplatelet drugs and anticoagulants can help prevent a variety of potentially life-threatening conditions for which individuals with stroke are at risk, such as myocardial infarction, pulmonary embolism, and deep vein thrombosis—which are caused by clots in the heart, lungs and deep veins of the legs, respectively. In recent years, the value of these drugs in treating and preventing stroke itself has been more closely scrutinized.

One focus of this research has been to determine if there is any benefit in giving antiplatelet drugs or anticoagulants during an acute ischemic stroke, as an adjunct to tPA, or as an alternative for people ineligible to receive tPA. In an international trial coordinated by researchers in the United Kingdom in the late 1990s, individuals received aspirin, subcutaneous heparin injections, or neither treatment within 48 hours of an ischemic stroke. Aspirin significantly reduced the risk of a recurrent ischemic stroke at two weeks. A similar benefit from heparin was offset by an increased risk of hemorrhagic stroke. Around the same time, NINDS-funded researchers tested whether acute stroke could be treated with intravenous Org 10172, a form of heparin considered less likely to cause bleeding. This study, Trial of Org 10172 in Acute Stroke Treatment (TOAST), found that Org 10172 produced no significant benefit. The study authors also developed the TOAST criteria, a set of guidelines for classifying different subtypes of ischemic stroke that are now widely used in other studies.

Another issue is whether individuals at risk for ischemic stroke should be placed on a daily maintenance program of aspirin or anticoagulants. For many years, aspirin and warfarin were used as a means of stroke prevention in individuals with AF, but until recently, this practice was based more on anecdotal evidence than on scientific data. A systematic analysis of warfarin's benefits was especially important since it is an expensive drug



Platelets (magnified here thousands of times) home to damaged areas of blood vessels and contribute to the formation of clots. Antiplatelet drugs can help reduce the risk of ischemic stroke.

Robert, a 74 year-old retiree…

…had just stepped inside after watering the lawn when he suddenly felt odd. He tried to speak to his wife, Alma, but realized that he couldn't. He held her hand and stared at her. He didn't know what was happening to him, but fortunately, she did.

As an avid reader of health information, Alma immediately recognized that Robert was having a stroke. She dialed 911, and about 30 minutes later, Robert was in an emergency room. Doctors quickly took pictures of Robert's brain using a CT scan and determined that his stroke was ischemic in nature. In other words, a clot was blocking the flow of blood to vital brain areas, including the speech center. They also determined that Robert was a good candidate for tPA, a clot-busting drug that had been approved for use against acute ischemic stroke by the Food and Drug Administration in 1996, just four years earlier.

While the doctors administered tPA intravenously, they asked Robert a series of simple questions to test his ability to think and speak – questions like "Do you know where you are?" and "Can you name your wife and children? Your grandchildren?" At first, his speech continued to fail him, but after a few minutes, he was answering every question. He was released from the hospital 6 days later, and after some speech therapy, he was soon reading to his grandchildren again.

During Robert's treatment and evaluation at the hospital, doctors discovered that he had atrial fibrillation (AF), which is an abnormal heart rhythm and a risk factor for stroke. He now takes warfarin, a medication that inhibits blood clotting and has proven effective for reducing the risk of stroke in people with AF and other stroke risk factors. He hasn't experienced any more strokes.

Robert and Alma have seven grandchildren and one great-granddaughter. Robert continues to enjoy reading to the youngest ones.

and, like heparin, is associated with an increased risk of hemorrhagic stroke. The NINDS Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) and the Stroke Prevention in Atrial Fibrillation (SPAF) trials showed that daily warfarin is best for people with AF who are over age 65 or who have additional vascular risk factors. Daily aspirin provides adequate protection against stroke among young people with AF.

Two other NINDS-sponsored trials compared the effectiveness of daily warfarin and aspirin for individuals who did not have AF, but who had experienced a prior stroke—and thus were at risk for another. The Warfarin vs. Aspirin Recurrent Stroke Study (WARSS) showed that aspirin was as effective as warfarin in preventing recurrent stroke in people with no history of AF or other cardioembolic causes of stroke. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial focused more narrowly on individuals with stenosis of arteries in the brain and was terminated early because of a high rate of adverse events in participants treated with warfarin. Both trials concluded that aspirin is equivalent to warfarin for reducing the risk of stroke in people without AF.

Medication for Subarachnoid Hemorrhage

The drug nimodipine is used to treat cerebral vasospasm, a complication that sometimes follows subarachnoid hemorrhage. This refers to a constriction of blood vessels in the brain that can significantly reduce blood flow, leading to ischemia and infarction. Although its precise origins are unclear, cerebral vasospasm is thought to be triggered in part by an influx of calcium into the smooth muscles that control blood vessel diameter. Nimodipine is a calcium antagonist, meaning that it works by blocking the entry of calcium into cells. Nimodipine has been shown to reduce infarction and improve outcome in individuals with subarachnoid hemorrhage.

Surgeries and Other Procedures

Surgery is sometimes used to clear the congested blood vessels that cause ischemic stroke or to repair the vascular abnormalities that contribute to hemorrhagic stroke.

A surgery called carotid endarterectomy involves removing plaque to widen the carotids, a pair of arteries that ascend each side of the neck and are the main suppliers of blood to the brain. Stenosis that narrows a carotid artery by more than 50 percent is considered clinically significant. In some cases, carotid stenosis is first detected after a person experiences a stroke or other symptoms, such as a TIA. It is also sometimes detected in the absence of symptoms, as when a physician presses a stethoscope to the neck and hears a bruit—a sound made by blood flowing past an obstruction. The presence of carotid stenosis can be confirmed by angiography or Doppler ultrasound.

Data from NINDS-funded research show that the risk of ischemic stroke from clinically significant asymptomatic carotid stenosis is about two to three percent per year (meaning that out of 100 individuals with this condition, two or three will have a stroke each year). The risk of ischemic stroke from clinically significant symptomatic carotid stenosis is much higher—about 25 percent during the first two years following the appearance of symptoms.

Jim, a 58 year-old businessman…

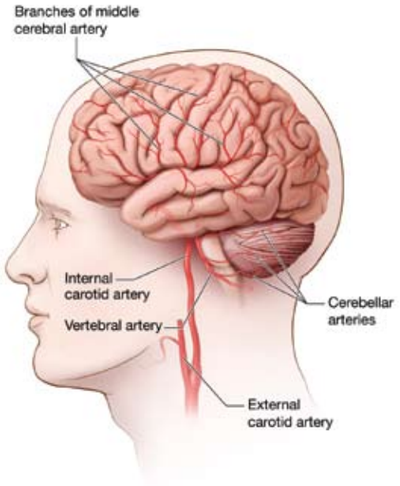
…was spending a Saturday morning preparing for a church retreat, when he was struck by a headache and a strange feeling in his throat. Thinking maybe he had strep throat, he asked his wife Judy to drive him to an urgent care center. He felt too drained to drive himself.

The urgent care doctor quickly recognized that Jim was having a stroke, and sent the couple to the nearest emergency department. On the way, Jim's speech slurred, the right side of his face drooped, and the limbs on his right side grew heavy.

At the hospital, a CT scan indicated damage to the left side of Jim's brainstem. This is the part of the brain that connects to the spinal cord, so the CT findings fit with the weakness Jim had on the right side of his body. The stroke was caused by a blood clot, but for medical reasons, Jim was not eligible for the clot-busting drug tPA.

Jim stayed under observation in intensive care for 3 days. When he was released, he could not walk or use his right hand, so he spent a month at an inpatient rehabilitation center, where he received physical and occupational therapy. When he left the center, he had little function in his right hand, but he was able to walk with a four-pronged cane.

It has been more than 7 years since Jim's stroke. He exercises regularly and can walk unassisted, but he still has trouble with his right hand. By participating in clinical research, he is receiving an experimental treatment called constraint-induced movement therapy. This involves wearing a large mitt that limits movement of his left hand, forcing him to use his right hand for daily activities. Researchers expect the therapy to be most effective within the first year after a stroke, but Jim has noticed some improvement. Although writing and eating remain easier with his left hand, he can do both with his right. He continues to be very active at church and in his community.



The carotid and vertebral arteries ascend through the neck and divide into branches that supply blood to different parts of the brain.

NINDS-supported research has compared the benefits of standard medical therapy alone (treatment with aspirin, blood pressure-lowering drugs, and cholesterol-lowering drugs) with standard medical therapy plus endarterectomy for both types of carotid stenosis. The Asymptomatic Carotid Atherosclerosis Study (ACAS) found that endarterectomy cut the risk of stroke in half among individuals with asymptomatic carotid stenosis of 60 percent or greater. The NINDS North American Symptomatic Carotid Endarterectomy Trial (NASCET) found major benefits for individuals with symptomatic carotid stenosis of 70 percent or greater. Their risk of stroke over a two-year period was cut to less than 10 percent.

Endarterectomy itself is associated with a small risk of stroke because the disruption of plaque during the procedure can send emboli into the bloodstream, or cause a clot at the site of surgery. NINDS supports the investigation of an alternative procedure known as carotid artery stenting, which involves inserting a stent (a tube-like device that is made of mesh-like material) into the carotid artery. The stent is compressed until the radiologist threads it into position, and is then expanded to mechanically widen the artery. It is also equipped with a downstream "umbrella" to catch dislodged plaque. The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) is designed to compare these two procedures in individuals with symptomatic carotid stenosis.

Several techniques are used to eliminate the vascular abnormalities linked to hemorrhagic stroke, or at least to reduce the risk that they will rupture. Arteriovenous malformations (AVMs) can be surgically removed through a procedure known as surgical resection. They can also be treated non-invasively (without the need to cut into the skull) using radiosurgery or embolization. Radiosurgery involves directing a beam of radiation at the AVM, while embolization involves injecting artificial emboli (usually made of foam) into the AVM to block it off from its parent vessel.

Clipping and coiling are procedures used to treat intracerebral aneurysms. Clipping involves opening the skull and placing a clip near the aneurysm, to separate it from its parent blood vessel. In endovascular coiling, a wire topped with a detachable coil is inserted into a leg artery and threaded into the aneurysm. Once in place, the coil is released into the aneurysm, where it stimulates blood clotting and strengthens the blood vessel wall. Stents are also used in some cases to divert blood flow away from an aneurysm.

Rehabilitation

Stroke rehabilitation includes physical therapy and other approaches intended to help individuals achieve long-term recovery from stroke. Physical therapy involves using exercises to restore movement and coordination. Many people also receive occupational therapy, which focuses on improving daily activities such as eating, drinking, dressing, bathing, reading, and writing. Speech therapy may help people who have problems producing or understanding speech. Finally, since depression, anxiety, and social isolation are common among individuals who have had a stroke, the potential benefits of psychological or psychiatric treatment should be considered.

Importantly, the goal of rehabilitation is not simply for the individual to cope with disability, but to relearn skills that have been lost. This relearning is made possible by the brain's plasticity—its ability to reorganize itself by forming new connections between neurons. Plasticity soars in the developing brain and wanes as the brain matures, but even the aged brain appears to retain some plasticity and thus some capacity to repair itself after a stroke.

Basic research on the brain has shown that the most active neural connections tend to become stronger while the quietest connections tend to weaken until they disappear. Inspired by these findings, researchers are testing a few innovative techniques that follow a "use it or lose it" approach to stroke rehabilitation.

One technique, called constraint-induced movement therapy (CIMT), focuses on improving upper limb function in people with stroke who are affected by hemiparesis (weakening on one side of the body). It involves constant restraint of the unaffected hand and arm with a mitt shaped like a boxing glove, so that the person is forced to use the affected hand and arm for daily activities. Meanwhile, the person receives regular training sessions to exercise the weakened arm. In the Extremity Constraint Induced Therapy Evaluation (EXCITE) trial, funded by NINDS and NICHD, individuals who experienced a hemiparetic stroke in the prior three to nine months received either CIMT for just two weeks or customary care, ranging from no treatment to standard physical therapy. Those who received CIMT were more likely to show improvement after one year, and much of this improvement was sustained even after two years. The Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (I-CARE) trial is testing the efficacy of CIMT combined with task-specific training and 30 hours of one-on-one therapy within one to three months after a stroke.

Another technique involves using a body weight-supported treadmill (BWST) to help people who have trouble walking. Individuals walk on a treadmill while being supported by an overhead harness, which protects them from falling and allows them to concentrate on coordination and speed. Recently, investigators have begun to combine BWST training with "overground" training, where individuals immediately practice what they have learned on the treadmill by walking with assistance and encouragement from a physical therapist. In the Locomotor Experience Applied Post-Stroke (LEAPS) trial, NINDS-funded investigators will compare outcomes at one year in people who receive either standard physical therapy or a program of BWST training plus overground training.

5. Research and Hope for the Future

Scientists continue to investigate ways to better understand, diagnose, and treat stroke. Much of this research is conducted by the stroke community at the NIH or through research grants to academic centers throughout the United States.

Prevention

Genetic Risk Factors

In an effort to make stroke prevention more effective and more personalized, NINDS is supporting research to identify additional risk factors (including genetic factors) involved in stroke. Several rare inherited disorders cause an unusual predisposition toward stroke. With an eye toward finding disease-specific treatments and gaining general insights into stroke, scientists have begun to hunt down the responsible genes.

For instance, a rare disorder called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) may offer clues to the mechanisms behind ischemic stroke. Younger individuals with CADASIL typically experience migraine that is accompanied by an increased sensitivity to light or sound, while older people experience TIAs and ischemic strokes. Researchers have traced the disease to mutations in the Notch3 gene, which encodes a protein on the surface of the smooth muscle cells that line blood vessels. Notch proteins, of which there are many, are also receptors for signals that guide cellular movements during embryonic development. Several researchers supported by NINDS are studying Notch function in the adult brain.

An alternative to studying rare genetic diseases that dramatically affect stroke risk is to search for common genetic variations that have more subtle effects—typically single-letter changes in the DNA code (or genome) called single nucleotide polymorphisms (SNPs). In a genome-wide association study, researchers scan the genome of thousands of individuals, some who have a disease and some who do not, to determine if any SNPs are more common in people with the disease.

In 2003, researchers completed a genome-wide association study of stroke in Iceland, where extensive genealogical records make it easier to trace genetic inheritance patterns. They reported that ischemic stroke was associated with variation in the phosphodiesterase-4D (PDE4D) gene. A recent study of about 500 American women (funded in part by NINDS) found that some variations in PDE4D increase the risk of ischemic stroke in women ages 15-49, and that the risk is further magnified by cigarette smoking. In other populations, researchers have failed to find a link between PDE4D and stroke.

More recently, researchers supported by NINDS found an association between intracranial aneurysms and SNPs located near genes on chromosomes 2, 8, and 9. The chromosome 9 gene, Sox 17, was already known to be required for proper development of blood vessels in laboratory animals, so it makes sense that this gene appears to affect the risk of aneurysm formation. Clinical tests for variations in Sox 17 and other genes might be used to predict a person's risk of developing an intracranial aneurysm.

There is evidence that clinical testing for SNPs might be useful for guiding preventative care in people who are already known to be at risk for stroke. For example, although it is known that children and adults with sickle cell disease are at high risk for stroke, it is not clear why some people with the disease experience strokes at an earlier age and with greater frequency. Researchers supported in part by NINDS have

NIH-Supported Resources for Human Genetic Research

- **The International HapMap is creating a catalog of SNPs and haplotypes (sets of associated SNPs) in different populations. This catalog is expected to contain up to 10 million SNPs upon completion, and is used by researchers to design genome-wide association studies.**
- **The NINDS Human Genetics Repository houses samples of DNA and cells that have been donated by individuals for use in genetic studies.**
- **The NIH Neuroscience Microarray Consortium provides researchers with services such as SNP genotyping and gene expression profiling (examining when and where specific genes are active in the body). It is funded by the NIH Neuroscience Blueprint, a joint effort among 16 subdivisions of NIH, including NINDS.**

Stroke Therapy Gets Cooler

Fever is a frequent complication of stroke and a predictor of poor outcome, so measures to bring body temperature to a normal level (about 37.5°C) are common in acute stroke care. Recently though, scientists have begun to explore whether hypothermia (cooling the body below its normal temperature) might have neuroprotective effects against stroke.

Many people have heard stories of children who drowned in icy cold water and recovered with surprisingly little neurological impairment. This recovery is possible (at least in part) in hypothermia because the brain slows its metabolic rate and consumes less energy. In the 1950s, scientists began investigating whether controlled hypothermia could prevent the neurological damage associated with severe cardiac arrest. Unfortunately, these early studies tested extreme reductions in body temperature and found a high rate of dangerous side effects. In 2002, however, two studies showed that mild to moderate hypothermia (32-36°C), which was induced with a cooling blanket in one study and ice packs in the other, led to improved neurological outcome after cardiac arrest.

Animal studies suggest that hypothermia not only helps the brain resist ischemia, but may directly inhibit other harmful reactions that occur during stroke, including excitotoxicity and reperfusion injury. A trial supported by the NINDS SPOTRIAS program will test whether hypothermia offers enough protection against stroke to extend tPA's effective time window to six hours after onset.

Several rare inherited disorders cause an unusual predisposition toward stroke. With an eye toward finding disease-specific treatments and gaining general insights into stroke, scientists have begun to hunt down the responsible genes.

found several SNPs in different genes that modify the risk of stroke associated with sickle cell disease. Thus, testing for these SNPs could be used to identify people with sickle cell disease who are at highest risk for stroke, and to provide them with early therapeutic intervention.

Finally, genetic testing might be useful for predicting how different people will respond to different stroke therapies. For example, because people metabolize warfarin at different rates, it is difficult to determine optimal dosing of the drug, which could cause severe bleeding if given in excess. Traditionally, physicians have had to estimate the initial dose based on a formula that includes the individual's age, blood pressure, and other factors, and then adjust the dose through trial and error. It is now known that certain variants in two genes, CYP2C9 and VKORC1, cause increased sensitivity to warfarin. Taking these variations into account and plugging them into the traditional formula appear to predict an optimal warfarin dosage with greater accuracy.

Biomarkers

In recent years, other risk factors have emerged that might be more appropriately called biomarkers. These are changes in the body (for example, changes in blood chemistry or gene expression) that indicate an ongoing disease process or a risk of disease but do not necessarily play causative roles in the disease.

In the late 1990s, for example, many studies (including the Framingham study) found an association between stroke and elevated blood levels of homocysteine, a relative of the amino acids the body uses to make proteins. Homocysteine levels tend to rise in people who consume inadequate amounts of the vitamins B_{12} and B_9 (folate), which are needed to convert homocysteine into useful amino acids. It is unclear whether elevated homocysteine plays a causative role in stroke or is just an innocent bystander. The NINDS Vitamin Intervention for Stroke Prevention (VISP) trial found that vitamin supplementation leading to modest reductions in homocysteine did not reduce the risk of recurrent stroke over a two-year period. It remains possible that B vitamin supplements are beneficial over a longer period or in people with no history of stroke.

Researchers also have discovered several biomarkers of advanced atherosclerosis that could be used to identify people in danger of stroke. For example, elevated levels of two proteins in the blood, C-reactive protein and phospholipase A_2, are associated with atherosclerosis and increased risk of stroke. Irregularities in the appearance of atherosclerotic plaques, observed by high-resolution ultrasound, are also tied to higher stroke risk.

Combination Therapies for Stroke Prevention

Many people at risk for stroke take multiple preventative medications, including antiplatelet drugs, ACE inhibitors, and/or statins. In 2006, NINDS-supported researchers completed the first study to explore whether using these three drugs in combination is more beneficial than using just one or two of them. The researchers examined the medication history and tracked the outcomes of more than 200 individuals who sought care within 24 hours of an ischemic stroke. Individuals taking all three drugs had strokes that were less severe, based on symptoms measured by the NIH Stroke Scale and on MRI scans showing they had less at-risk tissue surrounding the damaged regions of their brains. Individuals on triple therapy also had shorter hospital stays and better function at hospital discharge. Although these data are preliminary, they highlight the possibility of improving stroke outcomes by targeting multiple risk factors.

Acute Stroke and Post-Stroke Therapy

Better Thrombolysis in Ischemic Stroke

Although tens of thousands of people benefit from tPA each year, this represents only a small fraction of people affected by ischemic stroke. The use of tPA is limited by concerns that it could cause hemorrhage and many hospitals lack the infrastructure required to treat individuals within tPA's short window of efficacy. NINDS' professional outreach efforts are helping hospitals establish coordinated stroke care teams capable of rapidly delivering treatments, including tPA if warranted (see "Changing Stroke's Impact by Changing Attitudes," p. 32).

Meanwhile, research efforts are underway to reduce the risk of hemorrhage from tPA. For example, NINDS-funded investigators are testing derivatives of tPA that may carry less risk of hemorrhage. Another strategy is to tease apart tPA's destructive effect on the blood-brain barrier and identify drugs that block this effect. Along those lines, NINDS-funded studies have shown that proteins called matrix metalloproteinases (MMPs) degrade the blood-brain barrier during an acute stroke, and that treatment with tPA appears to enhance MMP activity. NINDS-funded investigators have found that tPA also increases blood-brain barrier permeability by acting through a protein called platelet-derived growth factor-CC (PDGF-CC). They showed that Gleevec©, a drug already approved for treating certain cancers, blocked PDGF-CC signaling and reduced hemorrhage in mice treated with tPA after ischemic stroke.

Research is also underway to enhance tPA's clot-busting effects and extend its window of efficacy beyond three hours. To that end, many clinical trials now include brain imaging protocols to evaluate the extent of salvageable penumbra in each individual. Researchers suspect that individuals with larger areas of salvageable brain tissue might have a better chance of benefiting from therapy delivered after the three-hour mark.

A strategy known as bridging therapy involves supplementing intravenous tPA (the standard means of tPA delivery) with intra-arterial tPA injected directly at the site of the clot. The NINDS Interventional Management of Stroke (IMS) study is comparing the effects of bridging therapy and standard intravenous tPA for ischemic stroke. Another strategy is to combine intravenous tPA with new generation anticoagulants and antiplatelet drugs. Clinical studies coordinated by the NINDS SPOTRIAS network are testing tPA in combination with argatroban (which inhibits the blood clotting protein thrombin) and eptifibatide (which inhibits adhesion proteins on the surface of platelets).

Innovative strategies include mechanically disrupting the clot as either a supplement or an alternative to tPA. Doppler ultrasound, the same technique used to image blood vessels and locate a clot, is being tested as a means of delivering sound waves capable of breaking apart the clot. The NINDS Combined Lysis of Thrombus in Brain Ischemia with Transcranial Ultrasound and Systemic TPA (CLOTBUST) study was a small trial that compared tPA plus ultrasound to tPA plus placebo. Results showed that individuals who received tPA plus continuous ultrasound were more likely to experience complete restoration of blood flow by two hours after the start of the procedure. In addition to sound energy, researchers have also tested light energy against acute ischemic stroke. In the placebo-controlled NeuroThera Effectiveness and Safety Trial (NEST-1), people who were ineligible to receive tPA received infrared laser light applied over the scalp. Although its mechanism is unclear, the treatment improved functional outcome when given within 24 hours of stroke onset.

Recently, the FDA approved two clot-removal devices for use in treating acute ischemic stroke. The Penumbra System involves threading a catheter through cerebral blood vessels to the site of blockage and vacuuming out the clot. Meanwhile, MERCI (Mechanical Embolus Removal in Cerebral Ischemia) is a corkscrew-like device that can be extended from the tip of a catheter and used to snare the clot and pull it out. Although both devices are effective at restoring blood flow when used within 8 hours of stroke onset, no data yet exists to indicate if their use improves outcome. The NINDS Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial is comparing MERCI to standard care within this time window.

An interruption in the brain's blood supply leads to a cascade of harmful reactions that may continue for hours to days, even after blood flow has been restored.

Controlling Blood Pressure and Blood Flow in Hemorrhagic Stroke

Hemorrhagic stroke is usually accompanied by acute hypertension. Aggressive lowering of blood pressure is sometimes used in an attempt to reduce bleeding and hematoma volume, but its value is unclear. In the NINDS Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) trial, investigators are using the drug nicardipine to lower blood pressure in individuals with acute intracerebral hemorrhage and acute hypertension. These individuals are being divided into three groups in order to test three target blood pressure levels.

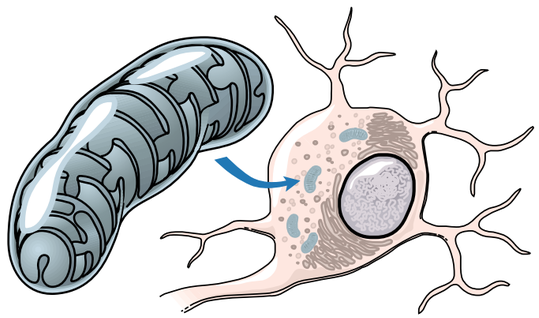
Just as anticoagulants are under study for treating acute ischemic stroke, drugs that promote coagulation are being eyed for their potential benefits against hemorrhagic stroke. Recombinant activated factor VII (rFVIIa), a modified version of a blood clotting factor, is FDA-approved to treat excessive bleeding in hemophilia. In two industry-sponsored trials, rFVIIa significantly reduced hematoma volume 24 hours after hemorrhagic stroke, but in one trial it failed to significantly reduce mortality at 90 days.

Neuroprotection

While some stroke treatments are aimed at correcting the vascular problems that cause stroke, another strategy, called neuroprotection, aims to shield neurons from the effects of stroke. An interruption in the brain's blood supply leads to a cascade of harmful reactions—mostly in the ischemic penumbra—that may continue for hours to days, even after blood flow has been restored. The most important reactions are excitotoxicity, reperfusion injury, and breakdown

of the blood-brain barrier. In recent years, thanks to an improved understanding of how these reactions unfold, researchers have begun to develop and test many neuroprotectant drugs.

Still, research on neuroprotectant drugs remains at a relatively early stage. Studies using animal models of stroke (mostly rodents) are essential to this research, just as they were for the development of tPA. In two common animal models of ischemic stroke, a string or suture is used to occlude either the carotid artery or the middle cerebral artery (a branch off of the carotid). These techniques allow researchers to carefully monitor the timing of post-stroke changes in the brain and to carefully plan the timing of therapeutic intervention. Several possible neuroprotectants have shown positive results when tested in an animal model, only to yield negative results in clinical trials. With each disappointment, however, investigators learn things that help them refine the development of candidate drugs; for example, by taking steps to eliminate drug side effects or changing the protocol for drug delivery. As in the case of tPA, there are strong indications that timing could mean everything for many neuroprotectant drugs.



Mitochondria are cellular factories that use oxygen and glucose to produce energy. When mitochondria run out of oxygen during a stroke, a chain reaction of damaging events can ensue.

Excitotoxicity and Reperfusion Injury

To understand how just a few moments of ischemia can lead to a cascade of damaging events in the brain, it is necessary to know something about how neurons extract energy from oxygen and glucose. Essential to energy production in all our cells are the mitochondria—cellular factories that use oxygen to break down glucose and convert it into the energy molecule ATP. During ischemia, mitochondrial production of ATP runs down and neurons lose control over the internal machinery that allows them to generate electrical and chemical signals.

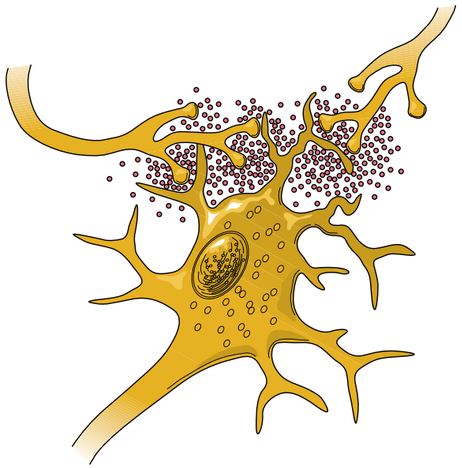
Ischemic neurons release excessive amounts of glutamate, a chemical signal (or neurotransmitter) that excites neighboring neurons. As these neurons become active and release their own glutamate, excitation builds upon itself and spreads through the brain. Inside each neuron, this wave of excitation triggers a variety of responses. It activates enzymes capable of remodeling a neuron's internal skeleton and outer membrane, and stimulates the production of oxygen-containing molecules that are capable of diffusing freely across the membrane and acting as short-lived, short-distance neurotransmitters. Although these processes are otherwise normal, the ramped-up excitation—or excitotoxicity—that accompanies stroke sends them into overdrive and causes neuronal damage. The over-excited neuron's skeleton and membrane begin to break down. Perhaps worst of all, the neuron churns out oxygen-containing free radicals, compounds that can degrade proteins, lipids, and DNA.

Meanwhile, if blood flow is successfully restored after an acute stroke, the reintroduction of oxygen to energy-starved tissues can lead to reperfusion injury. This refers to a burst in oxygen-containing free radicals that are produced when damaged mitochondria suddenly resume taking up oxygen to produce ATP.

Antioxidants, which neutralize oxygen-based free radicals, may have beneficial effects against both excitotoxicity and reperfusion injury. NINDS is supporting research to determine if individuals with acute ischemic stroke benefit from intravenous albumin, a blood protein with antioxidant properties. A pilot trial involving 80 individuals showed that albumin is safe when given within 16 hours of stroke. Results also showed that individuals treated with tPA tended to have better outcomes if they also received high-dose albumin. The Albumin in Acute Stroke (ALIAS) trial, a NETT-supported trial, has a target enrollment of nearly 900 individuals and will test the efficacy of albumin given within 5 hours of stroke, with or without tPA.

Glutamate antagonists have attracted considerable attention as a possible treatment for excitotoxicity. Most of these drugs work by blocking the interaction between glutamate and the NMDA receptor, which is a type of pore, or ion channel, which opens when glutamate attaches to it. Unfortunately, while these drugs have shown promise in the middle cerebral artery occlusion (MCAO) model of stroke, they have not been effective in individuals who have had a stroke. The likely reason is that the glutamate antagonists tested so far do not specifically target abnormal glutamate signaling. It is important to remember that while glutamate is pathologically elevated in ischemic brain tissue, it is also required for normal function in non-ischemic brain tissue. Thus, non-specific glutamate antagonists can cause serious side effects—such as hallucinations, extreme sedation, and respiratory depression—and the tolerated doses are apparently too low to suppress excitotoxicity.

To address this problem, NINDS is supporting research on a glutamate receptor blockade that is matched to the level of glutamate signaling. For example, the drug memantine is an open-channel blocker that slips into the NMDA receptor only after the receptor has already been opened by glutamate. Other glutamate antagonists under development would become active only when exposed to the slight increase in acidity that occurs in ischemic brain tissue. Finally, an innovative trial is testing if individuals who have experienced a stroke might benefit from intravenous magnesium sulfate delivered in the ambulance before they get to the hospital. Magnesium is abundant in the brain and



In a process known as excitotoxicity, neurons become damaged when nearby cells release excess levels of the chemical signal glutamate.

acts as a natural open-channel blocker of the NMDA receptor. In the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial, investigators hope to boost this natural blockade during the first few hours after stroke. A pilot trial showed that paramedics were able to deliver magnesium sulfate to 70 percent of individuals within two hours of onset, a finding that has positive implications for emergency stroke care in general.

Breakdown of the Blood-Brain Barrier

A hemorrhagic stroke necessarily tears open the blood-barrier barrier. But even an ischemic stroke can damage the blood-brain barrier, through reperfusion injury or other reactions. The barrier is composed of tightly interlocked endothelial cells within the blood vessel wall, surrounded by a dense meshwork of proteins, known as an extracellular matrix. During acute stroke, endothelial cells appear to release MMPs, which are protein-degrading enzymes that eat away at this extracellular matrix. (For more information, see "Better Thrombolysis in Ischemic Stroke" on p. 23.)

NINDS-funded research has led to an evolving view about the role of MMPs in stroke. Early studies on animal models confirmed that MMPs help destroy the blood-brain barrier during acute stroke, but more recent studies show that by several days after a stroke, the activity of MMPs might actually help repair damaged neurons and blood vessels. In this late phase, MMPs appear to liberate growth factors that are trapped in the extracellular matrix. Thus, researchers envision drugs that could be used to carefully adjust the activity of MMPs—first downward and then upward—in order to improve recovery from stroke.

Other Targets for Neuroprotection

Inflammation

Inflammation occurs when immune cells, or leukocytes, mobilize to an injured part of the body to clean up dead and dying cells. When a blood clot or hemorrhage occurs somewhere in the brain's vascular system, leukocytes accumulate at that site and invade the brain through openings in the blood-brain barrier. The first leukocytes to arrive release cytokines, which are chemicals that modulate the activity of other inflammatory cells. Some of these cytokines attract cells called macrophages (literally "big eaters"), which engulf and break down cellular debris.

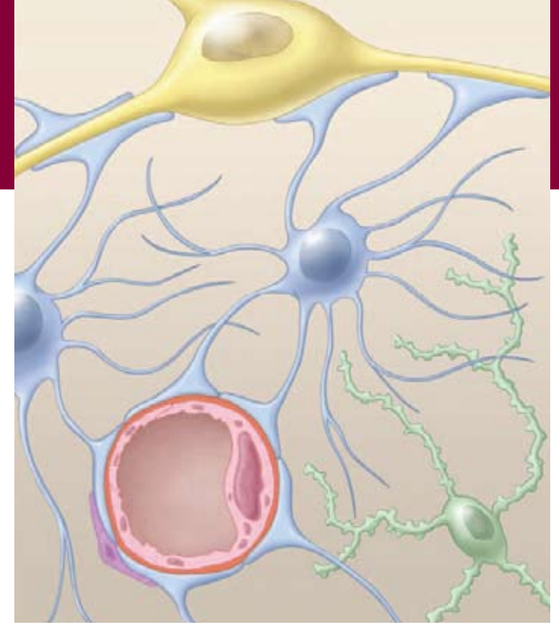
How much inflammation contributes to long-term damage after stroke is an open question; like other responses to stroke, certain types of inflammatory responses at the right time might even be beneficial. Still, one study showed that the anti-inflammatory cytokine interferon-beta stabilized the blood-brain barrier and reduced the size of the infarct when given to rats up to 6 hours following MCAO. Interferon-beta is already an FDA-approved treatment for multiple sclerosis. NINDS is supporting a clinical trial to assess the drug's safety in individuals with acute ischemic stroke.

Apoptosis and the Alzheimer's Connection

As neurons in the core of an ischemic infarct lose their ability to produce ATP, they undergo necrosis, the cellular equivalent of accidental death. In the ischemic penumbra, however, the buildup of free radicals may trigger a form of cell suicide known as apoptosis. An apoptotic cell activates protein-cutting enzymes called caspases that disassemble the cell's working parts. NINDS-funded investigators have shown that in the MCAO model of ischemic stroke, caspases become activated within 9 hours, and caspase inhibitors reduce the spread of ischemic injury during this time.

Apoptosis and the activation of caspases have also been implicated in Alzheimer's disease (AD). As researchers learn more about the role of apoptosis in AD, they are finding other connections between AD and stroke. Apoptosis is associated with increased activity of two enzymes known to generate beta-amyloid, which is the toxic protein fragment that accumulates in the brain during AD. Recent studies show that these enzymes, called beta- and gamma-secretase, are also activated after MCAO in rodents. These findings have led to the idea that abnormal blood flow might be a precipitating event for AD.

Researchers envision someday using drugs that could be used to carefully adjust the activity of matrix metalloproteinases (MMPs) in order to improve recovery from stroke.



The neurovascular unit consists of neurons (yellow), the blood vessels that supply them (pink), astrocytes (blue) and possibly other types of glial cells (green). By virtue of their contacts with neurons and blood vessels, astrocytes help match cerebral blood flow to neuronal energy demands.

Astrocytes and the Neurovascular Unit

Neurons may be the workhorses of the brain, but they are far outnumbered by glia. While these cells once were considered mere structural support in the brain (glia is Greek for "glue"), they actually serve important functions. Oligodendrocytes, for example, form sheaths that insulate the electrical signals relayed by neurons. Astrocytes, so named because they form branches that give them a star-like shape, are perhaps the most versatile type of glia and

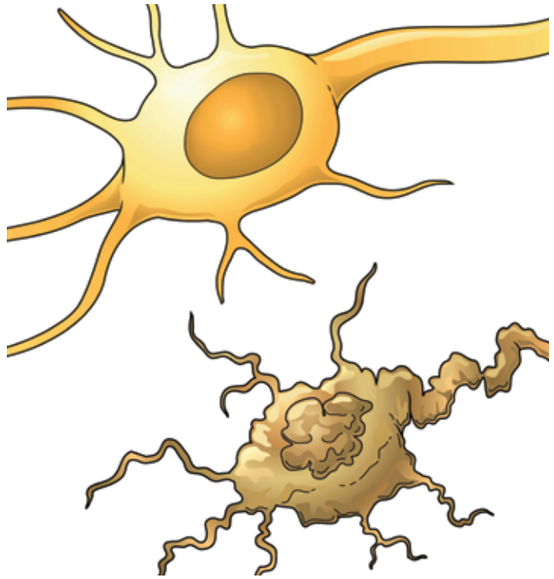
the most relevant to stroke. The branches of astrocytes make contact with neurons and with the endothelial cells of blood vessels. Together, these cell types form a structure recently named the neurovascular unit.

Stroke researchers have begun to direct more attention toward astrocytes and how they interact with other parts of the neurovascular unit. Thanks to their close contact with blood vessels, astrocytes appear able to regulate cerebral blood flow, helping match the delivery of blood to the activity and energy demands of different brain regions. Scientists hypothesize that a breakdown of cerebral blood flow regulation not only increases the risk of stroke, but might increase the risk of AD by impairing the clearance of beta-amyloid from the brain.

Astrocytes are able to store glucose, which probably allows them to serve as a reserve energy source for neurons. They are also capable of taking up glutamate and potentially "buffering" the effects of excitotoxicity. Finally, after stroke and other injuries to the brain, astrocytes enlarge, undergo shape changes, and begin producing signals that stimulate inflammation, a response called reactive astrocytosis. All of these properties have researchers looking at astrocytes as a possible target for neuroprotective drugs.

Neural Stem Cells

adult brain could not generate new neurons. It is now known that neural stem cells—the cells that build the embryonic brain—persist in pockets deep within the adult brain. Following stroke and other injuries, these cells make a weak attempt to replace neurons that have been lost. In rodents, stroke by MCAO leads to the birth of new neurons (called neurogenesis) and their migration to damaged brain regions, although most of the newly born neurons fail to survive long-term. Fortunately, as scientists learn more about this repair response, they are discovering possible ways to enhance it. For example, investigators funded by NINDS have found that astrocytes and endothelial cells provide neurons with a physical scaffold for migration, and that they release proteins that stimulate neuronal birth, migration, and survival. Delivering these neurotrophic proteins in the right combination at the right time might boost the survival of newborn neurons and of mature, damaged neurons that are struggling to stay alive.



After a stroke, neurons may undergo a type of cell suicide known as apoptosis, dismantling their internal machinery and even breaking down their DNA.

Transplantation of neural stem cells themselves also offers the possibility to repair damage caused by stroke. A few studies supported by NINDS have explored stem cell transplantation in rodent models of stroke, each using distinct strategies to increase the likelihood that the transplanted cells would reach the damaged parts of the brain and become functional neurons. In one study, mouse embryonic stem cells were primed to become neurons using genetic engineering, and then injected directly into the mouse brain one day after stroke. In another study, stem cells were isolated from the developing mouse brain, pre-sorted for a cell surface protein that helps them migrate through the extracellular matrix, and then injected into the carotid artery two days after stroke. A third study involved injecting human bone marrow stem cells into the rat carotid artery one day after stroke. In all three studies, some of the injected stem cells migrated to damaged parts of the brain and took on characteristics of neurons or glia. Moreover, all three studies found functional improvements in the treated rodents, some even lasting up to one year in the bone marrow study. Many issues remain to be resolved before stem cell transplants can move to clinical trials in individuals with acute stroke, including the site and timing of injection, how to track the fate of the cells after injection, and the type of cell most likely to yield benefit. Ever-present are concerns that transplanted stem cells could be destroyed by the body's immune defenses, or that they could divide uncontrollably and form tumors.

6. Changing Stroke's Impact by Changing Attitudes

As late as the 1950s, stroke treatment and prevention were almost non-existent. There were no medications for acute stroke and surgeries were still very experimental. Moreover, with very little knowledge about stroke risk factors, there was no basis for primary or secondary prevention. Mary Lasker, a health advocate and a powerful force behind the establishment of NINDS in 1950, once said that at the time, "Whether you recovered or not was really largely by chance."

NINDS has supported a variety of outreach efforts since the early 1990s to translate gains in research into gains in public health. In 1995, a NINDS-funded survey of about 20,000 households in and around Cincinnati, Ohio found that 68 percent of respondents could name one modifiable stroke risk factor and that 25 percent could name two (where the correct responses included hypertension, smoking, heart disease, diabetes, high cholesterol, and prior stroke or TIA). When the survey was repeated in 2000, 72 percent of respondents could name one risk factor and 32 percent could name two—a small but significant improvement.

Results from those surveys also suggest that people are getting better at recognizing the five common symptoms of stroke (see "Stroke Basics," p. 3), knowledge that could help save lives by reducing delays in treatment. In 1995, 57 percent of respondents could name at least one stroke warning sign, but by 2000, that number had increased to 70 percent.

Recognizing that lack of awareness about stroke remains a barrier to effective treatment, in May 2001, NINDS launched its *Know Stroke* campaign (www.stroke.nih.gov) to educate the public about stroke symptoms and risk factors, and emphasize the importance of treating stroke as a medical emergency. The campaign has produced a stroke education kit and multiple publications that are available in both English and Spanish. The *Know Stroke in the Community* campaign, launched in partnership between NINDS and the Centers for Disease Control and Prevention in 2004, recruits "Stroke Champions" who are trained to use these educational materials within their communities.

NINDS recognizes that providing resources and education for the medical profession is just as important as reaching out to the public at large. Although NINDS originally developed the NIH Stroke Scale in the early 1990s as a tool for evaluating people with stroke in clinical trials, the Scale's utility in clinical practice quickly became apparent. (For more information, see "Stroke Diagnostics and Brain Imaging," p. 7.) NINDS now links to an online version of the Scale, and offers an interactive DVD that provides simple instructions and case studies illustrating its use.

NINDS also supports efforts to provide hospitals with the organization they need to rapidly triage and treat people who have experienced a stroke. One lesson learned from tPA is that hospitals cannot put the best stroke treatments into practice unless they are capable of rapid case management. When tPA was approved in 1996, most hospitals were not equipped to utilize it within its short window of efficacy and, by 2000, only about one to two percent of individuals with acute ischemic stroke were receiving it nationwide.

That same year, the Brain Attack Coalition (BAC), a partnership that includes NINDS, several medical societies, and patient advocacy groups, developed a set of recommendations for establishing primary stroke centers. These are hospitals that are capable of providing emergency care for individuals with acute stroke. The recommendations emphasize creating an acute stroke team that is available around the clock and includes physicians, nurses, paramedics, and emergency department staff, with at least one physician who is an expert in cerebrovascular disease. The recommendations also call for rapid access to blood tests, brain imaging, and neurosurgery. The Joint Commission and many state health departments now use the recommendations to certify and evaluate primary stroke centers across the country.

Meanwhile, the SPOTRIAS and NETT programs create an infrastructure for acute stroke care at participating medical centers by supporting clinical testing of acute stroke therapies.

The number of individuals with ischemic stroke who receive tPA nationally remains at one to two percent. However, the experience at certified stroke centers and SPOTRIAS centers has shown that it is possible to improve an individual's access to tPA with a coordinated stroke team in place. Stroke centers designated by the state of New York (using BAC guidelines) treat more individuals with ischemic stroke with tPA and deliver it faster than nondesignated hospitals in the state. Similarly, Joint Commission-certified primary stroke centers have reported higher rates of tPA use after their certification. Finally, NINDS SPOTRIAS centers have reported that up to 15 percent of individuals with ischemic stroke are treated with tPA.

As more stroke therapies emerge from the research pipeline, NINDS will continue to support efforts to ensure that clinicians are well-equipped to implement them.

CREDITS:

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