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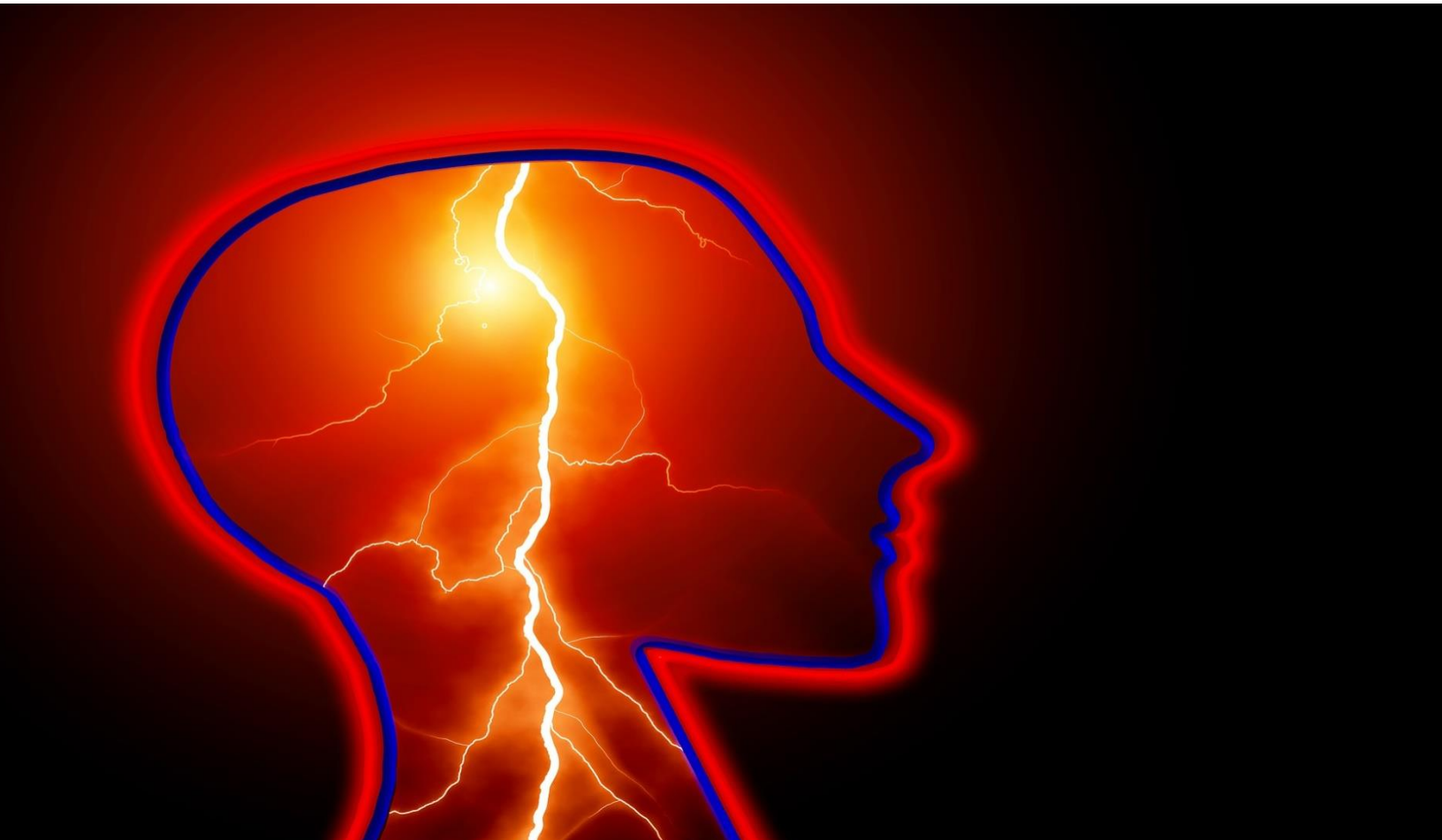
Stroke – Hope Through Research



Introduction

More than 2,400 years ago the father of medicine, Hippocrates, recognized and described stroke-the sudden onset of paralysis. Until recently, modern medicine has had very little power over this disease, but the world of stroke medicine is changing and new and better therapies are being developed every day. Today, some people who have a stroke can walk away from the attack with no or few disabilities *if they are treated promptly*. Doctors can finally offer stroke patients and their families the one thing that until now has been so hard to give: hope.

In ancient times stroke was called *apoplexy*,* a general term that physicians applied to anyone suddenly struck down with paralysis. Because many conditions can lead to sudden paralysis, the term apoplexy did not indicate a specific diagnosis or cause. Physicians knew very little about the cause of stroke and the only established therapy was to feed and care for the patient until the attack ran its course.

The first person to investigate the pathological signs of apoplexy was Johann Jacob Wepfer. Born in Schaffhausen, Switzerland, in 1620, Wepfer studied medicine and was the first to identify postmortem signs of bleeding in the brains of patients who died of apoplexy. From autopsy studies he gained knowledge of the *carotid* and *vertebral arteries* that supply the brain with blood. He also was the first person to suggest that apoplexy, in addition to being caused by bleeding in the brain, could be caused by a blockage of one of the main arteries supplying blood to the brain; thus stroke became known as a *cerebrovascular disease* ("cerebro" refers to a part of the brain; "vascular" refers to the blood vessels and arteries).

Medical science would eventually confirm Wepfer's hypotheses, but until very recently doctors could offer little in the area of therapy. Over the last two decades basic and clinical investigators, many of them sponsored and funded in part by the National Institute of Neurological Disorders and Stroke (NINDS), have learned a great deal about stroke. They have identified major risk factors for the disease and have developed surgical techniques and drug treatments for the prevention of stroke. But perhaps the most exciting new development in the field of stroke research is the recent approval of a drug treatment that can reverse the course of stroke if given during the first few hours after the onset of symptoms.

Studies with animals have shown that brain injury occurs within minutes of a stroke and can become irreversible within as little as an hour. In humans, brain damage begins from the moment the stroke starts and often continues for days afterward. Scientists now know that there is a very short window of opportunity for treatment of the most common form of stroke. Because of these and other advances in the field of cerebrovascular disease stroke patients now have a chance for survival and recovery.

* Terms in Italics are defined in the glossary.

Cost of Stroke to the United States

- total cost of stroke to the United States: estimated at about $43 billion / year
- direct costs for medical care and therapy: estimated at about $28 billion / year
- indirect costs from lost productivity and other factors: estimated at about $15 million / year
- average cost of care for a patient up to 90 days after a stroke: $15,000*
- for 10% of patients, cost of care for the first 90 days after a stroke: $35,000*
- percentage of direct cost of care for the first 90 days*:

initial hospitalization = 43%
rehabilitation = 16%
physician costs = 14%
hospital readmission = 14%
medications and other expenses = 13%

What is Stroke?

A stroke occurs when the blood supply to part of the brain is suddenly interrupted or when a blood vessel in the brain bursts, spilling blood into the spaces surrounding brain cells. In the same way that a person suffering a loss of blood flow to the heart is said to be having a heart attack, a person with a loss of blood flow to the brain or sudden bleeding in the brain can be said to be having a "brain attack."

Brain cells die when they no longer receive oxygen and nutrients from the blood or when they are damaged by sudden bleeding into or around the brain. *Ischemia* is the term used to describe the loss of oxygen and nutrients for brain cells when there is inadequate blood flow. Ischemia ultimately leads to *infarction*, the death of brain cells which are eventually replaced by a fluid-filled cavity (or *infarct*) in the injured brain.

When blood flow to the brain is interrupted, some brain cells die immediately, while others remain at risk for death. These damaged cells make up the *ischemic penumbra* and can linger in a compromised state for several hours. With timely treatment these cells can be saved. The ischemic penumbra is discussed in more detail in the **Appendix**.

Even though a stroke occurs in the unseen reaches of the brain, the symptoms of a stroke are easy to spot. They include sudden numbness or weakness, especially on one side of the body; sudden confusion or trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, or loss of balance or coordination; or sudden severe headache with no known cause. All of the symptoms of stroke appear **suddenly**, and often there is more than one symptom at the same time. Therefore stroke can usually be distinguished from other causes of dizziness or headache. These symptoms may indicate that a stroke has occurred and that medical attention is needed immediately.

There are two forms of stroke: *ischemic* - blockage of a blood vessel supplying the brain, and *hemorrhagic* - bleeding into or around the brain. The following sections describe these forms in detail.

Ischemic Stroke

An ischemic stroke occurs when an artery supplying the brain with blood becomes blocked, suddenly decreasing or stopping blood flow and ultimately causing a brain infarction. This type of stroke accounts for approximately 80 percent of all strokes. Blood clots are the most common cause of artery blockage and brain infarction. The process of clotting is necessary and beneficial throughout the body because it stops bleeding and allows repair of damaged areas of arteries or veins. However, when blood clots develop in the wrong place within an artery they can cause devastating injury by interfering with the normal flow of blood. Problems with clotting become more frequent as people age.

Blood clots can cause ischemia and infarction in two ways. A clot that forms in a part of the body other than the brain can travel through blood vessels and become wedged in a brain artery. This free-roaming clot is called an *embolus* and often forms in the heart. A stroke caused by an embolus is called an *embolic stroke*. The second kind of ischemic stroke, called a *thrombotic stroke*, is caused by *thrombosis*, the formation of a blood clot in one of the cerebral arteries that stays attached to the artery wall until it grows large enough to block blood flow.

Ischemic strokes can also be caused by ***stenosis***, or a narrowing of the artery due to the buildup of *plaque* (a mixture of fatty substances, including *cholesterol* and other lipids) and blood clots along the artery wall. Stenosis can occur in large arteries and small arteries and is therefore called *large vessel disease* or *small vessel disease*, respectively. When a stroke occurs due to small vessel disease, a very small infarction results, sometimes called a *lacunar infarction*, from the French word "lacune" meaning "gap" or "cavity."

The most common blood vessel disease that causes stenosis is *atherosclerosis*. In atherosclerosis, deposits of plaque build up along the inner walls of large and medium-sized arteries, causing thickening, hardening, and loss of elasticity of artery walls and decreased blood flow. The role of cholesterol and blood lipids with respect to stroke risk is discussed in the section on cholesterol under "**Who is at Risk for Stroke?**".

Hemorrhagic Stroke

In a healthy, functioning brain, neurons do not come into direct contact with blood. The vital oxygen and nutrients the neurons need from the blood come to the neurons across the thin walls of the cerebral capillaries. The glia (nervous system cells that support and protect neurons) form a *blood-brain barrier*, an elaborate meshwork that surrounds blood vessels and capillaries and regulates which elements of the blood can pass through to the neurons.

When an artery in the brain bursts, blood spews out into the surrounding tissue and upsets not only the blood supply but the delicate chemical balance neurons require to function. This is called a hemorrhagic stroke. Such strokes account for approximately 20 percent of all strokes.

Hemorrhage can occur in several ways. One common cause is a bleeding *aneurysm,* a weak or thin spot on an artery wall. Over time, these weak spots stretch or balloon out under high arterial pressure. The thin walls of these ballooning aneurysms can rupture and spill blood into the space surrounding brain cells.

Hemorrhage also occurs when arterial walls break open. Plaque-encrusted artery walls eventually lose their elasticity and become brittle and thin, prone to cracking. *Hypertension*, or *high blood pressure*, increases the risk that a brittle artery wall will give way and release blood into the surrounding brain tissue.

A person with an *arteriovenous malformation (AVM)* also has an increased risk of hemorrhagic stroke. AVMs are a tangle of defective blood vessels and capillaries within the brain that have thin walls and can therefore rupture.

Bleeding from ruptured brain arteries can either go into the substance of the brain or into the various spaces surrounding the brain. *Intracerebral hemorrhage* occurs when a vessel within the brain leaks blood into the brain itself. *Subarachnoid hemorrhage* is bleeding under the meninges, or outer membranes, of the brain into the thin fluid-filled space that surrounds the brain.

The subarachnoid space separates the arachnoid membrane from the underlying pia mater membrane. It contains a clear fluid (*cerebrospinal fluid* or *CSF*) as well as the small blood vessels that supply the outer surface of the brain. In a subarachnoid hemorrhage, one of the small arteries within the subarachnoid space bursts, flooding the area with blood and contaminating the cerebrospinal fluid. Since the CSF flows throughout the cranium, within the spaces of the brain, subarachnoid hemorrhage can lead to extensive damage throughout the brain. In fact, subarachnoid hemorrhage is the most deadly of all strokes.

Transient Ischemic Attacks

A *transient ischemic attack* (TIA), sometimes called a mini-stroke, starts just like a stroke but then resolves leaving no noticeable symptoms or deficits. The occurrence of a TIA is a warning that the person is at risk for a more serious and debilitating stroke. Of the approximately 50,000 Americans who have a TIA each year, about one-third will have an *acute stroke* sometime in the future. The addition of other risk factors compounds a person's risk for a recurrent stroke. The average duration of a TIA is a few minutes. For almost all TIAs, the symptoms go away within an hour. There is no way to tell whether symptoms will be just a TIA or persist and lead to death or disability. The patient should assume that all stroke symptoms signal an emergency and should not wait to see if they go away.

Recurrent Stroke

Recurrent stroke is frequent; about 25 percent of people who recover from their first stroke will have another stroke within 5 years. Recurrent stroke is a major contributor to stroke disability and death, with the risk of severe disability or death from stroke increasing with each stroke recurrence. The risk of a recurrent stroke is greatest right after a stroke, with the risk decreasing with time. About 3 percent of stroke patients will have another stroke within 30 days of their first stroke and one-third of recurrent strokes take place within 2 years of the first stroke.

How Do You Recognize Stroke?

Symptoms of stroke appear suddenly. Watch for these symptoms and be prepared to act quickly for yourself or on behalf of someone you are with:

- Sudden numbness or weakness of the face, arm, or leg, especially on one side of the body.
- Sudden confusion, trouble talking, 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.

If you suspect you or someone you know is experiencing any of these symptoms indicative of a stroke, ***do not wait. Call 911 emergency immediately.*** There are now effective therapies for stroke that must be administered at a hospital, but they lose their effectiveness if not given within the first 3 hours after stroke symptoms appear. ***Every minute counts!***

How is the Cause of Stroke Determined?

Physicians have several diagnostic techniques and imaging tools to help diagnose the cause of stroke quickly and accurately. The first step in diagnosis is a short neurological examination. When a possible stroke patient arrives at a hospital, a health care professional, usually a doctor or nurse, will ask the patient or a companion what happened and when the symptoms began. Blood tests, an electrocardiogram, and a brain scan, such CT or MRI, will often be done. One test that helps doctors judge the severity of a stroke is the standardized NIH Stroke Scale, developed by the NINDS. Health care professionals use the NIH Stroke Scale to measure a patient's neurological deficits by asking the patient to answer questions and to perform several physical and mental tests. Other scales include the Glasgow Coma Scale, the Hunt and Hess Scale, the Modified Rankin Scale, and the Barthel Index.

Imaging for the Diagnosis of Acute Stroke

Health care professionals also use a variety of imaging devices to evaluate stroke patients. The most widely used imaging procedure is the *computed*

tomography (CT) scan. Also known as a CAT scan or computed axial tomography, CT creates a series of cross-sectional images of the head and brain. Because it is readily available at all hours at most major hospitals and produces images quickly, CT is the most commonly used diagnostic technique for acute stroke. CT also has unique diagnostic benefits. It will quickly rule out a hemorrhage, can occasionally show a tumor that might mimic a stroke, and may even show evidence of early infarction. Infarctions generally show up on a CT scan about 6 to 8 hours after the start of stroke symptoms.

If a stroke is caused by hemorrhage, a CT can show evidence of bleeding into the brain almost immediately after stroke symptoms appear. Hemorrhage is the primary reason for avoiding certain drug treatments for stroke, such as thrombolytic therapy, the only proven acute stroke therapy for ischemic stroke (*see* section on "What Stroke Therapies are Available?"). Thrombolytic therapy cannot be used until the doctor can confidently diagnose the patient as suffering from an ischemic stroke because this treatment might increase bleeding and could make a hemorrhagic stroke worse.

Another imaging device used for stroke patients is the *magnetic resonance imaging (MRI) scan.* MRI uses magnetic fields to detect subtle changes in brain tissue content. One effect of stroke is the slowing of water movement, called *diffusion*, through the damaged brain tissue. MRI can show this type of damage within the first hour after the stroke symptoms start. The benefit of MRI over a CT scan is more accurate and earlier diagnosis of infarction, especially for smaller strokes, while showing equivalent accuracy in determining when hemorrhage is present. MRI is more sensitive than CT for other types of brain disease, such as brain tumor, that might mimic a stroke. MRI cannot be performed in patients with certain types of metallic or electronic implants, such as pacemakers for the heart.

Although increasingly used in the emergency diagnosis of stroke, MRI is not immediately available at all hours in most hospitals, where CT is used for acute stroke diagnosis. Also, MRI takes longer to perform than CT, and may not be performed if it would significantly delay treatment.

Other types of MRI scans, often used for the diagnosis of cerebrovascular disease and to predict the risk of stroke, are *magnetic resonance angiography (MRA)* and *functional magnetic resonance imaging (fMRI)*. Neurosurgeons use MRA to detect stenosis (blockage) of the brain arteries inside the skull by mapping flowing blood. Functional MRI uses a magnet to pick up signals from oxygenated blood and can show brain activity through increases in local blood flow. *Duplex Doppler ultrasound* and *arteriography* are two diagnostic imaging techniques used to decide if an individual would benefit from a surgical procedure called *carotid endarterectomy.* This surgery is used to remove fatty deposits from the carotid arteries and can help prevent stroke

Doppler ultrasound is a painless, noninvasive test in which sound waves above the range of human hearing are sent into the neck. Echoes bounce off the moving blood and the tissue in the artery and can be formed into an image. Ultrasound is fast, painless, risk-free, and relatively inexpensive compared to MRA and arteriography, but it is not considered to be as accurate as arteriography. Arteriography is an X-ray of the carotid artery taken when a special dye is injected into the artery. The procedure carries its own small risk of causing a stroke and is costly to perform. The benefits of arteriography over MR techniques and ultrasound are that it is extremely reliable and still the best way to measure stenosis of the carotid arteries. Even so, significant advances are being made every day involving noninvasive imaging techniques such as fMRI

Who is at Risk for Stroke?

Some people are at a higher risk for stroke than others. Unmodifiable risk factors include age, gender, race/ethnicity, and stroke family history. In contrast, other risk factors for stroke, like high blood pressure or cigarette smoking, can be changed or controlled by the person at risk.

Unmodifiable Risk Factors

It is a myth that stroke occurs only in elderly adults. In actuality, stroke strikes all age groups, from fetuses still in the womb to centenarians. It is true, however, that older people have a higher risk for stroke than the general population and that the risk for stroke increases with age. For every decade after the age of 55, the risk of stroke doubles, and two-thirds of all strokes occur in people over 65 years old. People over 65 also have a seven-fold greater risk of dying from stroke than the general population. And the *incidence* of stroke is increasing proportionately with the increase in the elderly population. When the baby boomers move into the over-65 age group, stroke and other diseases will take on even greater significance in the health care field.

Gender also plays a role in risk for stroke. Men have a higher risk for stroke, but more women die from stroke. The stroke risk for men is 1.25 times that for women. But men do not live as long as women, so men are usually younger when they have their strokes and therefore have a higher rate of survival than women. In other words, even though women have fewer strokes than men, women are generally older when they have their strokes and are more likely to die from them.

Stroke seems to run in some families. Several factors might contribute to familial stroke risk. Members of a family might have a genetic tendency for stroke risk factors, such as an inherited predisposition for hypertension or diabetes. The influence of a common lifestyle among family members could also contribute to familial stroke.

The risk for stroke varies among different ethnic and racial groups. The incidence of stroke among African-Americans is almost double that of white Americans, and twice as many African-Americans who have a stroke die from the event compared to white Americans. African-Americans between the ages of 45 and 55 have four to five times the stroke death rate of whites. After age 55 the stroke mortality rate for whites increases and is equal to that of African-Americans.

Compared to white Americans, African-Americans have a higher incidence of stroke risk factors, including high blood pressure and cigarette smoking. African-Americans also have a higher incidence and *prevalence* of some genetic diseases, such as diabetes and sickle cell anemia, that predispose them to stroke.

Hispanics and Native Americans have stroke incidence and mortality rates more similar to those of white Americans. In Asian-Americans stroke incidence and mortality rates are also similar to those in white Americans, even though Asians in Japan, China, and other countries of the Far East have significantly higher stroke incidence and mortality rates than white Americans. This suggests that environment and lifestyle factors play a large role in stroke risk.

The "Stroke Belt"

Several decades ago, scientists and statisticians noticed that people in the southeastern United States had the highest stroke mortality rate in the country. They named this region the *stroke belt*. For many years, researchers believed that the increased risk was due to the higher percentage of

African-Americans and an overall lower socioeconomic status (SES) in the southern states. A low SES is associated with an overall lower standard of living, leading to a lower standard of health care and therefore an increased risk of stroke. But researchers now know that the higher percentage of African-Americans and the overall lower SES in the southern states does not adequately account for the higher incidence of, and mortality from, stroke in those states. This means that other factors must be contributing to the higher incidence of and mortality from stroke in this region.

Recent studies have also shown that there is a *stroke buckle* in the stroke belt. Three southeastern states, North Carolina, South Carolina, and Georgia, have an extremely high stroke mortality rate, higher than the rate in other stroke belt states and up to two times the stroke mortality rate of the United States overall. The increased risk could be due to geographic or environmental factors or to regional differences in lifestyle, including higher rates of cigarette smoking and a regional preference for salty, high-fat foods.

Other Risk Factors

The most important risk factors for stroke are hypertension, heart disease, diabetes, and cigarette smoking. Others include heavy alcohol consumption, high blood cholesterol levels, illicit drug use, and genetic or congenital conditions, particularly vascular abnormalities. People with more than one risk factor have what is called "amplification of risk." This means that the multiple risk factors compound their destructive effects and create an overall risk greater than the simple cumulative effect of the individual risk factors.

Hypertension

Of all the risk factors that contribute to stroke, the most powerful is hypertension, or high blood pressure. People with hypertension have a risk for stroke that is four to six times higher than the risk for those without hypertension. One-third of the adult U.S. population, about 50 million people (including 40-70 percent of those over age 65) have high blood pressure. Forty to 90 percent of stroke patients have high blood pressure before their stroke event.

A systolic pressure of 120 mm of Hg over a diastolic pressure of 80 mm of Hg* is generally considered normal. Persistently high blood pressure greater than 140 over 90 leads to the diagnosis of the disease called hypertension. The impact of hypertension on the total risk for stroke decreases with increasing age, therefore factors other than hypertension play a greater role in the overall stroke risk in elderly adults. For people without hypertension, the absolute risk of stroke increases over time until around the age of 90, when the absolute risk becomes the same as that for people with hypertension.

Like stroke, there is a gender difference in the prevalence of hypertension. In younger people, hypertension is more common among men than among women. With increasing age, however, more women than men have hypertension. This hypertension gender-age difference probably has an impact on the incidence and prevalence of stroke in these populations.

Antihypertensive medication can decrease a person's risk for stroke. Recent studies suggest that treatment can decrease the stroke incidence rate by 38 percent and decrease the stroke fatality rate by 40 percent. Common hypertensive agents include adrenergic agents, beta-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, and vasodilators.

Heart Disease

After hypertension, the second most powerful risk factor for stroke is heart disease, especially a condition known as *atrial fibrillation*. Atrial fibrillation is irregular beating of the left atrium, or left upper chamber, of the heart. In people with atrial fibrillation, the left atrium beats up to four times faster than the rest of the heart. This leads to an irregular flow of blood and the occasional formation of blood clots that can leave the heart and travel to the brain, causing a stroke.

Atrial fibrillation, which affects as many as 2.2 million Americans, increases an individual's risk of stroke by 4 to 6 percent, and about 15 percent of stroke patients have atrial fibrillation before they experience a stroke. The condition is more prevalent in the upper age groups, which means that the prevalence of atrial fibrillation in the United States will increase proportionately with the growth of the elderly population. Unlike hypertension and other risk factors that have a lesser impact on the ever-rising absolute risk of stroke that comes with advancing age, the influence of atrial fibrillation on total risk for stroke increases powerfully with age. In people over 80 years old, atrial fibrillation is the direct cause of one in four strokes.

Other forms of heart disease that increase stroke risk include malformations of the heart valves or the heart muscle. Some valve diseases, like *mitral valve stenosis* or *mitral annular calcification*, can double the risk for stroke, independent of other risk factors.

Heart muscle malformations can also increase the risk for stroke. Patent foramen ovale (PFO) is a passage or a hole (sometimes called a "shunt") in the heart wall separating the two atria, or upper chambers, of the heart. Clots in the blood are usually filtered out by the lungs, but PFO could allow emboli or blood clots to bypass the lungs and go directly through the arteries to the brain, potentially causing a stroke. Research is currently under way to determine how important PFO is as a cause for stroke. Atrial septal aneurysm (ASA), a congenital (present from birth) malformation of the heart tissue, is a bulging of the septum or heart wall into one of the atria of the heart. Researchers do not know why this malformation increases the risk for stroke. PFO and ASA frequently occur together and therefore amplify the risk for stroke. Two other heart malformations that seem to increase the risk for stroke for unknown reasons are left atrial enlargement and left ventricular hypertrophy. People with left atrial enlargement have a larger than normal left atrium of the heart; those with left ventricular hypertrophy have a thickening of the wall of the left ventricle.

Another risk factor for stroke is cardiac surgery to correct heart malformations or reverse the effects of heart disease. Strokes occurring in this situation are usually the result of surgically dislodged plaques from the aorta that travel through the bloodstream to the arteries in the neck and head, causing stroke. Cardiac surgery increases a person's risk of stroke by about 1 percent. Other types of surgery can also increase the risk of stroke.

Blood Cholesterol Levels

Most people know that high cholesterol levels contribute to heart disease. But many don't realize that a high cholesterol level also contributes to stroke risk. Cholesterol, a waxy substance produced by the liver, is a vital body product. It contributes to the production of hormones and vitamin D and is an integral component of cell membranes. The liver makes enough cholesterol to fuel the body's needs and this natural production of cholesterol alone is not a large contributing factor to atherosclerosis, heart disease, and stroke. Research has shown that the danger from cholesterol comes from a dietary intake of foods that contain high levels of cholesterol. Foods high in saturated fat and cholesterol, like meats, eggs, and dairy products, can increase the amount of total cholesterol in the body to alarming levels, contributing to the risk of atherosclerosis and thickening of the arteries.

Cholesterol is classified as a lipid, meaning that it is fat-soluble rather than water-soluble. Other lipids include fatty acids, glycerides, alcohol, waxes,

steroids, and fat-soluble vitamins A, D, and E. Lipids and water, like oil and water, do not mix. Blood is a water-based liquid, therefore cholesterol does not mix with blood. In order to travel through the blood without clumping together, cholesterol needs to be covered by a layer of protein. The cholesterol and protein together are called a *lipoprotein*.

There are two kinds of cholesterol, commonly called the "good" and the "bad." Good cholesterol is *high-density lipoprotein*, or *HDL*; bad cholesterol is *low-density lipoprotein*, or *LDL*. Together, these two forms of cholesterol make up a person's *total serum cholesterol* level. Most cholesterol tests measure the level of total cholesterol in the blood and don't distinguish between good and bad cholesterol. For these total serum cholesterol tests, a level of less than 200 mg/dL[**] is considered safe, while a level of more than 240 is considered dangerous and places a person at risk for heart disease and stroke.

Most cholesterol in the body is in the form of LDL. LDLs circulate through the bloodstream, picking up excess cholesterol and depositing cholesterol where it is needed (for example, for the production and maintenance of cell membranes). But when too much cholesterol starts circulating in the blood, the body cannot handle the excessive LDLs, which build up along the inside of the arterial walls. The buildup of LDL coating on the inside of the artery walls hardens and turns into arterial plaque, leading to stenosis and atherosclerosis. This plaque blocks blood vessels and contributes to the formation of blood clots. A person's LDL level should be less than 130 mg/dL to be safe. LDL levels between 130 and 159 put a person at a slightly higher risk for atherosclerosis, heart disease, and stroke. A score over 160 puts a person at great risk for a heart attack or stroke.

The other form of cholesterol, HDL, is beneficial and contributes to stroke prevention. HDL carries a small percentage of the cholesterol in the blood, but instead of depositing its cholesterol on the inside of artery walls, HDL returns to the liver to unload its cholesterol. The liver then eliminates the excess cholesterol by passing it along to the kidneys. Currently, any HDL score higher than 35 is considered desirable. Recent studies have shown that high levels of HDL are associated with a reduced risk for heart disease and stroke and that low levels (less than 35 mg/dL), even in people with normal levels of LDL, lead to an increased risk for heart disease and stroke.

A person may lower his risk for atherosclerosis and stroke by improving his cholesterol levels. A healthy diet and regular exercise are the best ways to lower total cholesterol levels. In some cases, physicians may prescribe cholesterol-lowering medication, and recent studies have shown that the newest types of these drugs, called reductase inhibitors or statin drugs, significantly reduce the risk for stroke in most patients with high cholesterol. Scientists believe that statins may work by reducing the amount of bad cholesterol the body produces and by reducing the body's inflammatory immune reaction to cholesterol plaque associated with atherosclerosis and stroke.

[*] mm of Hg-or millimeters of mercury-is the standard means of expressing blood pressure, which is measured using an instrument called a sphygmomanometer. Using a stethoscope and a cuff that is wrapped around the patient's upper arm, a health professional listens to the sounds of blood rushing through an artery. The first sound registered on the instrument gauge (which measures the pressure of the blood in millimeters on a column of mercury) is called the systolic pressure. This is the maximum pressure produced as the left ventricle of the heart contracts and the blood begins to flow through the artery. The second sound is the diastolic pressure and is the lowest pressure in the artery when the left ventricle is relaxing. *return to "**Hypertension**" section*

[**] mg/dL describes the weight of cholesterol in milligrams in a deciliter of blood. This is the standard way of measuring blood cholesterol levels. *return to "**Blood Cholesterol Levels**" section*

Diabetes

Diabetes is another disease that increases a person's risk for stroke. People with diabetes have three times the risk of stroke compared to people without diabetes. The relative risk of stroke from diabetes is highest in the fifth and sixth decades of life and decreases after that. Like hypertension, the relative risk of stroke from diabetes is highest for men at an earlier age and highest for women at an older age. People with diabetes may also have other contributing risk factors that can amplify the overall risk for stroke. For example, the prevalence of hypertension is 40 percent higher in the diabetic population compared to the general population.

Modifiable Lifestyle Risk Factors

Cigarette smoking is the most powerful modifiable stroke risk factor. Smoking almost doubles a person's risk for ischemic stroke, independent of other risk factors, and it increases a person's risk for subarachnoid hemorrhage by up to 3.5 percent. Smoking is directly responsible for a greater percentage of the total number of strokes in young adults than in older adults. Risk factors other than smoking - like hypertension, heart disease, and diabetes - account for more of the total number of strokes in older adults.

Heavy smokers are at greater risk for stroke than light smokers. The relative risk of stroke decreases immediately after quitting smoking, with a major reduction of risk seen after 2 to 4 years. Unfortunately, it may take several decades for a former smoker's risk to drop to the level of someone who never smoked.

Smoking increases the risk of stroke by promoting atherosclerosis and increasing the levels of blood-clotting factors, such as fibrinogen. In addition to promoting conditions linked to stroke, smoking also increases the damage that results from stroke by weakening the *endothelial wall* of the cerebrovascular system. This leads to greater damage to the brain from events that occur in the secondary stage of stroke.

High alcohol consumption is another modifiable risk factor for stroke. Generally, an increase in alcohol consumption leads to an increase in blood pressure. While scientists agree that heavy drinking is a risk for both hemorrhagic and ischemic stroke, in several research studies daily consumption of smaller amounts of alcohol has been found to provide a protective influence against ischemic stroke, perhaps because alcohol decreases the clotting ability of *platelets* in the blood. Moderate alcohol consumption may act in the same way as aspirin to decrease blood clotting and prevent ischemic stroke. Heavy alcohol consumption, though, may seriously deplete platelet numbers and compromise blood clotting and blood viscosity, leading to hemorrhage. In addition, heavy drinking or binge drinking can lead to a rebound effect after the alcohol is purged from the body. The consequences of this rebound effect are that blood viscosity (thickness) and platelet levels skyrocket after heavy drinking, increasing the risk for ischemic stroke.

The use of illicit drugs, such as cocaine and crack cocaine, can cause stroke. Cocaine may act on other risk factors, such as hypertension, heart disease, and vascular disease, to trigger a stroke. It decreases relative cerebrovascular blood flow by up to 30 percent, causes vascular constriction, and inhibits vascular relaxation, leading to narrowing of the arteries. Cocaine also affects the heart, causing arrhythmias and rapid heart rate that can lead to the formation of blood clots.

Marijuana smoking may also be a risk factor for stroke. Marijuana decreases blood pressure and may interact with other risk factors, such as hypertension and cigarette smoking, to cause rapidly fluctuating blood pressure levels, damaging blood vessels.

Other drugs of abuse, such as amphetamines, heroin, and anabolic steroids (and even some common, legal drugs, such as caffeine and L-asparaginase and pseudoephedrine found in over-the-counter decongestants), have been suspected of increasing stroke risk. Many of these drugs are vasoconstrictors, meaning that they cause blood vessels to constrict and blood pressure to rise.

Head and Neck Injuries

Injuries to the head or neck may damage the cerebrovascular system and cause a small number of strokes. Head injury or traumatic brain injury may cause bleeding within the brain leading to damage akin to that caused by a hemorrhagic stroke. Neck injury, when associated with spontaneous tearing of the vertebral or carotid arteries caused by sudden and severe extension of the neck, neck rotation, or pressure on the artery, is a contributing cause of stroke, especially in young adults. This type of stroke is often called "beauty-parlor syndrome," which refers to the practice of extending the neck backwards over a sink for hair-washing in beauty parlors. Neck calisthenics, "bottoms-up" drinking, and improperly performed chiropractic manipulation of the neck can also put strain on the vertebral and carotid arteries, possibly leading to ischemic stroke.

Infections

Recent viral and bacterial infections may act with other risk factors to add a small risk for stroke. The immune system responds to infection by increasing inflammation and increasing the infection-fighting properties of the blood. Unfortunately, this immune response increases the number of clotting factors in the blood, leading to an increased risk of embolic-ischemic stroke.

Genetic Risk Factors

Although there may not be a single genetic factor associated with stroke, genes do play a large role in the expression of stroke risk factors such as hypertension, heart disease, diabetes, and vascular malformations. It is also possible that an increased risk for stroke within a family is due to environmental factors, such as a common sedentary lifestyle or poor eating habits, rather than hereditary factors.

Vascular malformations that cause stroke may have the strongest genetic link of all stroke risk factors. A vascular malformation is an abnormally formed blood vessel or group of blood vessels. One genetic vascular disease called CADASIL, which stands for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CADASIL is a rare, genetically inherited, congenital vascular disease of the brain that causes strokes, subcortical dementia, migraine-like headaches, and psychiatric disturbances. CADASIL is very debilitating and symptoms usually surface around the age of 45. The exact incidence of CADASIL in the United States is unknown.

Medications

Medication or drug therapy is the most common treatment for stroke. The most popular classes of drugs used to prevent or treat stroke are *antithrombotics* (*antiplatelet agents* and *anticoagulants*) and *thrombolytics*.

Antithrombotics prevent the formation of blood clots that can become lodged in a cerebral artery and cause strokes. Antiplatelet drugs prevent clotting by decreasing the activity of platelets, blood cells that contribute to the clotting property of blood. These drugs reduce the risk of blood-clot formation, thus reducing the risk of ischemic stroke. In the context of stroke, physicians prescribe antiplatelet drugs mainly for prevention. The most widely known and used antiplatelet drug is aspirin. Other antiplatelet drugs include clopidogrel, ticlopidine, and dipyridamole. The NINDS sponsors a wide range of clinical trials to determine the effectiveness of antiplatelet drugs for stroke prevention.

Anticoagulants reduce stroke risk by reducing the clotting property of the blood. The most commonly used anticoagulants include *warfarin* (also known as *Coumadin*®), *heparin,* and *enoxaparin* (also known as *Lovenox*). The NINDS has sponsored several trials to test the efficacy of anticoagulants versus antiplatelet drugs. The Stroke Prevention in Atrial Fibrillation (SPAF) trial found that, although aspirin is an effective therapy for the prevention of a second stroke in most patients with atrial fibrillation, some patients with additional risk factors do better on warfarin therapy. Another study, the Trial of Org 10127 in Acute Stroke Treatment (TOAST), tested the effectiveness of low-molecular weight heparin (Org 10172) in stroke prevention. TOAST showed that heparin anticoagulants are not generally effective in preventing recurrent stroke or improving outcome.

Thrombolytic agents are used to treat an ongoing, acute ischemic stroke caused by an artery blockage. These drugs halt the stroke by dissolving the blood clot that is blocking blood flow to the brain. *Recombinant tissue plasminogen activator (rt-PA)* is a genetically engineered form of t-PA, a thombolytic substance made naturally by the body. It can be effective if given intravenously within 3 hours of stroke symptom onset, but it should be used only after a physician has confirmed that the patient has suffered an ischemic stroke. Thrombolytic agents can increase bleeding and therefore must be used only after careful patient screening. The NINDS rt-PA Stroke Study showed the efficacy of t-PA and in 1996 led to the first FDA-approved treatment for acute ischemic stroke. Other thrombolytics are currently being tested in clinical trials.

Neuroprotectants are medications that protect the brain from secondary injury caused by stroke *(see* **Appendix***)*. Although no neuroprotectants are FDA-approved for use in stroke at this time, many are in clinical trials. There are several different classes of neuroprotectants that show promise for future therapy, including glutamate antagonists, antioxidants, apoptosis inhibitors, and many others.

Surgery

Surgery can be used to prevent stroke, to treat acute stroke, or to repair vascular damage or malformations in and around the brain. There are two prominent types of surgery for stroke prevention and treatment: carotid endarterectomy and *extracranial/intracranial (EC/IC) bypass*.

Carotid endarterectomy is a surgical procedure in which a doctor removes fatty deposits (plaque) from the inside of one of the carotid arteries, which are located in the neck and are the main suppliers of blood to the brain. As mentioned earlier, the disease atherosclerosis is characterized by the buildup of plaque on the inside of large arteries, and the blockage of an artery by this fatty material is called stenosis. The NINDS has sponsored two large clinical trials to test the efficacy of carotid endarterectomy: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Trial (ACAS). These trials showed that carotid endarterectomy is a safe and effective stroke prevention therapy for most people with greater than 50 percent stenosis of the carotid arteries when performed by a qualified and experienced neurosurgeon or vascular surgeon.

Currently, the NINDS is sponsoring the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), a large clinical trial designed to test the effectiveness of carotid endarterectomy versus a newer surgical procedure for carotid stenosis called stenting. The procedure involves inserting a long, thin catheter tube into an artery in the leg and threading the catheter through the vascular system into the narrow stenosis of the carotid artery in the

neck. Once the catheter is in place in the carotid artery, the radiologist expands the stent with a balloon on the tip of the catheter. The CREST trial will test the effectiveness of the new surgical technique versus the established standard technique of carotid endarterectomy surgery.

EC/IC bypass surgery is a procedure that restores blood flow to a blood-deprived area of brain tissue by rerouting a healthy artery in the scalp to the area of brain tissue affected by a blocked artery. The NINDS-sponsored EC/IC Bypass Study tested the ability of this surgery to prevent recurrent strokes in stroke patients with atherosclerosis. The study showed that, in the long run, EC/IC does not seem to benefit these patients. The surgery is still performed occasionally for patients with aneurysms, some types of small artery disease, and certain vascular abnormalities.

One useful surgical procedure for treatment of brain aneurysms that cause subarachnoid hemorrhage is a technique called *"clipping."* Clipping involves clamping off the aneurysm from the blood vessel, which reduces the chance that it will burst and bleed.

A new therapy that is gaining wide attention is the *detachable coil* technique for the treatment of high-risk intracranial aneurysms. A small platinum coil is inserted through an artery in the thigh and threaded through the arteries to the site of the aneurysm. The coil is then released into the aneurysm, where it evokes an immune response from the body. The body produces a blood clot inside the aneurysm, strengthening the artery walls and reducing the risk of rupture. Once the aneurysm is stabilized, a neurosurgeon can clip the aneurysm with less risk of hemorrhage and death to the patient.

Post-Stroke Rehabilitation	
Type	**Goal**
Physical Therapy (PT)	Relearn walking, sitting, lying down, switching from one type of movement to another
Occupational Therapy (OT)	Relearn eating, drinking, dressing, bathing, cooking, reading, writing, toileting
Speech Therapy	Relearn language and communications skills, including swallowing.
Psychological/Psychiatric Therapy	Alleviate some mental and emotional problems

Rehabilitation Therapy

Stroke is the number one cause of serious adult disability in the United States. Stroke disability is devastating to the stroke patient and family, but therapies are available to help rehabilitate post-stroke patients.

For most stroke patients, physical therapy (PT) is the cornerstone of the rehabilitation process. A physical therapist uses training, exercises, and physical manipulation of the stroke patient's body with the intent of restoring movement, balance, and coordination. The aim of PT is to have the stroke patient relearn simple motor activities such as walking, sitting, standing, lying down, and the process of switching from one type of movement to another.

Another type of therapy involving relearning daily activities is occupational therapy (OT). OT also involves exercise and training to help the stroke patient relearn everyday activities such as eating, drinking, dressing, bathing, cooking, reading and writing, and toileting. The goal of OT is to help the patient become independent or semi-independent.

Speech and language problems arise when brain damage occurs in the language centers of the brain. Due to the brain's great ability to learn and change (called brain *plasticity*), other areas can adapt to take over some of the lost functions. Speech language pathologists help stroke patients relearn language and speaking skills, including swallowing, or learn other forms of communication. Speech therapy is appropriate for any patients with problems understanding speech or written words, or problems forming speech. A speech therapist helps stroke patients help themselves by working to improve language skills, develop alternative ways of communicating, and develop coping skills to deal with the frustration of not being able to communicate fully. With time and patience, a stroke survivor should be able to regain some, and sometimes all, language and speaking abilities.

Many stroke patients require psychological or psychiatric help after a stroke. Psychological problems, such as depression, anxiety, frustration, and anger, are common post-stroke disabilities. Talk therapy, along with appropriate medication, can help alleviate some of the mental and emotional problems that result from stroke. Sometimes it is also beneficial for family members of the stroke patient to seek psychological help as well.

For more information on rehabilitation, contact the National Rehabilitation Information Center , a service of the National Institute on Disability and Rehabilitation Research

What Disabilities Can Result From a Stroke?

Although stroke is a disease of the brain, it can affect the entire body. Some of the disabilities that can result from a stroke include paralysis, cognitive deficits, speech problems, emotional difficulties, daily living problems, and pain.

Paralysis:

A common disability that results from stroke is complete paralysis on one side of the body, called *hemiplegia*. A related disability that is not as debilitating as paralysis is one-sided weakness or *hemiparesis*. The paralysis or weakness may affect only the face, an arm, or a leg or may affect one entire side of the body and face. A person who suffers a stroke in the left hemisphere of the brain will show right-sided paralysis or paresis. Conversely, a person with a stroke in the right hemisphere of the brain will show deficits on the left side of the body. A stroke patient may have problems with the simplest of daily activities, such as walking, dressing, eating, and using the bathroom. Motor deficits can result from damage to the motor cortex in the frontal lobes of the brain or from damage to the lower parts of the brain, such as the cerebellum, which controls balance and coordination. Some stroke patients also have trouble swallowing, called *dysphagia*.

Cognitive deficits:

Stroke may cause problems with thinking, awareness, attention, learning, judgment, and memory. In some cases of stroke, the patient suffers a "neglect" syndrome. The neglect means that a stroke patient has no knowledge of one side of his or her body, or one side of the visual field, or is unaware of the deficit. A stroke patient may be unaware of his or her surroundings, or may be unaware of the mental deficits that resulted from the stroke.

Language deficits:

Stroke victims often have problems understanding or forming speech. A deficit in understanding or forming speech is called *aphasia*. Aphasia usually occurs along with similar problems in reading or writing. In most people, language problems result from damage to the left hemisphere of the brain. Slurred speech due to weakness or incoordination of the muscles involved in speaking is called *dysarthria*, and is not a problem with language. Because it can result from any weakness or incoordination of the speech muscles, dysarthria can arise from damage to either side of the brain.

Emotional deficits:

A stroke can lead to emotional problems. Stroke patients may have difficulty controlling their emotions or may express inappropriate emotions in certain situations. One common disability that occurs with many stroke patients is depression. Post-stroke depression may be more than a general sadness resulting from the stroke incident. It is a clinical behavioral problem that can hamper recovery and rehabilitation and may even lead to suicide. Post-stroke depression is treated as any depression is treated, with antidepressant medications and therapy.

Pain:

Stroke patients may experience pain, uncomfortable numbness, or strange sensations after a stroke. These sensations may be due to many factors including damage to the sensory regions of the brain, stiff joints, or a disabled limb. An uncommon type of pain resulting from stroke is called *central stroke pain* or *central pain syndrome (CPS)*. CPS results from damage to an area in the mid-brain called the thalamus. The pain is a mixture of sensations, including heat and cold, burning, tingling, numbness, and sharp stabbing and underlying aching pain. The pain is often worse in the extremities - the hands and feet - and is made worse by movement and temperature changes, especially cold temperatures. Unfortunately, since most pain medications provide little relief from these sensations, very few treatments or therapies exist to combat CPS.

What Special Risks do Women Face?

Some risk factors for stroke apply only to women. Primary among these are pregnancy, childbirth, and menopause. These risk factors are tied to hormonal fluctuations and changes that affect a woman in different stages of life. Research in the past few decades has shown that high-dose oral contraceptives, the kind used in the 1960s and 1970s, can increase the risk of stroke in women. Fortunately, oral contraceptives with high doses of estrogen are no longer used and have been replaced with safer and more effective oral contraceptives with lower doses of estrogen. Some studies have shown the newer low-dose oral contraceptives may not significantly increase the risk of stroke in women.

Other studies have demonstrated that pregnancy and childbirth can put a woman at an increased risk for stroke. Pregnancy increases the risk of stroke as much as three to 13 times. Of course, the risk of stroke in young women of childbearing years is very small to begin with, so a moderate increase in risk during pregnancy is still a relatively small risk. Pregnancy and childbirth cause strokes in approximately eight in 100,000 women. Unfortunately, 25 percent of strokes during pregnancy end in death, and hemorrhagic strokes, although rare, are still the leading cause of maternal death in the United States. Subarachnoid hemorrhage, in particular, causes one to five maternal deaths per 10,000 pregnancies.

A study sponsored by the NINDS showed that the risk of stroke during pregnancy is greatest in the post-partum period - the 6 weeks following childbirth. The risk of ischemic stroke after pregnancy is about nine times higher and the risk of hemorrhagic stroke is more than 28 times higher for post-partum women than for women who are not pregnant or post-partum. The cause is unknown.

In the same way that the hormonal changes during pregnancy and childbirth are associated with increased risk of stroke, hormonal changes at the end of the childbearing years can increase the risk of stroke. Several studies have shown that menopause, the end of a woman's reproductive ability marked by the termination of her menstrual cycle, can increase a woman's risk of stroke. Fortunately, some studies have suggested that hormone replacement therapy can reduce some of the effects of menopause and decrease stroke risk. Currently, the NINDS is sponsoring the Women's Estrogen for Stroke Trial (WEST), a randomized, placebo-controlled, double-blind trial, to determine whether estrogen therapy can reduce the risk of death or recurrent stroke in postmenopausal women who have a history of a recent TIA or non-disabling stroke. The mechanism by which estrogen can prove beneficial to postmenopausal women could include its role in cholesterol control. Studies have shown that estrogen acts to increase levels of HDL while decreasing LDL levels.

Are Children at Risk For Stroke?

The young have several risk factors unique to them. Young people seem to suffer from hemorrhagic strokes more than ischemic strokes, a significant difference from older age groups where ischemic strokes make up the majority of stroke cases. Hemorrhagic strokes represent 20 percent of all strokes in the United States and young people account for many of these.

Clinicians often separate the "young" into two categories: those younger than 15 years of age, and those 15 to 44 years of age. People 15 to 44 years of age are generally considered young adults and have many of the risk factors mentioned above, such as drug use, alcohol abuse, pregnancy, head and neck injuries, heart disease or heart malformations, and infections. Some other causes of stroke in the young are linked to genetic diseases.

Medical complications that can lead to stroke in children include intracranial infection, brain injury, vascular malformations such as moyamoya syndrome, occlusive vascular disease, and genetic disorders such as sickle cell anemia, tuberous sclerosis, and Marfan's syndrome.

The symptoms of stroke in children are different from those in adults and young adults. A child experiencing a stroke may have seizures, a sudden loss of speech, a loss of expressive language (including body language and gestures), hemiparesis (weakness on one side of the body), hemiplegia (paralysis on one side of the body), dysarthria (impairment of speech), convulsions, headache, or fever. It is a medical emergency when a child shows any of these symptoms.

In children with stroke the underlying conditions that led to the stroke should be determined and managed to prevent future strokes. For example, a recent clinical study sponsored by the National Heart, Lung, and Blood Institute found that giving blood transfusions to young children with sickle cell anemia greatly reduces the risk of stroke. The Institute even suggests attempting to prevent stroke in high-risk children by giving them blood transfusions before they experience a stroke.

Most children who experience a stroke will do better than most adults after treatment and rehabilitation. This is due in part to the immature brain's great plasticity, the ability to adapt to deficits and injury. Children who experience seizures along with stroke do not recover as well as children who do not have seizures. Some children may experience residual hemiplegia, though most will eventually learn how to walk.

What Research is Being Done by the NINDS?

The NINDS is the leading supporter of stroke research in the United States and sponsors a wide range of experimental research studies, from investigations of basic biological mechanisms to studies with animal models and clinical trials.

Currently, NINDS researchers are studying the mechanisms of stroke risk factors and the process of brain damage that results from stroke. Some of this brain damage may be secondary to the initial death of brain cells caused by the lack of blood flow to the brain tissue. This secondary wave of brain injury is a result of a toxic reaction to the primary damage and mainly involves the excitatory neurochemical, *glutamate*. Glutamate in the normal brain functions as a chemical messenger between brain cells, allowing them to communicate. But an excess amount of glutamate in the brain causes too much activity and brain cells quickly "burn out" from too much excitement, releasing more toxic chemicals, such as caspases, cytokines, monocytes, and oxygen-free radicals. These substances poison the chemical environment of surrounding cells, initiating a cascade of degeneration and programmed cell death, called *apoptosis*. NINDS researchers are studying the mechanisms underlying this secondary insult, which consists mainly of inflammation, toxicity, and a breakdown of the blood vessels that provide blood to the brain. Researchers are also looking for ways to prevent secondary injury to the brain by providing different types of neuroprotection for salvagable cells that prevent inflammation and block some of the toxic chemicals created by dying brain cells. From this research, scientists hope to develop neuroprotective agents to prevent secondary damage. For more information on excitotoxicity, neuroprotection, and the ischemic cascade,

Basic research has also focused on the genetics of stroke and stroke risk factors. One area of research involving genetics is gene therapy. Gene therapy involves putting a gene for a desired protein in certain cells of the body. The inserted gene will then "program" the cell to produce the desired protein. If enough cells in the right areas produce enough protein, then the protein could be therapeutic. Scientists must find ways to deliver the therapeutic DNA to the appropriate cells and must learn how to deliver enough DNA to enough cells so that the tissues produce a therapeutic amount of protein. Gene therapy is in the very early stages of development and there are many problems to overcome, including learning how to penetrate the highly impermeable *blood-brain barrier* and how to halt the host's immune reaction to the virus that carries the gene to the cells. Some of the proteins used for stroke therapy could include neuroprotective proteins, anti-inflammatory proteins, and DNA/cellular repair proteins, among others.

The NINDS supports and conducts a wide variety of studies in animals, from genetics research on zebrafish to rehabilitation research on primates. Much of the Institute's animal research involves rodents, specifically mice and rats. For example, one study of hypertension and stroke uses rats that have been bred to be hypertensive and therefore stroke-prone. By studying stroke in rats, scientists hope to get a better picture of what might be happening in human stroke patients. Scientists can also use animal models to test promising therapeutic interventions for stroke. If a therapy proves to be beneficial to animals, then scientists can consider testing the therapy in human subjects.

One promising area of stroke animal research involves hibernation. The dramatic decrease of blood flow to the brain in hibernating animals is extensive - extensive enough that it would kill a non-hibernating animal. During hibernation, an animal's metabolism slows down, body temperature drops, and energy and oxygen requirements of brain cells decrease. If scientists can discover how animals hibernate without experiencing brain damage, then maybe they can discover ways to stop the brain damage associated with decreased blood flow in stroke patients. Other studies are looking at the role of hypothermia, or decreased body temperature, on metabolism and neuroprotection.

Both hibernation and hypothermia have a relationship to *hypoxia* and *edema*. Hypoxia, or *anoxia*, occurs when there is not enough oxygen available for brain cells to function properly. Since brain cells require large amounts of oxygen for energy requirements, they are especially vulnerable to hypoxia. Edema occurs when the chemical balance of brain tissue is disturbed and water or fluids flow into the brain cells, making them swell and burst, releasing their toxic contents into the surrounding tissues. Edema is one cause of general brain tissue swelling and contributes to the secondary injury associated with stroke.

The basic and animal studies discussed above do not involve people and fall under the category of preclinical research; clinical research involves people. One area of investigation that has made the transition from animal models to clinical research is the study of the mechanisms underlying brain plasticity and the neuronal rewiring that occurs after a stroke.

New advances in imaging and rehabilitation have shown that the brain can compensate for function lost as a result of stroke. When cells in an area of the brain responsible for a particular function die after a stroke, the patient becomes unable to perform that function. For example, a stroke patient with an infarct in the area of the brain responsible for facial recognition becomes unable to recognize faces, a syndrome called facial agnosia. But, in time, the person may come to recognize faces again, even though the area of the brain originally programmed to perform that function remains dead. The plasticity of the brain and the rewiring of the neural connections make it possible for one part of the brain to change functions and take up the more important functions of a disabled part. This rewiring of the brain and restoration of function, which the brain tries to do automatically, can be helped with therapy. Scientists are working to develop new and better ways to help the brain repair itself to restore important functions to the stroke patient.

One example of a therapy resulting from this research is the use of *transcranial magnetic stimulation (TMS)* in stroke rehabilitation. Some evidence suggests that TMS, in which a small magnetic current is delivered to an area of the brain, may possibly increase brain plasticity and speed up recovery of function after a stroke. The TMS device is a small coil which is held outside of the head, over the part of the brain needing stimulation. Currently, several studies at the NINDS are testing whether TMS has any value in increasing motor function and improving functional recovery.

Clinical Trials

Clinical research is usually conducted in a series of trials that become progressively larger. A phase I clinical trial is directly built upon the lessons learned from basic and animal research and is used to test the safety of therapy for a particular disease and to estimate possible efficacy in a few human subjects. A phase II clinical trial usually involves many subjects at several different centers and is used to test safety and possible efficacy on a broader scale, to test different dosing for medications or to perfect techniques for surgery, and to determine the best methodology and outcome measures for the bigger phase III clinical trial to come.

A phase III clinical trial is the largest endeavor in clinical research. This type of trial often involves many centers and many subjects. The trial usually has two patient groups who receive different treatments, but all other standard care is the same and represents the best care available. The trial may compare two treatments, or, if there is only one treatment to test, patients who do not receive the test therapy receive instead a placebo. The patients are told that the additional treatment they are receiving may be either the active treatment or a placebo. Many phase III trials are called double-blind, randomized clinical trials. Double-blind means that neither the subjects nor the doctors and nurses who are treating the subjects and determining the response to the therapy know which treatment a subject receives. Randomization refers to the placing of subjects into one of the treatment groups in a

way that can't be predicted by the patients or investigators. These clinical trials usually involve many investigators and take many years to complete. The hypothesis and methods of the trial are very precise and well thought out. Clinical trial designs, as well as the concepts of blinding and randomization, have developed over years of experimentation, trial, and error. At the present time, researchers are developing new designs to maximize the opportunity for all subjects to receive therapy.

Most treatments for general use come out of phase III clinical trials. After one or more phase III trials are finished, and if the results are positive for the treatment, the investigators can petition the FDA for government approval to use the drug or procedure to treat patients. Once the treatment is approved by the FDA, it can be used by qualified doctors throughout the country. The back packet of this brochure contains cards with information on some of the many stroke clinical trials the NINDS supports or has completed.

NINDS-Sponsored Stroke Clinical Trials: September 2012

Clinical trials give researchers a way to test new treatments in human subjects. Clinical trials test surgical devices and procedures, medications, rehabilitation therapies, and lifestyle and psychosocial interventions to determine how safe and effective they are and to establish the proper amount or level of treatment. Because of their scope and the need for careful analysis of data and outcomes, clinical trials are usually conducted in three phases and can take several years or more to complete.

- **Phase I** clinical trials are small (involving fewer than 100 people) and are designed to define side effects and tolerance of the medication or therapy.
- **Phase II** trials are conducted with a larger group of subjects and seek to measure the effects of a therapy and establish its proper dosage or level of treatment.
- **Phase III** trials often involve hundreds (sometimes thousands) of volunteer patients who are assigned to treatment and non-treatment groups to test how well the treatment works and how safe it is at the recommended dosage or level of therapy. Many of these trials use a controlled, randomized, double-blind study design. This means that patients are randomly assigned to groups and neither the subject nor the study staff knows to which group a patient belongs. Phase III randomized clinical trials are often called the gold standard of clinical trials.

NINDS conducts clinical trials at the NIH Clinical Center and also provides funding for clinical trials at hospitals and universities across the United States and Canada. Below are findings from some of the largest and most significant recent clinical trials in stroke, as well as summaries of some of the most promising clinical trials in progress.

Findings From Recently Completed Clinical Trials

The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)
The use of dilation and stenting techniques similar to those used to unclog and open heart arteries has been proposed as a less invasive alternative to carotid endarterectomy (surgery to remove the buildup of plaque within the carotid artery, which supplies blood to the head and neck). Carotid endarterectomy is considered the gold standard treatment for preventing stroke and other vascular events. Stenting is a newer, less invasive procedure in which an expandable metal stent (tube) is inserted into the carotid artery to keep it open after it has been widened with balloon dilation. The CREST study showed that the overall safety and effectiveness of the two procedures was largely the same—with equal benefits for both men and women, and for people who had previously had a stroke and for those who had not. Physicians will now have more options to tailor treatments for people at risk for stroke.

Carotid Occlusion Surgery Study (COSS)
The goal of this randomized clinical trial was to determine the preventive power of extracranial bypass surgery in a group of stroke survivors who have both a blocked carotid artery and an increased oxygen extraction fraction (or OEF, which indicates how hard the brain has to work to pull oxygen from the blood supply). An increased OEF has been shown to be a powerful and independent risk factor for subsequent stroke. Extracranial bypass surgery uses a healthy blood vessel to detour blood flow around the site of the blocked artery and results in increased blood flow to the brain. The results showed that in spite of the surgical success of improving cerebral blood flow, extracranial-intracranial bypass surgery did not demonstrate any benefit in reducing the risk of having a stroke recurrence due to the much better than expected recurrence rate in the non-surgical medical alone group.

Locomotor Experience Applied Post-Stroke (LEAPS)
Only 37 percent of stroke survivors are able to walk after the first week following their stroke. The investigators of the Locomotor Experience Applied Post-Stroke (LEAPS) trial set out to compare the effectiveness of the body-weight supported treadmill training with walking practice started at two different stages--two months post-stroke (early locomotor training) and six months post-stroke (late locomotor training). The locomotor training was also compared against a home exercise program managed by a physical therapist, aimed at enhancing patients' flexibility, range of motion, strength and balance as a way to improve their walking. The primary measure was each group's improvement in walking at one year after the stroke. The study found that stroke patients who had physical therapy at home improved their ability to walk just as well as those who were treated in a training program that requires the use of a body-weight supported treadmill device followed by walking practice. In addition, the study also found that patients continued to improve up to one year after stroke, defying conventional wisdom that recovery occurs early and tops out at six months.

Secondary Prevention of Small Subcortical Strokes (SPS3)
In this trial, investigators are testing new approaches to stroke prevention for people with a history of small subcortical strokes. The trial was designed to compare: 1) aspirin alone vs. combined antiplatelet therapy (aspirin and clopidogrel), and 2) intensive vs. standard blood pressure control. Subcortical strokes, also called lacunar strokes, occur when the thread-like arteries within cerebral tissue become blocked and halt blood flow to the brain. They account for up to one-fifth of all strokes in the U.S. and are especially common among people of Hispanic descent. In the antiplatelet component of SPS3, researchers have found that the combined antiplatelet therapy was about equal to aspirin in reducing stroke risk, but it almost doubled the risk of gastrointestinal bleeding. The blood pressure component of the trial is ongoing.

Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)
The best treatment for preventing another stroke or TIA in patients with narrowing of a brain artery is uncertain. The purpose of this trial was to compare the safety and effectiveness of aggressive medical treatment (i.e., intensive management of key stroke risk factors including blood pressure, cholesterol, and lifestyle modification) alone to aggressive medical therapy plus a Food and Drug Administration (FDA)-approved intracranial stent to prevent another stroke in individuals who recently had either a transient ischemic attack or non-disabling stroke. The results of this trial, which was stopped early, showed that the group that received the intensive medical management alone had better outcomes than the group who also received the stent. This study provides an answer to a long-standing question by physicians—what to do to prevent a devastating second stroke in a high risk population.

Ongoing Clinical Trials

Albumin in Acute Ischemic Stroke (ALIAS) Trial
Human serum albumin is a protein found in human blood plasma that may have neuroprotective benefit in stroke. The Albumin in Acute Ischemic Stroke trial will compare the use of intravenous albumin administered over a two- hour period to placebo among individuals with acute ischemic stroke, beginning within five hours of stroke onset. Individuals will also receive concurrent treatment with a thrombolytic drug given either intravenously or intra-arterially when appropriate. Patients receiving either albumin or placebo will be followed for one year. The primary outcome will be an assessment of neurological function at three months post-stroke.

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH II)
Intensive blood pressure management following an intracerebral hemorrhage (ICH) may slow the rate and magnitude of the hemorrhage. The primary goal of the Antihypertensive Treatment of Acute Cerebral Hemorrhage trial is to determine the efficacy and safety of intensive systolic blood pressure management in ICH patients treated within three hours of symptom onset. The approach of intensive systolic blood pressure control represents a strategy that can be made widely available without the need of specialized equipment and personnel. Therefore, it has the potential to make a major impact on outcome in patients with ICH.

A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)
Arteriovenous malformations (AVMs) are defects of the circulatory system comprised of tangles of arteries and veins that are present from birth. These defects, which can occur in the brain, spinal cord, or other organs, may cause symptoms such as headaches or seizures. AVM that have not ruptured may be left untreated until they become symptomatic or may undergo surgical radiation or endovascular treatment to prevent future rupture. In A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA), scientists will treat participants with unruptured brain AVMs either conservatively (medical management) or using invasive therapy (surgery, radiation, embolization) and follow their progress for at least five years to compare benefit in terms of reduced risk of subsequent stroke or AVM rupture. The outcome of this trial will indicate the best way to treat individuals with unruptured brain AVMs and offer doctors a more definitive standard of treatment.

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage, Phase III (CLEAR III)
The objective of the randomized Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage III study is to determine any benefit of the use of the clot-busting drug recombinant tissue plasminogen activator (t-PA) in conjunction with clot removal for intraventricular hemorrhage. The investigators will compare extraventricular draining (surgically inserting tubes that drain fluid from the brain's ventricles) plus t-PA with extraventricular draining plus placebo in managing and treating individuals with small intracerebral hemorrhage and large intraventricular hemorrhage. Participants will receive either t-PA or a placebo every eight hours for up to nine doses. Symptom onset must be within 24 hours prior to a diagnostic CT scan. The neurological function of the two groups will be compared at six months following treatment.

Field Administration of Stroke Therapy Magnesium Trial (FAST-MAG)
Currently, the drug t-PA—the only treatment shown to be effective in treating acute ischemic stroke—must be administered after hospital arrival and within the first three hours of stroke occurrence. There is a need for new treatments that can be administered safely at an earlier time. The purpose of this multicenter, randomized, double-blind trial is to determine if paramedic initiation of the neuroprotective agent magnesium sulfate in the ambulance is an effective and safe treatment for acute stroke. This study will compare magnesium sulfate, an experimental therapy for stroke, vs. placebo among ambulance-transported patients with acute stroke. This trial will also determine if paramedics can safely, effectively and rapidly start neuroprotective therapies for stroke.

Insulin Resistance Intervention after Stroke Trial (IRIS)
The Insulin Resistance Intervention after Stroke (IRIS) trial tests a therapy based on evidence that links insulin resistance to an increased risk for stroke or heart disease. The goal of the trial is to determine if pioglitazone, a drug used to treat Type 2 diabetes, is effective in lowering the risk for stroke and heart attack in a group of nondiabetic men and women who have recently had a stroke and developed insulin resistance. If this intervention is effective, it has the potential to benefit a large number of stroke survivors.

Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (I-CARE)
Building on the positive outcome of the EXCITE clinical trials, investigators in the Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (I-CARE) trial are testing an experimental arm therapy called Accelerated Skills Acquisition Program (ASAP). This therapy combines challenging, intensive, and meaningful practice of tasks of the participant's choice compared to two standard types of therapy (customary arm therapy totaling 30 hours, and customary arm therapy for a duration indicated on the therapy prescription). ASAP is targeted at the acute period of stroke recovery and will enroll participants who are within one to three months after their stroke. Based on compelling scientific data, this combined therapeutic approach is designed to capitalize on the brain's inherent recovery capability to improve upper limb function in people with stroke who have weakness on one side of the body.

Interventional Management of Stroke Trial (IMS III)
The Interventional Management of Stroke Trial (IMS III) is a large study that compares two different strategies for restoring blood flow to the brain in patients who have had a severe ischemic stroke. Patients are randomized to receive either the standard FDA-approved intravenous (IV) treatment of the clot-dissolving drug t-PA alone or a combination approach that provides both standard IV t-PA and an intra-arterial (IA) therapy using either t-PA delivered into the artery directly at the site of the clot or an FDA-approved device to remove the blood clot in the brain. Therapy using both approaches will be initiated within three hours of stroke onset. The trial will measure the ability of participants to live and function independently three months after the stroke. It will also determine and compare the safety and cost effectiveness of the combined IV/IA approach to the standard IV t-PA approach.

Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trial
A transient ischemic attack (TIA) is a brief episode of neurological dysfunction that often is a harbinger of disabling strokes. The primary goal of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial is to determine if the drug clopidogrel (used to reduce or prevent blood clots) combined with aspirin is effective in preventing ischemic stroke and myocardial infarction. Individuals over age 18 who can begin treatment within 12 hours of symptom onset will be enrolled. If trial results are positive, treatment with clopidogrel could reduce the burden of stroke in the U.S. and substantially reduce costs of care.

Stroke Hyperglycemia Insulin Network Effort Trial (SHINE)
Nearly 40 percent of patients who experience an ischemic stroke are hyperglycemic upon arriving at the hospital. Current research has indicated that severe or prolonged hyperglycemia is associated with poorer outcome and increased disability. At present there are no clear guidelines for treating this condition. The purpose of this clinical trial is to determine whether tight glucose control of hyperglycemia with three days of intravenous insulin therapy is superior to the standard therapy of glucose control with subcutaneous insulin. The results from this 1,400 participant clinical trial will guide clinical practice all over the nation and the world.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
http://www.ninds.nih.gov

Information also is available from the following organizations:

American Stroke Association: A Division of American Heart Association
7272 Greenville Avenue
Dallas, TX 75231-4596
strokeinfo@heart.org
http://www.strokeassociation.org
Tel: 1-888-4STROKE (478-7653)
Fax: 214-706-5231

Brain Aneurysm Foundation
269 Hanover Street, Building 3
Hanover, MA 02339
office@bafound.org
http://www.bafound.org
Tel: 781-826-5556 888-BRAIN02 (272-4602)

Brain Attack Coalition
31 Center Drive
Room 8A07
Bethesda, MD 20892-2540
http://www.stroke-site.org
Tel: 301-496-5751
Fax: 301-402-2186

National Stroke Association
9707 East Easter Lane
Suite B
Centennial, CO 80112-3747
info@stroke.org
http://www.stroke.org
Tel: 303-649-9299 800-STROKES (787-6537)
Fax: 303-649-1328

National Aphasia Association
350 Seventh Avenue
Suite 902
New York, NY 10001
naa@aphasia.org
http://www.aphasia.org
Tel: 212-267-2814 800-922-4NAA (4622)
Fax: 212-267-2812

Children's Hemiplegia and Stroke Assocn. (CHASA)
4101 West Green Oaks Blvd., Ste. 305
PMB 149
Arlington, TX 76016
info437@chasa.org
http://www.chasa.org
Tel: 817-492-4325

Hazel K. Goddess Fund for Stroke Research in Women
1217 South Flagler Drive
Suite 302
West Palm Beach, FL 33401
anne@thegoddessfund.org
http://www.thegoddessfund.org
Tel: 561-623-0504

Heart Rhythm Foundation
1400 K Street, NW
Suite 500
Washington, DC 20005
support@heartrhythmfoundation.org
http://www.heartrhythmfoundation.org
Tel: 202-464-3454
Fax: 202-464-3405

BrightFocus Foundation
22512 Gateway Center Drive
Clarksburg, MD 20871
info@brightfocus.org
http://www.brightfocus.org/alzheimers/
Tel: 1- 800-437-2423
Fax: 301-258-9454

Fibromuscular Dysplasia Society of America (FMDSA)
20325 Center Ridge Road Suite 620
Rocky River, OH 44116
admin@fmdsa.org
http://www.fmdsa.org/
Tel: 216-834-2410 888-709-7089

What Stroke Therapies are Available?

Physicians have a wide range of therapies to choose from when determining a stroke patient's best therapeutic plan. The type of stroke therapy a patient should receive depends upon the stage of disease. Generally there are three treatment stages for stroke: prevention, therapy immediately after stroke, and post-stroke rehabilitation. Therapies to prevent a first or recurrent stroke are based on treating an individual's underlying risk factors for stroke, such as hypertension, atrial fibrillation, and diabetes, or preventing the widespread formation of blood clots that can cause ischemic stroke in everyone, whether or not risk factors are present. Acute stroke therapies try to stop a stroke while it is happening by quickly dissolving a blood clot causing the stroke or by stopping the bleeding of a hemorrhagic stroke. The purpose of post-stroke rehabilitation is to overcome disabilities that result from stroke damage.

Therapies for stroke include medications, surgery, or rehabilitation.

Glossary

acute stroke-a stage of stroke starting at the onset of symptoms and last for a few hours thereafter.

agnosia-a cognitive disability characterized by ignorance of or inability to acknowledge one side of the body or one side of the visual field.

aneurysm -a weak or thin spot on an artery wall that has stretched or ballooned out from the wall and filled with blood, or damage to an artery leading to pooling of blood between the layers of the blood vessel walls.

anoxia-a state of almost no oxygen delivery to a cell, resulting in low energy production and possible death of the cell; *see* hypoxia.

anticoagulants-a drug therapy used to prevent the formation of blood clots that can become lodged in cerebral arteries and cause strokes.

antiplatelet agents-a type of anticoagulant drug therapy that prevents the formation of blood clots by preventing the accumulation of platelets that form the basis of blood clots; some common antiplatelets include aspirin and ticlopidine; *see* anticoagulants.

antithrombotics-a type of anticoagulant drug therapy that prevents the formation of blood clots by inhibiting the coagulating actions of the blood

protein thrombin; some common antithrombotics include warfarin and heparin; *see* anticoagulants.

aphasia-the inability to understand or create speech, writing, or language in general due to damage to the speech centers of the brain.

apoplexy-a historical, but obsolete term for a cerebral stroke, most often intracerebral hemorrhage, that was applied to any condition that involved disorientation and/or paralysis.

apoptosis- a form of cell death involving shrinking of the cell and eventual disposal of the internal elements of the cell by the body's immune system. Apoptosis is an active, non-toxic form of cell suicide that does not induce an inflammatory response. It is often called programmed cell death because it is triggered by a genetic signal, involves specific cell mechanisms, and is irreversible once initiated.

apraxia-a movement disorder characterized by the inability to perform skilled or purposeful voluntary movements, generally caused by damage to the areas of the brain responsible for voluntary movement.

arteriography-an X-ray of the carotid artery taken when a special dye is injected into the artery.

arteriovenous malformation (AVM)-a congenital disorder characterized by a complex tangled web of arteries and veins.

atherosclerosis-a blood vessel disease characterized by deposits of lipid material on the inside of the walls of large to medium-sized arteries which make the artery walls thick, hard, brittle, and prone to breaking.

atrial fibrillation-irregular beating of the left atrium, or left upper chamber, of the heart.

blood-brain barrier-an elaborate network of supportive brain cells, called glia, that surrounds blood vessels and protects neurons from the toxic effects of direct exposure to blood.

carotid artery-an artery, located on either side of the neck, that supplies the brain with blood.

carotid endarterectomy-surgery used to remove fatty deposits from the carotid arteries.

central stroke pain (central pain syndrome)-pain caused by damage to an area in the thalamus. The pain is a mixture of sensations, including heat and cold, burning, tingling, numbness, and sharp stabbing and underlying aching pain.

cerebral blood flow (CBF)-the flow of blood through the arteries that lead to the brain, called the cerebrovascular system.

cerebrospinal fluid (CSF)-clear fluid that bathes the brain and spinal cord.

cerebrovascular disease-a reduction in the supply of blood to the brain either by narrowing of the arteries through the buildup of plaque on the inside walls of the arteries, called stenosis, or through blockage of an artery due to a blood clot.

cholesterol-a waxy substance, produced naturally by the liver and also found in foods, that circulates in the blood and helps maintain tissues and cell membranes. Excess cholesterol in the body can contribute to atherosclerosis and high blood pressure.

"clipping"-surgical procedure for treatment of brain aneurysms, involving clamping an aneurysm from a blood vessel, surgically removing this ballooned part of the blood vessel, and closing the opening in the artery wall.

computed tomography (CT) scan-a series of cross-sectional X-rays of the brain and head; also called computerized axial tomography or CAT scan.

Coumadin®-a commonly used anticoagulant, also known as warfarin.

cytokines-small, hormone-like proteins released by leukocytes, endothelial cells, and other cells to promote an inflammatory immune response to an injury.

cytotoxic edema-a state of cell compromise involving influx of fluids and toxic chemicals into a cell causing subsequent swelling of the cell.

detachable coil-a platinum coil that is inserted into an artery in the thigh and strung through the arteries to the site of an aneurysm. The coil is released into the aneurysm creating an immune response from the body. The body produces a blood clot inside the aneurysm, strengthening the artery walls and reducing the risk of rupture.

duplex Doppler ultrasound-a diagnostic imaging technique in which an image of an artery can be formed by bouncing sound waves off the moving blood in the artery and measuring the frequency changes of the echoes.

dysarthria-a disorder characterized by slurred speech due to weakness or incoordination of the muscles involved in speaking.

dysphagia-trouble swallowing.

edema-the swelling of a cell that results from the influx of large amounts of water or fluid into the cell.

embolic stroke-a stroke caused by an embolus.

embolus-a free-roaming clot that usually forms in the heart.

endothelial wall-a flat layer of cells that make up the innermost lining of a blood vessel.

excitatory amino acids-a subset of neurotransmitters; proteins released by one neuron into the space between two neurons to promote an excitatory state in the other neuron.

extracranial/intracranial (EC/IC) bypass-a type of surgery that restores blood flow to a blood-deprived area of brain tissue by rerouting a healthy artery in the scalp to the area of brain tissue affected by a blocked artery.

functional magnetic resonance imaging (fMRI)-a type of imaging that measures increases in blood flow within the brain.

glia-also called neuroglia; supportive cells of the nervous system that make up the blood-brain barrier, provide nutrients and oxygen to the vital neurons, and protect the neurons from infection, toxicity, and trauma. Some examples of glia are oligodendroglia, astrocytes, and microglia.

glutamate-also known as glutamic acid, an amino acid that acts as an excitatory neurotransmitter in the brain.

hemiparesis-weakness on one side of the body.

hemiplegia-complete paralysis on one side of the body.

hemorrhagic stroke-sudden bleeding into or around the brain.

heparin-a type of anticoagulant.

high-density lipoprotein (HDL)-also known as the good cholesterol; a compound consisting of a lipid and a protein that carries a small percentage of the total cholesterol in the blood and deposits it in the liver.

homeostasis-a state of equilibrium or balance among various fluids and chemicals in a cell, in tissues, or in the body as a whole.

hypertension (high blood pressure)-characterized by persistently high arterial blood pressure defined as a measurement greater than or equal to 140 mm/Hg systolic pressure over 90 mm/Hg diastolic pressure.

hypoxia-a state of decreased oxygen delivery to a cell so that the oxygen falls below normal levels; *see* anoxia.

incidence-the extent or frequency of an occurrence; the number of specific new events in a given period of time.

infarct-an area of tissue that is dead or dying because of a loss of blood supply.

infarction-a sudden loss of blood supply to tissue, causing the formation of an infarct.

interleukins-a group of cytokine-related proteins secreted by leukocytes and involved in the inflammatory immune response of the ischemic cascade.

intracerebral hemorrhage-occurs when a vessel within the brain leaks blood into the brain.

ischemia-a loss of blood flow to tissue, caused by an obstruction of the blood vessel, usually in the form of plaque stenosis or a blood clot.

ischemic cascade-a series of events lasting for several hours to several days following initial ischemia that results in extensive cell death and tissue damage beyond the area of tissue originally affected by the initial lack of blood flow.

ischemic penumbra-areas of damaged, but still living, brain cells arranged in a patchwork pattern around areas of dead brain cells.

ischemic stroke-ischemia in the tissues of the brain.

lacunar infarction-occlusion of a small artery in the brain resulting in a small area of dead brain tissue, called a lacunar infarct; often caused by stenosis of the small arteries, called small vessel disease.

large vessel disease-stenosis in large arteries of the cerebrovascular system.

leukocytes-blood proteins involved in the inflammatory immune response of the ischemic cascade.

lipoprotein-small globules of cholesterol covered by a layer of protein; produced by the liver.

low-density lipoprotein (LDL)-also known as the bad cholesterol; a compound consisting of a lipid and a protein that carries the majority of the total cholesterol in the blood and deposits the excess along the inside of arterial walls.

magnetic resonance angiography (MRA)-an imaging technique involving injection of a contrast dye into a blood vessel and using magnetic resonance techniques to create an image of the flowing blood through the vessel; often used to detect stenosis of the brain arteries inside the skull.

magnetic resonance imaging (MRI) scan-a type of imaging involving the use of magnetic fields to detect subtle changes in the water content of tissues.

mitochondria-the energy producing organelles of the cell.

mitral annular calcification-a disease of the mitral valve of the heart.

mitral valve stenosis-a disease of the mitral heart valve involving the buildup of plaque-like material on and around the valve.

necrosis-a form of cell death resulting from anoxia, trauma, or any other form of irreversible damage to the cell; involves the release of toxic cellular material into the intercellular space, poisoning surrounding cells.

neuron-the main functional cell of the brain and nervous system, consisting of a cell body, an axon, and dendrites.

neuroprotective agents-medications that protect the brain from secondary injury caused by stroke.

oxygen-free radicals-toxic chemicals released during the process of cellular respiration and released in excessive amounts during necrosis of a cell; involved in secondary cell death associated with the ischemic cascade.

plaque-fatty cholesterol deposits found along the inside of artery walls that lead to atherosclerosis and stenosis of the arteries.

plasticity-the ability to be formed or molded; in reference to the brain, the ability to adapt to deficits and injury.

platelets-structures found in blood that are known primarily for their role in blood coagulation.

prevalence-the number of cases of a disease in a population at any given point in time.

recombinant tissue plasminogen activator (rt-PA)-a genetically engineered form of t-PA, a thrombolytic, anti-clotting substance made naturally by the body.

small vessel disease-a cerebrovascular disease defined by stenosis in small arteries of the brain.

stenosis-narrowing of an artery due to the buildup of plaque on the inside wall of the artery.

stroke belt-an area of the southeastern United States with the highest stroke mortality rate in the country.

stroke buckle-three southeastern states, North Carolina, South Carolina, and Georgia, that have an extremely high stroke mortality rate.

subarachnoid hemorrhage-bleeding within the meninges, or outer membranes, of the brain into the clear fluid that surrounds the brain.

thrombolytics-drugs used to treat an ongoing, acute ischemic stroke by dissolving the blood clot causing the stroke and thereby restoring blood flow through the artery.

thrombosis-the formation of a blood clot in one of the cerebral arteries of the head or neck that stays attached to the artery wall until it grows large enough to block blood flow.

thrombotic stroke-a stroke caused by thrombosis.

tissue necrosis factors-chemicals released by leukocytes and other cells that cause secondary cell death during the inflammatory immune response associated with the ischemic cascade.

total serum cholesterol-a combined measurement of a person's high-density lipoprotein (HDL) and low-density lipoprotein (LDL).

t-PA-see recombinant tissue plasminogen activator.

transcranial magnetic stimulation (TMS)-a small magnetic current delivered to an area of the brain to promote plasticity and healing.

transient ischemic attack (TIA)-a short-lived stroke that lasts from a few minutes up to 24 hours; often called a mini-stroke.

vasodilators-medications that increase blood flow to the brain by expanding or dilating blood vessels.

vasospasm-a dangerous side effect of subarachnoid hemorrhage in which the blood vessels in the subarachnoid space constrict erratically, cutting off blood flow.

vertebral artery-an artery on either side of the neck; *see* carotid artery.

warfarin-a commonly used anticoagulant, also known as Coumadin®.

Appendix

The Ischemic Cascade

The brain is the most complex organ in the human body. It contains hundreds of billions of cells that interconnect to form a complex network of communication. The brain has several different types of cells, the most important of which are *neurons*. The organization of neurons in the brain and the communication that occurs among them lead to thought, memory, cognition, and awareness. Other types of brain cells are generally called *glia* (from the Greek word meaning "glue"). These supportive cells of the nervous system provide scaffolding and support for the vital neurons, protecting them from infection, toxins, and trauma. Glia make up the blood-brain barrier between blood vessels and the substance of the brain.

Stroke is the sudden onset of paralysis caused by injury to brain cells from disruption in blood flow. The injury caused by a blocked blood vessel can occur within several minutes and progress for hours as the result of a chain of chemical reactions that is set off after the start of stroke symptoms. Physicians and researchers often call this chain of chemical reactions that lead to the permanent brain injury of stroke the *ischemic cascade*.

Primary Cell Death

In the first stage of the ischemic cascade, blood flow is cut off from a part of the brain (ischemia). This leads to a lack of oxygen (anoxia) and lack of nutrients in the cells of this core area. When the lack of oxygen becomes extreme, the *mitochondria*, the energy-producing structures within the cell, can no longer produce enough energy to keep the cell functioning. The mitochondria break down, releasing toxic chemicals called *oxygen-free radicals* into the cytoplasm of the cell. These toxins poison the cell from the inside-out, causing destruction of other cell structures, including the nucleus.

The lack of energy in the cell causes the gated channels of the cell membrane that normally maintain *homeostasis* to open and allow toxic amounts of calcium, sodium, and potassium ions to flow into the cell. At the same time, the injured ischemic cell releases *excitatory amino acids*, such as glutamate, into the space between neurons, leading to overexcitation and injury to nearby cells. With the loss of homeostasis, water rushes into the cell making it swell (called cytotoxic edema) until the cell membrane bursts under the internal pressure. At this point the nerve cell is essentially permanently injured and for all purposes dead (*necrosis* and infarction*).* After a stroke starts, the first cells that are going to die may die within 4 to 5 minutes. The response to the treatment that restores blood flow as late as 2 hours after stroke onset would suggest that, in most cases, the process is not over for at least 2 to 3 hours. After that, with rare exceptions, most of the injury that has occurred is essentially permanent.

Secondary Cell Death

Due to exposure to excessive amounts of glutamate, nitric oxide, free radicals, and excitatory amino acids released into the intercellular space by necrotic cells, nearby cells have a more difficult time surviving. They are receiving just enough oxygen from *cerebral blood flow (CBF)* to stay alive. A compromised cell can survive for several hours in a low-energy state. If blood flow is restored within this narrow window of opportunity, at present thought to be about 2 hours, then some of these cells can be salvaged and become functional again. Researchers funded by the NINDS have learned that restoring blood flow to these cells can be achieved by administrating the clot-dissolving thrombolytic agent t-PA within 3 hours of the start of the stroke.