STROKE (THROMBOTIC)

(Ischemic, Thrombotic, Embolic, and Transient Ischemic Attack)

Stroke is the third leading cause of death in developed countries (behind coronary heart disease and cancer). The consequences of a stroke are often devastating. About 25% of sufferers die as a result of the stroke or its complications, and almost 50% have moderate to severe health impairments and long-term disabilities, including partial paralysis and depression. Stroke is the leading cause of serious disability in the United States. Only 26% recover most or all normal health and function.

In this protocol, we discuss methods of preventing primary and secondary strokes, along with approaches to restoring function to brain cells that are damaged by a stroke (i.e. inducing and/or accelerating rehabilitation). Since some people may refer to this protocol if they have symptoms of an acute stroke, we begin with the initial steps involved in diagnosis and immediate treatment.

A stroke is defined as the sudden development of neurological symptoms usually caused by a decreased blood flow to the brain. Strokes often occur abruptly with the following symptoms:

- Sudden trouble standing or walking, dizziness, loss of balance or coordination.
- Sudden numbness of the face, arm or leg weakness, especially on one side of the body.
- Sudden confusion, trouble speaking or understanding.
- Sudden trouble seeing with one or both eyes.
- Sudden, severe headaches with no known cause.

Other important, but less common stroke symptoms include:

- Sudden nausea, fever and vomiting which is distinguished from a viral illness by the speed of onset (minutes or hours instead of several days)
- Brief loss of consciousness or a period of decreased consciousness (fainting, confusion, convulsions or coma)

WARNING: Any of the above signs may be only temporary and may last only a few minutes. Stroke Symptoms Source: Mayo Medical Clinic, 1999 and The National Stroke Association, 1999.

Immediate Response is Crucial

The time it takes to receive treatment is as important to stroke victims as it is for those suffering a heart attack! Not recognizing the symptoms of a stroke, or believing that stroke is untreatable, many people fail to respond to the warning symptoms of stroke and do not seek immediate medical attention.

Amazingly, 42% of stroke patients wait as long as 24 hours before presenting for medical treatment. That’s 21 hours too late! The delay in presenting at the emergency room results in a missed opportunity to effectively treat, and possibly reverse, the damage caused by thrombotic stroke. According to one published study, “Patients with milder symptoms, for whom treatment might be more effective, were less likely to arrive in time for therapy”. (Alberts, Bertels et al. 1990)

A conclusive body of evidence shows that specialized stroke centers, combined with educating the public about the importance of *time to treatment*, has decreased the incidence of death associated with all types of strokes.

Aggressive Stroke Therapy

Health care providers still do not treat stroke as aggressively as they do heart attack. Many therapies that are proven to work are not made available to the acute stroke patient presenting in the emergency room.

Further contributing to stroke deaths is the belief by many health care providers that stroke is untreatable, leading to an attitude of "watchful waiting" with an onset of a stroke, instead of being focused on treating the stroke as a medical emergency. The National Stroke Association succinctly described this problem as follows: "These outdated attitudes serve as the largest obstacle to the effective prevention and emergency treatment of strokes."

The use of computerized tomography (CT) and Doppler ultrasonography has made radical changes in early diagnosis of ischemic and hemorrhagic strokes. These advances have resulted in declines in stroke mortality. In the 1980s, the development of MRI imaging further improved evaluation of persons with cerebrovascular disease.

Tissue plasminogen activator

The FDA approved the use of a tissue plasminogen activator (t-PA) in June 1996 to treat strokes. t-PA had already been approved to dissolve clots that occur in the coronary arteries (which cause an acute heart attack), but the FDA has delayed approving t-PA to treat ischemic stroke for many years. Millions of cases of death and permanent paralysis occurred because of the FDA's delay in approving t-PA in treating stroke caused by abnormal blood clotting in the brain's arteries. Physicians affiliated with the Life Extension Foundation were using t-PA in emergency rooms to treat ischemic stroke years before the FDA gave its official seal of approval.

t-PA (sold under the brand name Activase) should be administered immediately (or within 3 hours) after a stroke in order to dissolve the clot that is preventing blood from reaching a portion of the brain. It is a natural clot-dissolving substance produced by the body and can literally blow open the blood clot in the brain that is causing the acute ischemic brain damage characteristic of a stroke.

In a recent study, 30% more stroke victims were able to regain full use of their faculties after receiving t-PA. Even today, patients may encounter severe resistance from emergency room physicians who are reluctant to administer it, even if a patient's life is at stake. In some cases, surgery may be needed to remove any blockage of blood vessels going to the brain since it is important to get the blood circulating to the brain.

While t-PA can dissolve the blood clot that causes a blood-vessel blockage, there are other complications that occur during ischemic stroke that have to be addressed if permanent brain damage is to be prevented. Any interruption in blood flow causes an oxygen imbalance (hypoxia) that results in massive free radical damage. It is critically important to have antioxidants in your bloodstream when t-PA is administered to reduce the free radical damage that will occur when blood flow is restored.

Heparin

Heparin is a natural polysaccharide normally found in mast cells. Heparin increases the activity of antithrombin III, preventing the conversion of fibrinogen to fibrin. Heparin must be administered parenterally (by IV) because it is not absorbed in the GI tract. Because of this, heparin may be used in acute care situations, but not usually in stroke prevention.

Silent Strokes

The debilitating stroke depicted on television shows or movies has severe symptoms. Most strokes, however, are not as dramatic. Often the symptoms are minor and transient and may be ignored or dismissed as unimportant. Over time these silent strokes lead to memory loss and other neurological problems. According to one study, by the time people reach their 70's, one in three suffers a silent stroke every year. (Leary 2001)

Of particular concern to stroke victims is that silent strokes occur frequently, causing neurological damage days or weeks after the initial crisis. A recent study found that one-forth of stroke survivors had at least one silent stroke during the two years following their initial stroke. (Corea, Henon et al. 2001)

The Underlying Causes

We often consider "heart attack" as a "life or death" health event. Strokes have been given less attention, but the new realization that the disease is an acute event has now led to stroke being referred to as a "brain attack." Thrombotic strokes are a major cause of brain attacks, and are caused in part by atherosclerosis, hypertension, and procedures that cause abnormal arterial blood clot formation (thrombosis) such as atrial fibrillation and heart valve replacement.

As with almost all cardiovascular disease, strokes are generally the result of several underlying diseases which work to stop or reduce the flow of blood to the brain, causing disability or death.

Blood Clots

The majority of strokes occur when a blood clot blocks the flow of oxygenated blood to a portion of the brain. This type of stroke, caused by a blood clot blocking, or "plugging," a blood vessel, is called *ischemic stroke.* An ischemic stroke can be caused by a blood clot that forms inside the artery of the brain (*a thrombotic stroke*), or by a clot that forms somewhere else in the body and travels to the brain (*an embolic stroke*). In healthy individuals, blood clotting is beneficial. When you are bleeding from a wound, blood clots work to stop the bleeding. In the case of ischemic stroke, abnormal blood clotting blocks large as well as small arteries in the brain, cutting off blood flow, resulting in a clinical diagnosis of ischemic, thrombotic, or embolic stroke.

Ischemic strokes account for 83% of all strokes, and occur as either an embolic or thrombotic stroke. Thrombotic strokes represent 52% of all ischemic strokes. Thrombotic strokes are caused by unhealthy blood vessels becoming clogged with a buildup of fatty deposits, calcium, and blood clotting factors such as fibrinogen and cholesterol. We generally refer to this as atherosclerotic disease. Simplistically, what happens with a thrombotic stroke is that our bodies regard these "buildups" as multiple, infinitesimal, repeated injuries to the blood vessel wall. Our own bodies react to these injuries, and, just as they would if we were bleeding from a small wound, respond by forming blood clots. Unfortunately, in the case of thrombotic strokes, these blood clots get caught on the plaque on the vessel walls and reduce or stop blood flow to the brain. That's when we suffer a brain attack.

Two types of thrombosis can cause a stroke: large vessel thrombosis and small vessel disease. Thrombotic stroke occurs most often in the large arteries, magnifying the impact and devastation of disease. Most large vessel thrombosis is caused by a combination of long-term atherosclerosis followed by rapid blood clot formation. Many thrombotic stroke patients have coronary artery disease, and heart attacks are a frequent cause of death in patients who have suffered this type of brain attack.

The second type of thrombotic stroke is small vessel disease, which occurs when blood flow is blocked to a very small arterial vessel. Little is known about the specific causes of small vessel disease, but it is often closely linked to hypertension and is an indicator of atherosclerotic disease.

In an embolic stroke, a blood clot forms somewhere in the body (usually the heart) and travels through the bloodstream to the brain. Once in the brain, the clot eventually travels to a blood vessel

small enough to block its passage. The clot lodges there, blocking the blood vessel and causing a stroke.

The other type of stroke is called hemorrhagic stroke and is not caused by a blood clot. A hemorrhagic stroke, also known as a cerebral hemorrhage, occurs when a blood vessel in the brain breaks or ruptures and bleeds. This type of stroke occurs less frequently than ischemic stroke. Hemorrhagic strokes are discussed in a separate protocol.

Risk Factors

The risk factors for thrombotic strokes are the presence of hypertension, atherosclerosis, high LDL-cholesterol, excessive blood-clotting factors (such as fibrin and fibrinogen), heart valve defects, diabetes, and aging. High serum levels of homocysteine, fibrinogen and/or C-reactive protein may be the strongest predictive risk factors.

Uncontrollable Risk Factors

- **Increasing age**. The chance of having a stroke more than doubles for each decade of life after age 55. While strokes are common among the elderly, substantial numbers of people less than 65 also have strokes.
- **Gender**. Overall, men have about a 19% greater chance of a stroke than women. Among people under age 65, the risk for men is even greater when compared to that of women.
- **Family history**. The chance of a stroke is greater in people who have a family history of strokes.
- **Race** African-Americans have a much higher risk of death and disability from a stroke than Caucasians, in part because African- Americans have a greater incidence of high blood pressure.
- **Diabetes mellitus**. Diabetes is an independent risk factor for stroke and is strongly correlated with high blood pressure. While diabetes is treatable, having it still increases a person's risk of a stroke. People with diabetes often also have high cholesterol and are overweight, increasing their risk even more.

Controllable Risk Factors

- **High blood pressure**. High blood pressure is the most prominent risk factor for stroke. In fact, stroke risk varies directly with blood pressure. More widespread treatment of high blood pressure is a key reason for the decline in the death rates for strokes.
- **High blood levels of homocysteine, C-reactive protein and/or fibrinogen.** The safe ranges of these blood indicators will be described later in this protocol, along with steps that can be taken if excess levels of these stroke risk factors are detected.
- **Heart disease**. A diseased heart increases the risk of a stroke. In fact, people with heart problems have more than twice the risk of a stroke as those with hearts that work normally. Atrial fibrillation (the rapid, uncoordinated beating of the heart's upper chambers), in particular, raises the risk for stroke. Heart attack is also the major cause of death among survivors of a stroke.
- **High cholesterol.** High cholesterol can directly and indirectly increase stroke risk by clogging blood vessels and putting people at greater risk of coronary heart disease, another important stroke risk factor.

- **Sleep disordered breathing.** Sleep apnea is a major cardiovascular and stroke risk factor increasing blood pressure rates which may cause stroke or heart attack. Studies also indicate that people with sleep apnea develop dangerously low levels of oxygen in the blood while carbon dioxide levels rise, possibly causing blood clots or even strokes to occur. Diagnosing sleep apnea early may be an important stroke prevention tool.
- **Prior stroke**. The risk of a stroke for someone who has already had one is several times that of a person who has not.
- **Carotid artery disease**. The carotid arteries in your neck supply blood to your brain. A carotid artery damaged by atherosclerosis (a fatty buildup of plaque in the artery wall) may become blocked by a blood clot, which may result in a stroke. If you have a diseased carotid artery, your health care provider may hear an abnormal sound in your neck, called a bruit, when listening with a stethoscope.
- **Transient ischemic attacks** (TIAs). TIAs are "mini-strokes" that produce stroke-like symptoms, but no lasting damage. They are strong predictors of a stroke. A person who has had one or more TIAs is almost 10 times more likely to have a stroke than someone of the same age and sex who hasn't. WARNING: TIAs are extremely important stroke warning signs. Don't ignore them!
- **High red blood cell count**. A moderate or marked increase in the red blood cell count is a risk factor for stroke. The reason is that more red blood cells thicken the blood and make clots more likely.

Lifestyle Factors

- **Cigarette smoking**. In recent years studies have shown cigarette smoking, including secondhand cigarette smoke, to be an important risk factor for stroke. The nicotine and carbon monoxide in cigarette smoke damage the cardiovascular system in many ways. The use of oral contraceptives combined with cigarette smoking also greatly increases stroke risk.
- **Excessive alcohol intake**. Excessive drinking (an average of more than 1 drink per day for women and more than 2 drinks per day for men) and binge drinking can raise blood pressure; contribute to obesity, high triglycerides, cancer, and other diseases; and cause heart failure, leading to stroke.
- **Weight.** Excess weight puts a strain on the entire circulatory system. It also makes people more likely to have other stroke risk factors such as high cholesterol, high blood pressure and diabetes.

Other potential risk factors

- **Geographic location**. Stroke is more common in the southeastern United States than in other areas. These are the so-called "stroke belt" states. The age-adjusted death rates from a stroke are much higher in these states than in the rest of the country.
- **Season and climate**. Stroke deaths occur more often during periods of extremely hot or cold temperatures.
- **Socioeconomic factors**. There is some evidence that people of lower income and educational levels have a higher risk for stroke.

- **Certain kinds of drug abuse**. Intravenous drug abuse carries a high risk of stroke from cerebral embolisms. Cocaine use has been closely related to strokes, heart attacks, and a variety of other cardiovascular complications. Some of them have been fatal even in first-time cocaine users.

WARNING: Recognizing stroke symptoms and realizing that the symptoms require immediate emergency treatment can save your life!

Stroke Prevention

There are conventional drugs that can be prescribed to reduce the risk of a second stroke:

- Appropriate treatment of hypertension (high blood pressure) clearly reduces the risk of stroke. Refer to the Hypertension section of the Cardiovascular Disease Protocol for information about controlling blood pressure that your doctor may be overlooking.
- Low-dose aspirin is considered first-line therapy for the stroke prevention in those with high risk, or after heart valve replacement
- Anti-coagulant drugs such as Coumadin (Warfarin) interfere with the initiation of the coagulation cascade, and significantly reduce the risk that a blood clot will form.
- Anti-platelet drugs such Ticlid (ticlopidine) inhibit platelet aggregation, thereby reducing the risk of a new blood clot forming in the brain

The use of anticoagulant drugs involves frequent blood testing and adjusting of dose since the anti-coagulating response to these drugs varies between individuals. These drugs DON'T do anything to the clots that may already have been formed. The side effects of anticoagulant drugs mandates careful monitoring, and some people avoid these drugs because of the risk of serious side effects.

A more benign approach is to combine aspirin with nutrients like ginkgo biloba, melatonin, fish oil, garlic, and green tea extract that are relatively free of side effects.

Low-Dose Aspirin

Low-dose aspirin is the anti-platelet agent of choice for stroke prevention. The Second European Stroke Prevention Study reported risk reductions for aspirin treatment, when compared with a placebo, to be as high as 27.6%. (Sivenius, Cunha et al. 1999)

Aspirin has shown such a potent effect in preventing strokes that the use of anticoagulants such as heparin to treat ischemic strokes decreased from 1985 to 1990, whereas the use of aspirin increased by more than 50% as reported in the Minnesota Stroke Survey published in the *Journal of Stroke and Cerebral Diseases*. (McGovern, Pankow et al. 1996)

An article published in journal *Thrombosis Research* described a study on patients who had survived a stroke or transient ischemic attack (TIA). The research showed that the use of a low-dose aspirin (50 mg) reduced the incidence of stroke by 18 to 28% when study participants consumed aspirin over a period of time. (Investigators 1998)

One of the main side effects of aspirin is bleeding which may be due to a combination of its irritant action on the stomach or a prolonged bleeding time. Tinnitus also occurs at high doses. Aspirin is contraindicated for those at high risk of hemorrhagic stroke.

Aspirin is considered by many to be a "miracle" drug and may have many undiscovered health benefits. Aspirin inhibits prostanglandin E2 and C-reactive protein, which have been linked to many chronic inflammatory conditions.

Warfarin

Warfarin (Coumadin) is the drug of choice for thrombosis prophylaxis (prevention). Its uses include prophylaxis for myocardial infarction, stroke, arterial thromboembolism, and deep venous thrombosis. Warfarin is also used in patients with prosthetic (artificial) heart valves.

Warfarin was originally isolated from sweet clover in 1939. It is the active ingredient in commercial rat poison and insecticide. Warfarin interferes with the synthesis of vitamin K, which forms several essential coagulation factors. Warfarin prolongs prothrombin time (PT) and thromboplastin time (APTT). Prothrombin time is used to guide treatment. The International Normalization Ratio (INR) is becoming the new standard to monitor anti-coagulation treatment.

The International Normalization Ratio

The International Normalization Ratio (INR) standardizes prothrombin time to a control batch of thromboplastin (as the sensitivity of commercial thromboplastin reagents is variable), which allows comparisons between different samples and laboratories.

INR = (patient PT / control PT) x ISI (International Sensitivity Index)

The target INR is 2.5, with a range of 2 to 3. A target of 2 with a range of 1.6 to 2.5 may be used in elderly patients to reduce the risk of hemorrhage. Some authorities, however, disregard age and recommend the higher target of 2.5.

Side Effects and Contraindications for Warfarin

Bleeding is the primary adverse effect of warfarin therapy and is related to the intensity of anticoagulation, length of therapy, the patient's underlying clinical state, and the use of other drugs that may affect blood coagulation or interfere with warfarin’s metabolism.

- Minor bleeding complications include bleeding from mucous membranes, subconjunctival hemorrhage (bleeding under the mucous membranes covering the eyes and inner eyelids), hematuria (blood in the urine), epistaxis (nosebleed), and ecchymoses (purple patches on the skin).
- Major bleeding complications include bleeding from the gastrointestinal tract, intracranial bleeding, and retroperitoneal bleeding. Massive hemorrhage usually involves the gastrointestinal tract but may involve the spinal cord or cerebral, pericardial, pulmonary, adrenal, or hepatic sites.

Warfarin has an extremely long list of contraindications and drug interactions (see below). Of particular concern is its use in elderly patients because they are more susceptible to the effects of anticoagulants, and have an increased possibility of hemorrhage.

- Warfarin is contraindicated in alcoholism, aneurysm, breast-feeding, elderly, endocarditis, hemophilia, hemorrhage, hepatic disease, hypertension, intramuscular injections, leukemia, lumbar puncture, peptic ulcer disease, pericardial effusion, polycythemia vera, pregnancy, protein C deficiency, protein S deficiency, psychosis, surgery, vasculitis, vitamin C deficiency, and vitamin K deficiency.
- Warfarin interacts with a large number of common drugs, including acetaminophen, aspirin, barbiturates, some antibiotics, estrogens, ethanol, heparin, influenza virus vaccine, lovastatin, NSAIDs, oral contraceptives, thrombolytic agents, and thyroid hormones. Your

physician must be informed of all prescription and over-the-counter medications you are taking before beginning warfarin therapy.

- Adverse side effects to warfarin include agranulocytosis, alopecia (hair loss), anorexia, bleeding, chondrodysplasia punctata, cleft palate, diarrhea, exfoliative dermatitis, fetal abortion, intracranial hemorrhage, intraocular hemorrhage, leukopenia, nausea/vomiting, pruritus (itching), purple-toe syndrome, skin necrosis, and urticaria.

Ticlopidine

Ticlopidine (Ticlid) inhibits platelet aggregation by interfering with the binding of fibrinogen to the platelet membrane. Ticlopidine is a prescription drug that may be of value as an alternative to aspirin. Ticlopidine is often considered in patients that have a high risk of thrombotic stroke and are intolerant of aspirin.

- Ticlopidine is contraindicated in blood disorders such as hemorrhage, coagulopathy, intercranial hemorrhage, neutropenia, and thrombocytopenia. It is not used before surgery. Ticlopidine is also contraindicated in hepatic (liver) disease and hypercholesterolemia.
- Ticlopidine has drug reactions with antacids, anticoagulants, aspirin, cimetidine, cyclosporine, digoxin, theophylline and thrombolytic agents.
- Ticlopidine has a large number of side effects, including agranulocytosis, anemia, arthropathy, cholestasis, diarrhea, dyspepsia, elevated hepatic enzymes, hemolysis, hepatitis, hypercholesterolemia, hyponatremia, interstitial pneumonitis, jaundice, nausea/vomiting, nephrotic syndrome, neutropenia, pancytopenia, peripheral neuropathy, pruritus, purpura, serum sickness, thrombocytopenia, thrombotic thrombocytopenic purpura (TTP), and urticaria vasculitis.

An analysis of 18 trials documented a 23% reduction in stroke risk with anti-platelet agents. The drug ticlopidine was found to be the most effective anti-platelet agent, but its adverse side effects frequently restrict its long-term use. (Albers 1995)

A recent review of clinical trials compared aspirin and ticlopidine. Ticlopidine was found to be modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk, but there is uncertainty about the size of the additional benefit. Ticlopidine was associated with less gastrointestinal hemorrhage and other upper gastrointestinal upset than aspirin, but commonly had side effects of skin rash and diarrhea. Ticlopidine was also associated with developing side effects of neutropenia and thrombotic thrombocytopenic purpura. (Hankey, Sudlow et al. 2000)

Cholesterol-Lowering Drugs

Recent studies have found that statin drugs (HMG-CoA reductase inhibitors) may be of benefit in reducing the incidence of ischemic stroke for patients with established coronary artery disease. (Vaughan and Delanty 1999) (Vaughan, Delanty et al. 2001a) (Vaughan, Delanty et al. 2001b) (Furberg 1999) The beneficial effects os statin drugs in stroke prevention may be due to several mechanisms, including:

- Lowering cholesterol levels
- Anti-atherosclerotic, anti-inflammatory, and anti-thrombotic actions of statins that occur within the blood and in plaque

- Statins may also protect against cerebral ischemia through beneficial modulation of the brain endothelial nitric oxide system. Statins both up-regulate endothelial nitric oxide synthase (eNOS) and inhibit inducible nitric oxide synthase (iNOS), effects that may protect the nervous system.

A recent study examined the protective effects of Mevacor (mevastatin) in male mice. Mevastatin (2 mg/kg or 20 mg/kg per day) was administered to male mice for 7, 14, or 28 days before inducing a middle cerebral artery occlusion. Mevastatin increased levels of endothelial nitric oxide synthase mRNA and protein, reduced infarct size, and improved neurological deficits in a dose- and time-dependent manner. The greatest protection was seen with 14- and 28-day high-dose treatment (26% and 37% infarct reduction, respectively). Cholesterol levels were reduced after only 28 days of treatment and did not correlate with infarct reduction. Baseline absolute cerebral blood flow was 30% higher after 14-day high-dose treatment. (Amin-Hanjani, Stagliano et al. 2001)

Mevacor (mevastatin) and other statin drugs used to lower cholesterol are available by perscription.

Novel Factors For Preventing Primary or Secondary Stroke

Homocysteine

Homocysteine, an intermediate molecule formed from methionine, has been shown to be a risk factor for cardiovascular disease, including atherosclerosis, heart attack and stroke. Elevated homocysteine levels are found in 20-40% of patients with heart disease. Elevated homocysteine is present in as many as 50% of patients with stroke! Measuring and reducing homocysteine levels is an important preventive highly recommended by the Life Extension Foundation since as early as 1981 (almost two decades before it was recognized by conventional medicine). (Selhub and D'Angelo 1998) (Boden-Albala and Sacco 2000) (Hankey and Eikelboom 2001)

The exact mechanism by which homocysteine promotes artereosclerosis is currently being investigated. Several mechanisms have been proposed: (Sarkar and Lambert 1999)

- Homocysteine accumulates in endothelial cells causing endothelial dysfunction and injury followed by platelet activation and thrombus formation.
- Homocysteine stimulates the proliferation of smooth muscle cells which line arteries, a central component in atherogenesis.
- Homocysteine induces endothelial cell injury due to the generation of hydrogen peroxide which damages endothelial cells, exposing the underlying cell matrix and smooth muscle cells. This, in turn, promotes the activation of platelets and leukocytes to repair the injury (the blood clotting system)
- Homocysteine increases nitric oxide production by activating transcription factor NF.
- Homocysteine leads to an overproduction of oxidative radicals (reactive oxygen species) that cause lipid peroxidation and oxidation of LDL cholesterol. These oxidized lipids form dense particles which are consumed by macrophages that create foam cells that accumulate in plaques on the endothelial cells lining arteries.
- Homocysteine also interferes with DNA repair which makes the blood vessels less pliable and more susceptible to plaque buildup.

Dr. Kilmer McCully reported that homocysteine plays a key role in every pathophysiological process that leads to arteriosclerotic plaque. Some consider homocysteine to be much worse than cholesterol. (McCully 1996)

Homocysteine, although toxic itself, is normally metabolized into other nutrients that are beneficial to the body, including cysteine, taurine and glutathione. Several natural supplements (including vitamin B6, vitamin B12, folic acid, zinc and methyl donors such as trimethylglycine, SAMe, and choline) are needed for homocysteine metabolism.

Fibrinogen

Fibrinogen is a blood protein that forms fibrin in a reaction that initiates the formation of blood clots. The entire mechanism is called coagulation (the process of changing from a liquid into a solid). If fibrinogen levels are too high, blood clots can form. If fibrinogen levels are too low, the blood will be too thin and a hemorrhage can result (see the Hemorrhagic Stroke protocol for more information.)

An article in the *New England Journal of Medicine* showed that those with high levels of fibrinogen were more than twice as likely to die of a heart attack. Ten large studies have confirmed that fibrinogen is a risk factor of equal or higher value than total cholesterol. (Wilhelmsen, Svardsudd et al. 1984) (Rosengren and Wilhelmsen 1996) (Beamer, Coull et al. 1998) (Ma, Hennekens et al. 1999)

Fibrinogen can be increased by several factors:

- Smoking increases fibrinogen. (Wilhelmsen, Svardsudd et al. 1984) (Lip 1995)
- Homocysteine can make fibrinogen more dangerous by inhibiting the production of plasminogen activators (substances that break down fibrin)
- Infections and exposure to cold have been shown to increase fibrinogen levels, which may explain why cardiovascular mortality is increased during the winter months (Khaw 1997) (Zhu, Nieto et al. 2001)
- Psychological and mental stress can increase fibrinogen levels. (Lip 1995)
- There appears to be a hormonal influence on fibrinogen. Increased fibrinogen levels and elevated platelet aggregration (with an increased risk of thrombosis) have been found in individuals that use oral contraceptives. (Lip 1995)

A study of 34 patients with thrombotic stroke and 58 matched controls found that stroke victims had a significantly higher level of fibrinogen. The researchers also found a correlation between fibrinogen levels and white blood cell aggregration. The authors proposed that enhanced white blood cell adhesion and aggregration with the subsequent release of free radicals may be one of the mechanisms of fibrinogen in the development of stroke. (Belch 1998)

Lipoprotein A

Lipoproteins are small molecules that carry lipids (fats, including cholesterol and triglycerides) in the blood. Lipoprotein (a) is an altered form of LDL that contains the apolipoprotein B-100 linked with apolipoprotein (a), which is structurally similar to plasminogen (a key protein in fibrinogen). Because of this similarity, lipoprotein (a) is considered to be very “sticky” and has been found to be a key component in blood clots. (Rath, Niendorf et al. 1989) (Beisiegel, Niendorf et al. 1990) (Rath and Pauling 1990a) (Rath and Pauling 1990b)

The lipoprotein (a) theory of heart disease was a central part of Linus Pauling's work. Drs. Pauling and Rath proposed that lipoprotein (a) acts as a surrogate (substitute) for vitamin C. They hypothesized that a deficiency of vitamin C resulted in the increased production of lipoprotein (a) which both hardened the arteries and caused blood clots. Linus Pauling recommended the use of high doses of pure vitamin C and lysine to suppress lipoprotein A levels.

Insulin Resistance, Syndrome X

Syndrome X is a cluster of symptoms (high triglycerides, reduced HDL, increased blood pressure, central obesity, and elevated uric acid) characterized by insulin resistance. The insulin does not have as strong an effect on lowering blood glucose. The pancreas responds by producing more insulin to stabilize blood glucose levels, but at a significant cost in terms of increased risk of cardiovascular disease. Syndrome X is considered to be a precursor of diabetes mellitus, a known risk factor for stroke. The question as to whether Syndrome X is an independant risk factor for stroke has been the subject of several recent research studies. While some have found a moderate increase in stroke risk, others have found no significant relationship. (Shinozaki, Naritomi et al. 1996) (Pyorala, Miettinen et al. 2000) (Adachi, Hirai et al. 2001)

Syndrome X is associated with carbohydrate metabolism problems and can be managed with dietary changes that focus on reducing total and simple carbohydrates (e.g. sugar, sweets, bread, pasta, and other "junk foods") and increasing protein and fats.

Inflammation

Chronic inflammation is associated with a variety of systemic diseases, including increasing fibrinogen levels (see above). C-reactive protein (CRP) is an early marker for systemic inflammation that rises before the erythrocyte sedimentation rate (ESR), the marker of inflammation used in conventional medicine. C-reactive protein appears to bind with LDL cholesterol, increasing its stickiness and vascular adherence. C-reactive protein is considered to be a highly sensitive risk factor for cardiovascular disease.

An article published in the journal *Stroke* described a study of 193 patients in which serum CRP was measured within 24 hours after an ischemic stroke, within 48 to 72 hours, and at discharge. CRP levels at admission and discharge were found to be predictors of new vascular events or death at 1 year. The CRP level at hospital discharge was the strongest indicator, with a hazards ratio of 7.42 (95% confidence interval). (Di Napoli, Papa et al. 2001)

An article published in the journal *Circulation* described the Women's Health Study in which CRP was measured in 122 healthy participants, and from 244 age and smoking matched controls. Higher CRP levels were found in women who developed cardiovascular events. Those with the highest levels had a 5-fold increased risk of any vascular event, and a 7-fold increased risk of myocardial infarction (MI) or stroke. The authors concluded that CRP was a strong independent risk factor for cardiovascular disease. (Ridker, Buring et al. 1998)

An article published in the journal *Stroke* described a study of in which CRP levels were measured in patients diagnosed with ischemic stroke. Survival in those with higher CRP levels (the average was 10.1 mg/L) was significantly worse than those with lower levels. Higher CRP levels were found to be an independent predictor of mortality together with age and stroke severity. (Muir, Weir et al. 1999)

Reducing inflammation in the body requires an approach that addresses the underlying cause, which may be chronic viral or bacterial infections. (Zhu, Quyyumi et al. 2000a) (Zhu, Quyyumi et al. 2000b) (Grau, Buggle et al. 1995)

Chronic inflammation is a component of most chronic diseases, including arthritis. Several "wonder" herbs that have multiple beneficial effects are anti-inflammatory. These include aspirin (derived from the bark of the White willow tree), turmeric (the yellow spice which contains curcumin), and the essential fatty acids found in oils.

Several studies have examined the relationship between CRP levels and the risk of future strokes or myocardial infarction. One article related plasma CRP levels to incidence of first ischemic stroke or transient ischemic attack (TIA) in the Framingham Study original cohort. CRP levels were measured in the previously frozen plasma samples of 591 men and 871 women free of stroke/TIA during their 1980 to 1982 clinic examinations, when their mean age was 69.7 years. During 12 to 14 years of follow-up, 196 ischemic strokes and TIAs occurred. Independent of age, men in the highest CRP quartile had 2 times the risk of ischemic stroke/TIA (RR=2.0, P=0.027), and women had almost 3 times the risk (RR=2.7, P=0.0003) compared with those in the lowest quartile. (Rost, Wolf et al. 2001)

The following tables show the relative risk of a future myocardial infarction (MI) or stroke in both men and women. A lower relative risk is desirable, and is correlated with lower values of CRP. Men have a much lower CRP level corresponding to the same relative risk as women. For a relative risk of 1.0, men would have to achieve CRP levels less than 0.55 and women less than 1.50. The difference reflects the higher incidence of myocardial infarction and stroke in men.

Relative Risks – Male

CRP (mg/L)	Future MI	Future Stroke
>2.11	2.9	1.9
1.15-2.10	2.6	1.9
0.56-1.14	1.7	1.7
<0.55	1.0	1.0

Relative Risks – Female

CRP (mg/L)	Future MI or Stroke
>7.30	5.5
3.80-7.30	3.5
1.50-3.70	2.7
<1.50	1.0

Of particular interest is that the standard reference range for CRP levels is less than 4.9 mg/L. This would correspond to a very high relative risk of future stroke or MI for both men and women, especially for men. The optimal range that knowledgeable researchers recommend is for CRP levels to be less than 2 mg/L, and preferably less than 1.3 mg/L.

Hormones

Hormones play a central role in regulating the body's metabolism, including neurological function and repair. DHEA and pregnenolone help coordinate brain cell activity and are protect neurons from damage. Aging causes a severe deficiency pregnenolone and DHEA production.

Conventional medicine has focused on the role of estrogen and stroke risk. At present a controversy exists over the increased risk of stroke associated with hormone replacement therapy and oral contraceptive use. Much of the information was based on early studies with high-dose preparations, particularly with oral contraceptives containing more than 50 micrograms of estradiol. (Goldstein, Adams et al. 2001)

Nitric Oxide

Nitric oxide is a soluble free gas naturally produced in the body (from the amino acid arginine) by endothelial cells, macrophages, and specific neurons in the brain. Nitric oxide plays several key roles in the body, including:

- Nitric oxide relaxes vascular smooth muscle, which causes vasodilation
- Nitric oxide reduces platelet aggregration and adhesion
- Nitric oxide produced by macrophages is cytotoxic to certain microbes and tumor cells.

Nitric oxide is synthesized from the amino acid arginine by the enzyme nitric oxide synthase. The reaction requires several nutritional cofactors, including:

- NADPH (nicotinamide adenine dinucleotide phosphate, a form of niacin)
- thiol (a sulfhydryl group, composed of sulfur and hydrogen)
- tetrahydrobiopterin (a chemical derived from folate)
- FAD (flavin adenine dinucleotide, a chemical derived from riboflavin)
- FMN (flavin mononucleotide, also derived from riboflavin)

Thus, nitric oxide synthesis requires vitamin B2 (riboflavin), vitamin B3 (niacin), and folate. (Ganong 1995)

Nitric oxide has been identified as having a key role in blood pressure regulation. Nitric oxide lowers blood pressure by stimulating the release of calcium from vascular smooth muscle cells, thereby causing the blood vessels to relax and dilate. There is now evidence that nitric oxide deficiency can cause hypertension and may also be involved in the pathogenesis of atherosclerosis. Nitric oxide donors (such as nitroglycerine and argenine) lower blood pressure and increase cerebral blood flow in patients with acute ischemic stroke.

Uncontrolled nitric oxide production, however, can lead to massive peripheral vasodilation and shock, particularly septic shock (caused by overwhelming bacterial infection). Nitric oxide can oxidize sulfhydryl groups on proteins and cause a depletion of cytosolic glutathione. It can also react with hydroxyl radicals to form the strong oxidant nitrogen dioxide. Nitric oxide has also been implicated in a variety of inflammatory diseases. Inhibitors of nitric oxide production are being tested clinically and may be of use in controlling conditions associated with excess oxidant production, such as in acute ischemic stroke. Interestingly, nitric oxide donors are also being tested for the same conditions due to its vasodilation effects. Nitroglycerine, a well-known drug for angina is a nitric oxide donor.

Nitroglycerine

Nitroglycerine (glyceryl trinitrate) is a drug commonly used to treat angina. Nitroglycerin is a nitric oxide donor. (Ikeda, Nara et al. 1997) (Castillo, Rama et al. 2000)

A double-blind randomized controlled trial examined the effects of the nitric oxide donor glyceryl trinitrate (Nitroglycerin), a known systemic and cerebral vasodilator, on 37 patients with recent (< 5 days) ischemic or hemorrhagic stroke. Transdermal glyceryl trinitrate significantly lowered blood pressure by 13.0/5.2 mmHg at day 1 and 9.3/5.0 mmHg at day 8. The lesser reduction at day 8 than day 1 suggests that tolerance to glyceryl trinitrate was developing. The authors concluded that transdermal glyceryl trinitrate lowered blood pressure by 5-8%, a clinically significant and relevant, but not excessive degree, in patients with acute stroke. (Bath, Pathansali et al. 2001)

Nitric oxide and its role in blood pressure regulation is the subject of recent scientific research, both with European drugs (aminoguanidine, discussed in the Innovate Drug Strategies section below) and natural supplements (arginine, vitamin B2, B3 and folic acid).

Lab Tests

For the last 50 years, medical doctors have concentrated on controlling blood pressure as the primary method of preventing stroke. As you can see, there are several other mechanisms involved. Assessing the status of the blood clotting system through accurate lab testing is central to assessing the risk of stroke.

- **Fibrinogen** levels are useful since fibrinogen is converted into fibrin under the influence of thrombin. Fibrinogen is often elevated after acute trauma or illness, inflammation, and as a side effect of birth control pills.
- **Prothrombin time** (PT) evaluates the time it takes for a clot to form after thromboplastin and calcium are added to the patient's plasma. Normal values are between 11 and 13 seconds. Prothrombin time is commonly used to monitor Coumadin therapy.
- **The International Normalization Ratio** (INR) is a new standard that has been developed to replace the prothrombin time. The target INR is 2.5, with a range of 2 to 3. A target of 2 with a range of 1.6 to 2.5 may be used for those at high risk.

The following markers may be predictive for the risk of stroke:

- **Triglyceride** levels have been found to be a predictor of myocardial infarction and elevated serum triglycerides have been specifically tied to the occurrence of atherothrombotic stroke and transient ischemic attacks.
- **Homocysteine** levels has been shown to be a risk factor for cardiovascular disease, including atherosclerosis, heart attack, and stroke.
- **C-reactive protein** (CRP) is a sensitive marker of inflammation in the body. Inflammation may be a crucial factor in atherosclerosis and is considered to be a strong predictor of myocardial infarction and stroke. (Di Napoli, Papa et al. 2001) (Ridker 2001)

In addition, overall cardiovascular risk should also be assessed with the following lab tests:

- **Total, HDL and LDL cholesterol** levels have been associated with cardiovascular risk for well over 40 years.

A comprehensive health assessment would also include measurements of the body's hormones, including DHEA, testosterone, estradiol and progesterone (for women).

It is important to realize that conventional medicine uses blood tests as a diagnostic tool. Standard reference ranges are based on statistics that find the average value for all people taking the test, including both healthy and unhealthy people.

Blood test	Reference Range	Optimal Levels
Cholesterol	Up to 199 mg/dL	Between 180-200 mg/dL
LDL Cholesterol	Up to 129 mg/dL	Under 100 mg/dL
HDL Cholesterol	35-150 mg/dL	55-150 mg/dL
Triglycerides	Up to 199 mg/dL	40-100 mg/dL
Glucose	65-109 mg/dL	70-100 mg/dL
Homocysteine	5-15 micromol/L	Under 7.2 micromol/L
Fibrinogen	200-400 mg/dL	200-300 mg/dL
ProThrombin Time PT	generally 11-15 seconds	See INR
International Normalization Ratio, INR	2 – 3, target = 2.5	1.6 - 2.5, target = 2
DHEA	Men: over 80 mcg/dL Women: over 35 mcg/dL	Men: 400-560 mcg/dL Women: 350-430 mcg/dL
CRP	Up to 4.9 mg/L	Under 2 mg/L Some suggest < 1.3 mg/L

Drug Strategies For Prevention, Treatment and Possible Rehabilitation

In the 1960s hypertension was identified as a treatable risk factor for stroke, and the decline in the incidence of and mortality from a stroke began when doctors began implementing aggressive anti-hypertensive therapies. In the 1970s aspirin was first demonstrated effective in preventing strokes, though few doctors prescribe aspirin even to this day to reduce the risk of ischemic stroke. Cigarette smoking has been proven conclusively to be a major risk factor for stroke, and smoking cessation produces a significant risk reduction within 2 years.

Researchers now believe there are an immense number of mechanisms at work causing brain cell damage and death following a stroke. Each of these mechanisms represents a potential route for intervention, as well as prevention. Given the multidimensional nature of ischemic brain cell injury,

stroke experts predict that no single drug will be able to completely protect the brain during a stroke. More likely, a combination of agents will be necessary for full recovery potential.

Most strokes culminate in a core area of cell death (infarction) in which blood flow is so drastically reduced that the cells usually cannot recover. This threshold seems to occur when cerebral blood flow is 20% of normal or less. Brain cells ultimately die as a result of the actions of calcium-activated proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes), and free radicals formed as a result of the ischemic cascade.

Without neuroprotective agents, nerve and brain cells may be irreversibly damaged within several minutes. This knowledge is leading to unprecedented therapy development. Expanding knowledge regarding the nature of ischemic brain cell injury is leading researchers to focus on the development of calcium antagonists, glutamate antagonists, antioxidants, and other types of neuroprotective agents. As discussed above, the use of Hydergine to treat acute stroke may be the most effective therapy to combine with t-PA to prevent permanent brain damage.

Those who have already suffered neurologic impairment caused by ischemic stroke may also consider the following drugs:

Hydergine

The most potent antioxidant that a hospital pharmacy normally stocks for the treatment of strokes is Hydergine. You should insist that the emergency room doctor administer 10 mg of Hydergine sublingually, and another 10 mg of Hydergine orally in liquid form. Hydergine is a powerful antioxidant that reduces free radical damage. Hydergine will increase the amount of oxygen delivered to the brain, enhance the energy metabolism of brain cells, and protect brain cells against both the low- and high-oxygen environments that ischemic stroke victims often encounter. (Marc-Vergnes 1974; Saletu, Grunberger et al. 1990)

Hydergine is used in Europe and the rest of the world as a treatment for stroke, but most emergency room physicians in the United States are reluctant to prescribe it because the FDA does not recognize its value in preventing brain-cell death. Paralyzed stroke victims consume billions of health care dollars every year, and the reason most *ischemic* stroke victims are permanently paralyzed is that the FDA has stopped patients from being treated with medications to prevent brain-cell death.

Piracetam

Piracetam, a nootropic medication similar to pyroglutamate (an amino acid), would be useful in the treatment of ischemic stroke if it were approved in the United States for acute use. Piracetam appears to protect brain cells from injury and death during a stroke, thereby lessening the potential for permanent neurological damage. The recommended dosage for piracetam is 4800 mg taken orally. Piracetam is not currently available in the United States, but has been successfully used in Europe for 25 years as reported in the *Journal of Pharmacopsychiatry*. (De Reuck and Van Vleymen 1999)

A Belgian study indicated that piracetam may be very beneficial if administered within seven hours after the onset of a stroke. (De Deyn, Reuck et al. 1997)

An article published in the journal *Stroke* described a double-blind, placebo-controlled study of piracetam used to improve language recovery in post-stroke aphasia. Twenty-four stroke patients were assigned to receive either placebo or 2400 mg of piracetam twice a day. After six weeks the piracetam group showed improvement in six language functions, compared with only three in the placebo group. The authors concluded that piracetam as an adjunct to speech therapy improves the recovery of several language functions. (Kessler, Thiel et al. 2000)

A review of three studies of piracetam in ischemic stroke, however, did not find sufficient evidence to support routine use. The authors concluded that more clinical trials are needed. (Ricci, Celani et al. 2000)

Nimodipine

Nimodipine is a European drug especially recommended for head trauma victims. Nimodipine (brand name Nimotop) is a calcium channel blocker specific to the central nervous system. It prevents movement of calcium into the cells of blood vessels, thereby relaxing the vessels and increasing the supply of blood and oxygen. It dramatically improves cerebral blood flow. Nimodipine is an FDA-approved drug used to prevent and treat problems caused by a burst blood vessel around the brain but has been ignored by most neurologists treating victims of stroke and other age-related neurological diseases.

An article by Pantoni et al. (Pantoni, Rossi et al. 2000) described a 26 week, multi-national, double-blind, placebo-controlled study of nimodipine in patients with multi-infarct dementia. This study failed to show a significant effect of nimodipine on cognitive, social or global assessments. However, a lower incidence of cerebrovascular and cardiac events was observed in the nimodipine-treated patients in comparison with the placebo group. A subgroup analysis found that those with patients with subcortical vascular dementia performed better on the majority of neuropsychological tests and functional scales in comparison with patients on placebo. (Pantoni, Bianchi et al. 2000)

Studies on the use of nimodipine on thrombotic and ischemic stroke have shown mixed results (Horn, DeHaan et al 2001; Chua and Ng 2001). In one study, low dose nimodipine therapy was shown over high dose therapy to positively affect systolic and diastolic blood pressure (Ahmed, Nasman et al. 2000) However, in a second study, higher dose nimodipine was more effective than lower dose therapy (240 vs. 120 mg daily) in reducing cerebrospinal fluid calcium, thereby improving cerebral blood flow (Bereczki, Fekete et al. 2000)

There is a delayed response to nimodipine therapy. Nimodipine is recommended for at least 21 days in subarachnoid hemorrhage, and its beneficial effects in migraine prophylaxis usually become apparent after one or two months of therapy. This delayed benefit may be the reason why nimodipine has not found to be effective in several clinical studies.

Nimodipine is highly recommended as long-term therapy for thrombotic stroke patients because of its well known effect on increasing cerebral blood flow and because its tolerance in most individuals. The most common side effect is hypotension. Rapid elimination rates correspond to a half-life of 1-2 hours which necessitates frequent dosing (e.g. every four hours). The recommended dose of nimodipine is 30 mg, three times a day.

Aminoguanidine

Aminoguanidine is being studied for use in stroke because of its action as an inducible nitric oxide synthase inhibitor. (Fassbender, Fatar et al. 2000)

Aminoguanidine is one of the most widely used drugs in Europe. It works by preventing cross links caused by glycosylation (a chemical reaction between blood sugar and protein). Animal studies have found that aminoguanidine can prevent diabetic, atherosclerotic blood vessel aging, and molecular cross-linking in cells throughout the body. Aminoguanidine also prevents destructive cross-linking of collagen and elastin fibers in the brain, which is a primary cause of mental degeneration in the elderly.

An article published in *Brain Research* described a study of aminoguanidine in a rat model of middle cerebral artery occlusion. Daily injections of aminoguanidine (100 mg/kg) began six hours after the occlusion. Treatment resulted in a slowing of the growth of ischemic lesions. Interestingly,

serial measurements of nitric oxide and nitric oxide synthase activity found no difference between the treatment and placebo groups, which suggested that the neuroprotective effects of aminoguanidine may be due to mechanisms other than nitric oxide metabolism. (Cash, Beech et al. 2001)

An earlier study published in the journal *Brain Research* also used aminoguanidine in a rat model of middle cerebral artery occlusion. The authors found that treatment for a longer period of time (more than 2 days) decreased the volume of ischemic injury. The average reduction was 21% at 3 days and 30% at 4 days. (Zhang and Iadecola 1998)

An article published in the journal *Stroke* described a study of aminoguanidine used to treat rats with induced cerebral artery occlusion. Aminoguanidine (320 mg/kg IP) administered 15 minutes after the onset of ischemia resulted in a significant reduction of infarct volume. Protection was also measured when aminoguanidine was administerd 1 or 2 hours after the onset of ischemia. (Cockroft, Meistrell et al. 1996)

Aminoguanidine and Piracetam are European drugs that are not approved for use in the United States by the FDA. They can, however, be purchased from offshore pharmacies for personal use.

Carnosine

Since it is difficult for Americans to obtain aminoguanidine, a nutrient called carnosine should be considered. Carnosine has demonstrated potent anti-glycosylation properties and protects brain cells by additional mechanisms. Carnosine is a peptide made from the amino acids beta-alanine and L-histidine. Several researchers have proposed that carnosine may be of benefit in protecting against stroke. Carnosine acts to regulate the metabolism of zinc and copper which play a major role in the modulation of central nervous system excitability. (Suslina, Federova et al. 2000) (Trombley, Horning et al. 2000) (Horning, Blakemore et al. 2000)

In a recent study published in *Brain Research Bulletin*, rats were subjected to 45 minutes of reduced blood flow (ischemia) to the brain. The result was massive injury that caused 67% of the animals to die. In a group pre-treated with carnosine, only 30% died in response to the ischemic injury, and a significant protective effect was shown to cell membranes and cerebral enzyme levels. The scientists that conducted the study concluded that “carnosine protects against oxidative injury and thereby increases the survival of the animals.”

Based on extrapolations from this new study and previous reports, the risk of acute death from a stroke in someone taking carnosine every day might be reduced by more than 50% and the chances of significant neuronal impairment that could cause paralysis would also be lowered. The volume of published data on carnosine show multiple benefits including anti-oxidant, anti-glycating, aldehyde quenching, and metal chelating actions

In order to derive benefit from carnosine, enough must be consumed to saturate the carnosinase enzyme to make free carnosine available to the body.

Nutrients To Aid in Brain Cell Rehabilitation and To Help Prevent New Strokes

Any disruption of blood flow to the brain causes massive free radical damage that induces much of the reperfusion injury to brain cells characteristic of strokes. When blood flow is interrupted and subsequently restored (re-perfused), tissues release iron that provides a catalyst for the formation of

free radicals that often permanently damage brain cells. The Life Extension Foundation has spent millions of dollars conducting research that involves developing methods of protecting the brain cells from injury caused by blood-flow disruption. The use of antioxidant nutrients, drugs, and hormones, along with specific calcium-channel blockers and cell membrane–stabilizing agents, provides enormous protection to brain cells.

If you know that an ischemic stroke is occurring, antioxidant vitamins and herbs such as ginkgo biloba would be of benefit. Magnesium in an oral dose of 1500 mg is a safe nutrient to relieve an arterial spasm, a common problem in thrombotic strokes. If you take high-potency antioxidant nutrients at least 3 times a day, your chances of fully recovering from an ischemic stroke may be significantly improved.

For those who have already suffered brain damage caused by ischemic stroke, a wide-range of nutrients may be considered to aid in possible neurological recovery via several different mechanisms. The suggested doses of the nutrients listed below are contained in the summary that appears at the end of this protocol.

One of the most powerful aspects of natural supplements is that they have several different mechanisms by which they exert their beneficial effects. The supplements have been arranged in sections based on their primary action. A few supplements, however, are so important that they are in a section by themselves:

- CDP-Choline (Citicholine) is very near to being approved as a drug for the treatment of stroke.
- Ginkgo biloba is a powerful antioxidant, inhibitor of platelet aggregration, enhances cerebral blood flow, and is well-known for its beneficial effect on memory and cognitive function.
- Essential fatty acids, such as alpha linolenic acid and docosahexaenoic acid, are important in neurological repair because the brain is composed almost entirely of fatty acids. They also have very strong anti-inflammatory properties.
- Antioxidant therapy is important in stroke recovery to reduce the oxidative damage that occurs following cellular injury. Antioxidants, such as vitamin C, vitamin E and alpha-lipoic acid have been found to be beneficieal in stroke.
- Minerals play in an essential role in neurologic function primarily as neurotransmitters. Calcium, magnesium, potassium and selenium are important nutrients.
- Hormones have a definite influence on metabolism, including neurological function and repair.
- Nitric oxide metabolism is the focus of recent scientific investigation for its effect on cerebral blood flow and blood pressure
- Vinpocetine and theanine are natural supplements that may be of benefit in stroke
- A healthy diet is an essential part of any wellness plan and recent studies have confirmed the beneficial effect of fruits and vegetables on cardiovascular risk

CDP-Choline

Choline and pantothenic acid (vitamin B5) are used to produce acetylcholine, the major neurotransmitter that transmits nerve impulses between neurons. Choline is also needed for cell membrane integrity, and to move fats in and out of cells. Choline is, therefore, essential for proper

brain function as the brain is composed of millions of nerve cells and is composed almost entirely of fats.

CDP-choline is a unique form of choline that readily passes through the blood-brain barrier directly into brain tissue. CDP-choline is a rate-limiting intermediate in the biosynthesis of phosphatidylcholine, an important component of the neural cell membrane. CDP-choline (citicholine, cytidine-5'-diphosphocholine) may reduce central nervous system ischemic injury by stabilizing cell membranes and reducing free radical generation.

CDP-choline has been found to be of value in studies on animals and humans. Citicoline is approved in Europe and Japan for use in stroke, head trauma, and other neurological disorders. It is presently being evaluated in phase II/III stroke trials in the United States. (D'Orlando and Sandage 1995)

Animal Studies of CDP Choline

- CDP-choline alone and in combination with urokinase resulted in a significant decrease in neuronal damage in a study on rats with focal ischemia induced by occlusion of the middle cerebral artery. (Shuaib, Yang et al. 2000)
- CDP-choline was shown to significantly attenuate blood-brain barrier (BBB) dysfunction after transient forebrain ischemia was induced in gerbils. CDP-choline substantially attenuated edema at 3 days and reduced neuronal death after 6-day reperfusion. (Rao, Hatcher et al. 1999)
- In a study of rats with induced carotid artery embolisms, CDP-choline was shown to reduce the median infarct size from 37% in the control group to 22% at a dose of 250 mg/kg and 11% at a dose of 500 mg/kg. CDP-choline was also studied in combination with recombinant tissue plasminogen activator (rtPA). The infarct size was 24% with rtPA 5 mg/kg, 11% with rtPA and 250 mg/kg CDP-choline, and 19% with rtPA and 500 mg/kg CDP-choline. (Andersen, Overgaard et al. 1999)
- A study examined the effects of CDP-choline with medial cerebral artery occlusion induced in spontaneous hypertensive rats. CDP-choline significantly improved behavioral dysfunction. (Aronowski, Strong et al. 1996)
- A study of CDP-choline used to treat ischemia induced in rats demonstrated that CDP-choline significantly reduced infarct volume with a trend towards reducing brain edema and mortality. (Schabitz, Weber et al. 1996)

Human Studies of CDP Choline

Four studies of intravenously administered CDP-choline have been conducted outside the United States:

- A multi-center double-blind placebo-controlled study of citicoline (1000 mg per day intravenously for 14 days was conducted on patients with acute, moderate to severe cerebral infarction. One hundred thirty-three patients received CDP-choline treatment, and 139 received placebo. The group treated with CDP-choline showed significant improvements in level of consciousness compared with the placebo-treated group, and CDP-choline was an entirely safe treatment. (Tazaki, Sakai et al. 1988)
- A double-blind placebo-controlled study of citicoline (750 mg per day intravenously for 10 days) used within 48 hours of stroke onset showed a significant improvement on a quantified neurological assessment scale rating motor strength, muscular force, sensation,

higher cortical function, and ambulation at 90 days. Patients treated with citicoline were significantly more likely to be ambulatory compared with placebo-treated patients at 90 days. (Goyas, Bastard et al. 1980)

- A second double-blind, placebo-controlled trial of intravenous citicoline (250 mg three times a day for 10 days) in stroke patients treated within 48 hours of their symptoms found that a significantly higher percentage of patients had a very good to fairly good recovery with citicoline versus placebo treatment at 10 days after stroke. (Boudouresques and Michel 1980)
- A small double-blind, placebo-controlled study examined the effects of citicoline (1000 mg per day of intravenous for 30 days) or placebo in 19 patients with acute stroke treated within 48 hours. In comparison to their baseline assessments, 76% of the citicoline-treated patients demonstrated improvement compared with only 31% of the placebo-treated patients. (Corso, Arena et al. 1982)

Two trials of orally administered CDP-choline have been conducted in the United States by Clark et al:

- A randomized, double-blind, multi-center trial of CDP-choline was conducted on 259 stoke patients. Both the 500-mg per day citicoline group and the 2,000-mg per day citicoline (orally) group had a significant improvement in terms of the percent of patients who had a favorable outcome on the Barthel Index at 90 days. There were no drug-related serious adverse events or deaths in this study. This study suggests that oral citicoline can be used safely with minimal side effects in acute stroke treatment. Citicoline appears to improve functional outcome and reduce neurologic deficit with 500 mg of citicoline appearing to be the optimal dose. (Clark, Warach et al. 1997)
- In follow-up study, published in the journal *Stroke*, 394 patients with acute (24 hours) ischemic stroke received either citicholine (500 mg orally daily) or placebo for 6 weeks. No difference was found between the placebo and citicholine-treated groups. The authors, however, found a significantly higher percentage of patients with mild strokes in the placebo group (34%) than those treated with citicholine (22%). The researchers also found a similar discrepancy in the previous study (above). (Clark, Warach et al. 1997) Reanalysis of the data found that the 2000 mg dose provided the greatest therapeutic effect (instead of the 500 mg dose.) For this reason, the authors have chosen to use the 2000 mg dose in future trials. (Clark, Williams et al. 1999)

Another key difference was evident between the US and non-US trials. Those conducted in the United States by Clark et al used oral doses of citicholine (500 and 2000 mg), whereas the non-US trials used intravenous citicholine at various concentrations and doseages (750 mg per day, 250 mg three times a day, and 1000 mg per day). (Clark, Williams et al. 1999) Unfortunately, the FDA may never approve Citicholine as a drug based on the results of the second US study.

Ginkgo Biloba

Ginkgo biloba is the oldest living species of tree with individual trees living as long as 1,000 years. Ginkgo is most commonly recommended to help with memory loss and Alzheimer's disease. It is a powerful antioxidant and inhibitor of platelet aggregration, making a powerful combination for circulatory disorders, such as atherosclerosis.

Ginkgo appears not only to protect against free radicals and abnormal blood clotting, but also enhances neuronal metabolic rates that are severely impaired as a result of ischemic insult.

The conclusions of a report of 40 clinical trials stated that "positive results have been reported for ginkgo biloba extracts in the treatment of cerebral insufficiency." (Kleijnen and Knipschild 1992)

Earlier 1995 double-blind placebo-controlled trials of ginkgo biloba extract involving 55 patients with acute cerebral ischemia showed a significant improvement in cognitive function based on the Matthews scale. (Garg, Nag et al. 1995)

Gingko biloba was used with heart patients in a treadmill test in France. The doctors concluded "In a comparison of the differences before and after treatment, the areas of ischemia decreased by 38%" after its use. (Mouren, Caillard et al. 1994)

A French study of mice at the Universite de la Mediterranee, Marseille, France in 1998 says that "neuroprotective drugs such as ginkgo biloba extract could prevent the ischemia-induced impairment." (Pierre, Jamme et al. 1999)

A Japanese study found that ginkgo biloba increased cerebral blood flow and reduced infarct volume and ischemic brain damage resulting from middle cerebral artery occlusion induced rats. (Zhang, Hayashi et al. 2000)

Essential Fatty Acids

Essential fatty acids are important in both stroke prevention and during the repair of brain tissue damaged by stroke. The brain is almost entirely composed of fatty acids. The Framingham study confirmed that the friendly fats have a beneficial effect on stroke prevention. Essential fatty acids include alpha linolenic acid (ALA) found in Perilla and flax seed oils and docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) found in cold-water fish oil.

Alpha-linolenic acid

Alpha linolenic acid, an omega-3 fatty acid, may be the most efficient fatty acid in the prevention of stroke by helping to prevent abnormal blood clotting (Renaud 2001) Perilla oil and flax seed oil are rich sources of alpha-linolenic acid.

An article published in the journal *Vascular Medicine* described the Edinburgh Artery Study of over 1100 subjects examined in a random sample survey. Measurements of the fatty acid levels in red cells found that alpha-linolenic acid was significantly lower in those with stroke and lower limb disease. (Leng, Taylor et al. 1999)

These findings were confirmed in another study of 96 men with incidental stroke and 96 matched controls who were enrolled in the Multiple Risk Factor Intervention Trial. Statistical analysis of fatty acid levels found a 28% and 37% decrease in the risk of stroke with alpha-linolenic acid depending on the increase above average levels. Interestingly, an increase in stearic acid (a food additive derived from beef) was associated with a 37% increase in the risk of stroke. (Simon, Fong et al. 1995)

Docosahexaenoic acid (from fish oil)

Docosahexaenoic acid (DHA) from fish oil has been shown to prevent the development of hypertension in stroke-prone spontaneous hypertensive rats. Measurements also found that dietary DHA resulted in a decrease of arachadonic acid (a fatty acid from animal meat that increases inflammation), and restored the inferior learning performance observed in the control group. (Minami, Kimura et al. 1997) (Kimura 2000)

Another study found that omega-3 oils, such as fish, perilla, and flaxseed oils, prolonged the survival time of stroke-prone spontaneous hypertensive rats by about 10% as compared to the omega-6 safflower oil. They also found that rapeseed (canola) oil shortened the survival time by about 40%. (Miyazaki, Takemura et al. 2000)

An article published in *JAMA* described the Nurses' Health Study which found that dietary intake of fish and omega-3 polyunsaturated fatty acids were inversely associated with the risk of thrombotic infarction, primarily among women who did not regularly take aspirin. (Iso, Rexrode et al. 2001)

An article published in the journal *Stroke* described a study of 552 men in the town of Zutphen, The Netherlands between 1960 and 1970. Fewer strokes occurred among the 301 men who always reported fish consumption than among the men who changed fish consumption habits or did not consume fish at all during the study. The authors concluded that these results suggest that consumption of at least one portion of fish per week may be associated with a reduced stroke incidence. (Keli, Feskens et al. 1994)

Antioxidants

Vitamin C

Vitamin C may be useful in stroke because of its antioxidant properties. (Grzegorczyk, Rutkowski et al. 2001)

Although ascorbic acid does not pass the blood-brain barrier, its oxidized form, dehydroascorbic acid (DHAA) does. A study published in the *Proceedings of the National Academy of Science* compared the effects of ascorbic acid and DHAA used to treat mice after induction of cerebral artery occlusion. Both DHAA and ascorbic acid reduced infarct volume when given before the ischemia, but only DHAA had an effect when administered after the ischemia. DHAA (250 mg/kg or 500 mg/kg) administered 3 hours after the ischemia reduced infarct volume by 6- to 9-fold, to only 5% with the highest DHAA dose. (Huang, Agus et al. 2001)

A recent article published in the journal *Stroke* described a 20-year study in Japan that examined vitamin C levels and the risk of stroke. Strong inverse associations were observed between serum vitamin C concentration and all stroke, cerebral infarction, and hemorrhagic stroke. (Yokoyama, Date et al. 2000)

Vitamin E

Vitamin E is well-known for its antioxidant, anti-inflammatory and anti-platelet effects. Vitamin E increases the production of prostaglandin I2, a platelet aggregration inhibitor and vasodilator. Vitamin E has also been found to increase HDL (the "good" cholesterol).

The Life Extension Foundation recommends the complete spectrum of vitamin E be used including alpha tocopherol, gamma tocopherol and the tocotrienols. Vitamin E should be used with care (under the advise of a knowledgeable physician) in patients on anticoagulant drugs (Coumadin).

Alpha-Lipoic Acid

Alpha-lipoic acid is a commercially available supplement with a variety of actions that may be beneficial during acute stroke. These actions include inhibiting platelet and leukocyte activation and adhesion, reducing free radical generation, and increasing cerebral blood flow.

The effects of alpha-lipoic acid were studied on strokes induced in mice. Alpha-lipoic acid (100 mg/kg subcutaneous injection) or placebo was administered 1.5 hours before transient middle cerebral artery occlusion was induced. Infarct volume was significantly reduced, and neurologic function was significantly improved in the alpha-lipoic acid group as compared to placebo. (Clark, Rinker et al. 2001)

Most of the tissue damage that occurs from a stroke is observed during reperfusion, which is primarily attributed to oxidative injury from the production of oxygen free radicals. During the process, antioxidants such as glutathione and alpha-lipoic acid are depleted. Pretreatment with alpha-lipoic acid in rats subjected to reperfusion following cerebral ischemia dramatically reduced the mortality rate from 78% to 26% during 24 hours of reperfusion. (Panigrahi, Sadguna et al. 1996)

Another study examined the neuroprotective effects of alpha-lipoic acid using models of focal cerebral ischemia in mice and rats. Alpha-lipoic acid was able to reduce the infarct area only when it was administered subcutaneously one to two hours before the occlusion of the middle cerebral artery. (Wolz and Krieglstein 1996)

Minerals

Calcium, magnesium, and potassium are the most abundant minerals in the body. They play an important role in many of the functions of the body.

Calcium

Calcium is the most abundant mineral in the body, with most of it located in the bones and teeth. Calcium is needed for the transmission of signals between neurons. Ionized calcium initiates the formation of blood clots. It stimulates the release of thromboplastin from platelets and is a cofactor in the conversion of prothrombin to thrombin.

An article published in the journal *Stroke* described a study of calculated dietary intakes of calcium, potassium, and magnesium in the Nurses' Health Study cohort. Women in the highest quintile of calcium intake had an adjusted relative risk of ischemic stroke of 0.69 compared with those in the lowest quintile; for potassium intake the corresponding relative risk was 0.72. The authors concluded that low calcium intake (and perhaps low potassium intake) may contribute to increased risk of ischemic stroke in middle-aged American women. (Iso, Stampfer et al. 1999)

Magnesium

Magnesium regulates the absorption of calcium and complements its actions. Calcium functions to contract muscles, while magnesium relaxes them. Taking too much magnesium will loosen the stools causing diarrhea. Magnesium also functions to decrease coagulation, while calcium is involved in increasing coagulation. A proper ratio between calcium and magnesium is important to maintain.

The use of magnesium in acute stroke is, at present, controversial. Several studies report positive effect, while others do not. There are several reasons for this. The time to treatment is an important variable as the damage from a stroke happens quickly. Studies in rats show that magnesium is extremely effective if used within 2 hours, but the effectiveness rapidly decreases. A six hour window of opportunity is recommended. (Yang, Li et al. 2000)

One interesting article published in the journal *Alcohol* proposed that intravenous magnesium may be particularly useful in alcohol-induced hemorrhagic strokes, which are preceded by a rapid fall in intracellular free magnesium ions. They also propose that women are more prone to this fall in magnesium due to the hormonal effects on free magnesium. In support of this hypothesis, they state

that premenstrual tension headaches and alcohol-induced headaches (e.g., hangovers) can be ameliorated with intravenous injections of magnesium sulfate. (Altura and Altura 1999) (Babu, Cheng et al. 1999)

In a randomized, placebo-controlled, double-blind study examined the effects of magnesium sulfate given intravenously during the first 24 hours following a stroke. Intravenous magnesium was shown to have a significant positive effect. (Lampl, Gilad et al. 2001)

Potassium

Potassium is also used by the body for conducting impulses between neurons. Potassium works with sodium to maintain muscle tone, blood pressure and water balance. Studies have shown that a low potassium diet is related to a higher incidence of stroke (Bazzano, He et al. 2001). In a study reported in *Circulation*, diets rich in potassium, magnesium, and cereal fiber reduced the risk of stroke, particularly among hypertensive men. The authors conluded that potassium supplements may also be beneficial, but because of potential risks, use should be carefully monitored. (Ascherio, Rimm et al. 1998)

Selenium

Selenium is a trace mineral that is involved in the synthesis of glutathione peroxidase, a key detoxification enzyme. A study examined the association between serum selenium concentration and five-year risk of cardiovascular disease in 1,110 men aged 55 to 74 years in two rural areas of Finland. In the total cohort, all-cause and cardiovascular deaths were associated significantly with serum selenium of less than 45 mcg/L, with an adjusted relative risk of 1.4 and 1.6, respectively. Among men free of stroke at the outset, low serum selenium was associated significantly with stroke mortality, and adjusted relative risk of 3.7. (Virtamo, Valkeila et al. 1985)

Homocysteine-Lowering Supplements

Elevated levels of serum homocysteine strongly predicts stroke risk. Homocysteine detoxification requires several nuitrients including vitamin B6, vitamin B12 (cobalamin), and folic acid. Although these three vitamins are currently well-publicized, other nutritional factors are also involved in detoxifying homocysteine. Methyl donors, such as trimethylglycine (TMG) and SAMe are also needed.

B Vitamins and Trimethylglycine (TMG)

Currently, several studies are underway to evaluate the effectiveness of lowering homocysteine with vitamins. The Vitamins in Stroke Prevention (VISP) study is evaluating vitamin B6, B12, and folic acid in patients at least 35 years old that had a non-disabling ischemic stroke within 120 days, and high plasma homocysteine. (Spence, Howard et al. 2001)

Homocysteine is of particular concern for those at risk of stroke and victims of stroke. Supplementation with vitamin B6, vitamin B12, folic acid and trimethylglycine are essential for stroke risk reduction in those whose homocysteine levels are above 7.2 (micro mol/L) of blood. The methylating effects of TMG produce SAMe, which has been shown to ease depression and remyelinate nerve cells. TMG should be taken with the B vitamin cofactors mentioned above for the full effects to be reached.

SAMe

S-adenosyl-L-methionine (SAMe) is an amino acid made naturally in the body. It has been shown to be a potent anti-depressant in several double-blind studies. SAMe is so effective that it has rapidly become one ot the best-selling dietary supplements in the United States. Recent studies found that SAMe increases glutathione levels, and decreases free radical activity. SAMe also inhibits lipid peroxidation. SAMe is a methyl donor that improves brain methylation, which may account for its anti-depressant properties.

In experiments with rats, SAMe was found to increase cellular energy levels (ATP and c-AMP), and suppress the elevation of lactic acid that commonly follows ischemia. The study authors concluded that SAMe protected energy failure and accelerated recovery from ischemia and that it is beneficial for treatment of cerebral ischemia in the acute stage. (Katayama, Shimizu et al. 1985)

Cholesterol-Lowering Supplements

Policosanol

Policosanol is a natural supplement made from sugar cane. The main ingredient is octacosanol. Octacosanol is an alcohol found in the waxy film that plants have over their leaves and fruit. The leaves and rinds of citrus fruits and wheat germ oil contain octacosanol. Caviar, which reportedly has health benefits, contains high amounts of octacosanol.

Octacosanol is a “long chain fatty alcohol” (similar to cholesterol which is also an alcohol). Policosanol is a combination of octacosanol and several other long chain fatty alcohols—hence the name “poli”-cosanol. Keeping octosanol together with other naturally occurring fatty alcohols makes it more stable. There is evidence that octosanol also works better when it’s combined with other fatty alcohols.

In recent research, policosanol has shown the following benefits:

Lowers cholesterol.

Several studies have compared policosanol with provastatin, lovastatin and simvastatin. Policosanol was found to be more effective than all three at lowering LDL and total cholesterol, increasing HDL cholesterol, and improving the ratios of LDL to HDL, and total cholesterol to HDL. (Castano, Mas et al. 1999) (Crespo, Illnait et al. 1999) (Prat, Roman et al. 1999)

Inhibits the oxidation of LDL.

Oxidized LDL is dangerous. It promotes the destruction of blood vessels by creating a chronic inflammatory response. Oxidized LDL can also provoke metalloproteinase enzymes. (Xu, Meisel et al. 1999) These enzymes promote blood vessel destruction, partly by interfering with HDL’s protective effect. Studies show that rats treated with policosanol have fewer foam cells, reflecting less inflammatory response causing less blood vessel destruction. (Menendez, Fraga et al. 1999) (Noa, de la Rosa et al. 1996) (Lindstedt, Saarinen et al. 1999)

Reduces the proliferation of cells.

Healthy arteries are lined with a smooth layer of cells so that blood can race through with no resistance. One of the features of diseased arteries is that this layer becomes thick and overgrown with cells. As the artery narrows, blood flow slows down or is blocked completely. Policosanol was tested for its ability to stop the proliferation of these cells (Noa et al. 1998). According to the results,

policosanol's ability to stop cell overgrowth "is in agreement with the antiproliferative effects reported for other lipid-lowering drugs, such as most of the statins." (Negre-Aminou P 1996)

Inhibits the formation of clots.

Policosanol may work synergistically with aspirin in this respect. In a comparison of aspirin and policosanol, aspirin was better at reducing one type of platelet aggregation (clumping together of blood cells). But policosanol was better at inhibiting another type. Together, policosanol and aspirin worked better than either alone. (Arruzazabala, Valdes et al. 1997) (Stusser, Batista et al. 1998) A related effect is that significant reductions in the level of thromboxane occur in humans after two weeks of policosanol. (Carbajal, Arruzazabala et al. 1998) Thromboxane is a blood vessel-constricting eicosanoid produced by platelets. (Note: eicosanoids are powerful chemicals created in cells that can do things like create fever to kill infections, make blood vessels in lungs expand so you can breathe, and reduce inflammation. The body could not function without eicosanoids. Problems arise when eicosanoid reactions are disrupted by drugs, disease, poor diet and other factors that interfere with their natural balance).

Decreases thrombus weight.

Policosanol was shown to significantly decreases the thrombus weight in venous thrombosis experimentally induced in rats, with the protective effect persisting up to 4 hours after its oral administration. (Carbajal, Arruzazabala et al. 1994)

Garlic

Garlic is a well-known herb that is of great benefit in decreasing the risk of arteriosclerosis. It has been shown to decrease total and LDL-cholesterol, increase HDL-cholesterol, reduce serum triglyceride and fibrinogen concentration, lower arterial blood pressure and promote organ perfusion, enhance fibrinolysis, inhibit platelet aggregation, and lower plasma viscosity.

In a prospective, 4-year clinical trial, standardized garlic caused a 9 to 18% reduction and 3% regression in plaque volume, a decrease in LDL level by 4%, and an increase in HDL concentration by 8%, and lowering in blood pressure by 7%. These effects resulted in a reduction of relative cardiovascular risk for infarction and stroke by more than 50%. (Siegel, Walter et al. 1999)

Hormones

Maintaining healthy hormone levels may assist in rehabilitating neurological impairment due to stroke. Hormone levels naturally decline with aging. These declines contribute to numerous degenerative illnesses such as cardiovascular disease, immune impairment, cancer cell proliferation, and memory decline. The Life Extension Foundation has long endorsed hormone supplementation to prevent or reverse the signs of aging in both men and women. Several hormones have demonstrated an ability to facilitate brain cell energy, maintain proper levels of acetylcholine, and protect brain cell membrane function. These hormones help restore youthful synchronization of nerve impulses within the brain. Individuals who are experiencing cognitive decline from the effects of a stroke are advised to have their hormone levels checked and to discuss hormone replacement with their physician.

DHEA

Pregnenolone and DHEA improve brain cell activity and enhance memory. (Pregnenolone is converted into DHEA in the body.) DHEA is the most plentiful steroid hormone in the human body, but its exact function is unknown. What is known is that its concentration plummets with age: its daily

production drops from 30 mg at age 20 to less than 6 mg at age 80. DHEA is naturally synthesized in abundance in young people from pregnenolone in the brain and the adrenal glands. It is known to affect the excitability of neurons in the hippocampus, the part of the brain responsible for memory.

Current findings suggest that DHEA enhances memory by facilitating the induction of neural plasticity, the condition that permits the neurons (nerve cells of the brain) to change in order to record new memories. Studies have shown that DHEA not only improves memory deficits, but also relieves depression in older people and increases perceived physical and psychological well-being. DHEA has been shown to help preserve youthful neurological function. Together, pregnenolone and DHEA help to maintain the brain cells' ability to store and retrieve information in short-term memory.

A recent study found that DHEA and 7-oxo-DHEA-acetate, which is formed from DHEA, completely reversed the memory deficit induced by an injection of scopolamine in young mice. Only 7-oxo-DHEA-acetate was effective, however, in similar tests on older mice. (Shi, Schulze et al. 2000)

An article published in the journal *Stroke* described a sudy of DHEA-S used to treat rabbits exposed to ischemia induced by temporary occlusion of infrarenal aorta. Treatment with DHEA-S 5 minutes after the ischemia significantly prolonged the duration of ischemia associated with a 50% probability of permanent paraplegia (paralysis of the lower extremities). The beneficial results were still measurable after four days. The authors concluded that DHEA-S may have substantial therapeutic benefit for the treatment of ischemic stroke. (Lapchak, Chapman et al. 2000)

Pregnenolone

Pregnenolone has been described as "the most potent memory enhancer yet found," according to an article in the *Proceedings of of the National Academy of Sciences*. (Flood, Morley et al. 1995) Pregnenolone is a hormone formed from cholesterol that is a precursor to the other hormones, including progesterone, testosterone, estrogen and DHEA.

Recent research has proposed that pregnenolone may play a role in stroke through role in regulating the balance between excitation and inhibition in the central nervous system. Pregnenolone enhances N-methyl-D-aspartate (NMDA)-gated currents in spinal cord neurons, while inhibiting receptors for the inhibitory amino acids glycine and gamma-aminobutyric acid, as well as non-NMDA glutamate receptors. (Wu, Gibbs et al. 1991)

Melatonin

Melatonin is one of the most potent antioxidants known and readily crosses the blood-brain barrier to provide protection against free radicals generated after cellular injury (such as during a stroke). Melatonin has thousands of published research studies showing its benefits for almost every chronic disease, including cardiovascular disease, age-associated immune impairment, Alzheimer’s and Parkinson’s disease. Melatonin induces drowsiness and is commonly used in insomnia.

Consideration should be given to the use of melatonin as part of an integrated treatment for thrombotic stroke. According to a 1998 report, “Melatonin is one of the most powerful scavengers of free radicals. Because it easily penetrates the blood-brain barrier, this antioxidant may, in the future, be used for the treatment of Alzheimer’s and Parkinson’s diseases, stroke, nitric oxide, neurotoxicity and hyperbaric oxygen exposure”. (Bubenik, Blask et al. 1998)

A study conducted at the University of Texas Health Sciences Center in San Antonio, Texas and reported in the November 1998 *Journal of Neuroscience Research*, indicates that “Considering melatonin’s relative lack of toxicity and ability to enter the brain, these results along with previous evidence suggest that melatonin, which is a natural substance, may be useful in combating free radical–induced neuronal injury in acute situations such as strokes.” (Tan, Manchester et al. 1998)

In laboratory experiments funded by the Life Extension Foundation, where severe brain ischemia is artificially induced, the addition of melatonin to a "cocktail" of antioxidants, calcium-channel antagonists, and cell membrane–stabilizing agents provided significant protection against brain damage.

An article published in the journal *Stroke* described a sudy of DHEA-S used to treat rabbits exposed to ischemia induced by temporary occlusion of infrarenal aorta. Treatment with DHEA-S 5 minutes after the ischemia significantly prolonged the duration of ischemia associated with a 50% probability of permanent paraplegia (paralysis of the lower extremities). The beneficial results were still measurable after four days. The authors concluded that DHEA-S may have substantial therapeutic benefit for the treatment of ischemic stroke. (Lapchak, Chapman et al. 2000)

Testosterone

As men age past year 40, hormonal changes occur that perceptibly inhibit physical, sexual, and cognitive function. The outward appearance of a typical middle-aged male shows increased abdominal fat and shrinkage of muscle mass, a hallmark effect of hormone imbalance. A loss of feeling of wellbeing, sometimes manifesting as depression, is a common psychological complication of hormone imbalance. (Barrett-Connor, Von Muhlen et al. 1999; Rabkin, Wagner et al. 1999; Schweiger, Deuschle et al. 1999; Seidman and Walsh 1999; Winters 1999)

According to Jonathan Wright, M.D., author of the book *Maximize Your Vitality & Potency*, the following effects have been reported in response to low testosterone levels:

- Loss of ability to concentrate
- Moodiness and emotionality
- Touchiness and irritability
- Great timidity
- Feeling weak
- Inner unrest
- Memory failure
- Reduced intellectual agility
- Passive attitudes
- General tiredness
- Reduced interest in surroundings
- Hypochondria

The above feelings can all be clinical symptoms of depression, and testosterone replacement therapy has been shown to alleviate these conditions.

In a study conducted on healthy older men, short-term testosterone administration was shown to enhance cognitive function. Cherrier et al. described a randomized, double-blind, placebo-controlled study of 25 healthy volunteers aged 50 to 80 years. Participants received weekly intramuscular injections of either 100 mg testosterone enanthate or placebo (saline) for 6 weeks. Circulating total testosterone was raised an average of 130% from baseline at week 3 and 116% at week 6 in the treatment group. Estradiol increased an average of 77% at week 3 and 73% at week 6 in the treatment group. The treatment group had significant improvements in cognition for spatial memory (recall of a

walking route), spatial ability (block construction), and verbal memory (recall of a short story) compared with baseline and the placebo group. (Cherrier, Asthana et al. 2001)

A study of 144 men with acute ischemic stroke and 47 healthy male controls found that both total and free testosterone were inversely associated with stroke severity and 6 month survival. Total testosterone was significantly inversely associated with infarct size. The authors concluded that these results supported the idea that testosterone affects the pathogenesis of ischemic stroke in men. (Jeppesen, Jorgensen et al. 1996)

Human Growth Hormone

Human growth hormone (HGH) is produced naturally by the pituitary gland and secreted during sleep hours. HGH steadily declines during aging from a high of 300 to 450 mg/mL as a young adult to as low as 30 mg/mL in the elderly. A minimun of HGH must be present in the body to maintain a healthy immune system and brain functioning. HGH is present in cerebrospinal fluid and is able to cross the blood-brain barrier to reach receptor sites on the hypothalamus, pituitary, and hippocampus. The hippocampus controls a significant amount of cognitive functioning and memory.

Researchers have found low levels of HGH in several neurological disorders including Alzheimer's disease, Parkinson's disease, MS, and stroke. Considerable research has been done on the effects of HGH over the past decade. In studies on middle aged and elderly people, HGH supplementation has increased muscle mass, skin thickness, and bone mass, while decreasing body fat. In patients with senile dementia and Alzheimer's disease, noticeable improvements have been observed with sustained use. Researchers theorize that HGH increases blood flow to the brain, regenerates neuronal dendrites and axons, and helps to rebuild protein that leads to the formation of RNA and DNA.

An article published in the journal *Neurology* described a study of the hormonal patterns in eight stroke patients and five matched healthy volunteers. Nocturnal plasma hormone measurements showed low growth hormone levels and elevated prolactin concentrations. Cortisol levels, however, were normal. The authors concluded: "suprahypothalmic lesions influence hypothalamus function so as to facilitate prolactin secretion and inhibit growth hormone release." (Culebras and Miller 1984)

Nitric Oxide Donors

Recently, researchers have hypothesized that measures which may provide protection from ischemic stroke (such as ample dietary intakes of potassium, arginine, fish oil, and selenium) can have a favorable impact on endothelium-dependent vasodilation. Protection afforded by exercise training, estrogen replacement, statin drugs, green tea polyphenols, and cruciferous vegetables may reflect increased expression of the endothelial nitric oxide synthase. Further, insulin-like growth factor I (IGF-I) activity stimulates endothelial nitric oxide production, and may explain the protection associated with the higher-protein diets common in Japan. (McCarty 2000)

Arginine

Arginine may be useful in ischemic strokes because it is a nitric oxide donor. A recent study examined the use of L-arginine to prevent experimental ischemic stroke in rats. L-arginine was administered at the time of ischemia, and at 6 and 24 hours later. The areas of neuronal necrosis were reduced by 99%, 96%, and 89%, respectively. The study also examined L-arginine in combination with a calcium antagonist (TMB-8) and found that the combination of TMB-8 and L-arginine is more

effective in treating ischemic stroke by simultaneously reducing calcium-activated proteolysis and improving cerebral blood flow than using TMB-8 or L-arginine alone. (Hong and Hwang 2000)

Certain cautions must be exercised when supplementing with arginine:

- Diabetics and borderline diabetics should use arginine with care, as it may worsen or improve the diabetes.
- Children, teenagers and pregnant or lactating women should not use arginine (or growth hormone stimulators) except uder the care of a knowledgable physician
- Arginine sometimes reactivates latent herpes virus infections. Those with ocular or brain herpes should avoid it.
- Arginine should be used with care in those with psychosis, as they may experience a worsening of symptoms.
- Arginine should always be taken with antioxidants

Vinpocetine

Vinpocetine is derived from vincamine, the major indole alkaloid from the periwinkle plant. Vinpocetine has been used for many years in Europe to enhance memory and mental function. Vinpocetine improves blood supply to the brain, increases oxygen and glucose use by the brain, increases the vasodilation response to hypoxia (oxygen deficiency) and reduces abnormal coagulation of the blood.

An article published in the *European Journal of Neurology* described a study of 30 patients diagnosed with acute ischemic stroke. The National Institute of Health Stroke Scale was marginally (but significantly) better in the group treated with vinpocetine at 3 months. No significant adverse effects were seen. The authors concluded that a full-scale trial of vinpocetine was feasible and warrented. (Feigin, Doronin et al. 2001)

Theanine

Theanine is an amino acid found in green tea that has a tranquilizing effect on the brain. Theanine increases GABA (gamma-amino butyric acid), an inhibitory neurotransmitter, while caffeine decreases it. Theanine creates a sense of well-being and relaxation without drowsiness.

An article published in *Neuroscience Letters* described a study in which theanine was given to gerbils 30 minutes before an ischemic stroke was induced by bilateral occlusion of the carotid artery. The number of intact neurons in the hippocampus were assessed seven days after the ischemic event. Pretreatment with theanine was found to prevent neuronal death in a dose-dependant manner. (Kakuda, Yanase et al. 2000)

Fruits and Vegetables

An article published in *JAMA* evaluated the relationship between fruit and vegetable intake and cardiovascular disease in two prospective cohort studies: the Nurses' Health Study and the Health Professionals' Follow-up Study. After controlling for standard cardiovascular risk factors, those with diets containing over 5 servings of fruit and vegetables per day had 31% risk reduction compared with the group that consumed the least amount. An increment of one serving per day of fruits or vegetables was associated with a 6% lower risk of ischemic stroke. Cruciferous vegetables, green leafy

vegetables, citrus fruit including juice, and citrus fruit juice contributed most to the apparent protective effect of total fruits and vegetables. The authors concluded that these data support a protective relationship between consumption of fruit and vegetables (particularly cruciferous and green leafy vegetables and citrus fruit and juice) and ischemic stroke risk. (Joshipura, Ascherio et al. 1999) (Suter 1999)

Resveratrol, (3,4',5-trihydroxystilbene), is a phytoestrogen (plant-based estrogen) found in the skins of most grapes. Its neuroprotective effects are attributed to its antioxidant, vasodilating, and anti-platelet aggregrating actions. An article published in *Life Sciences* described a study of resveratrol and infarct size. A middle cerebral artery occlusion was induced in rats 15 minutes after pre-treatment with resveratrol. Resveratrol significantly reduced the total infarction volume. (Huang, Tsai et al. 2001) Supplemental grape seed-skin extract is a good source of resveratrol.

Consulting Your Physician

When over the counter supplements such as aspirin, vitamins, herbs, and oils are used as the primary anti-thrombotic therapy, the risk of undesirable side effects is reduced significantly. Although over the counter medications such as aspirin and natural therapies come with a lower risk of hemorrhaging, they should not be substituted for prescription medication if you are at a high risk for thrombosis.

In all circumstances requiring anticoagulation therapy or anti-thrombotic therapy, your doctor should be consulted if you desire to substitute your medication because the risk can be life-threatening and the appropriate therapeutic dosing is crucial. Since medications such as Coumadin and heparin have a very narrow therapeutic range, anyone on these medications should have his or her blood tested frequently for one or more of the following: PT, PTT, INR. Once the effective dose is achieved, blood testing is recommended every 2-4 weeks to monitor the medication blood levels and avoid overdosing which could lead to hemorrhaging. Blood levels should be more closely monitored if over the counter drugs or natural supplements that affect the clotting cascade are added to the regimen. Some of these supplements include vitamin E, ginkgo biloba, coenzyme Q10, garlic, ginseng, St. John’s wort, green tea, vitiamin C, vitamin A, policosinol, Dong Quai, white willow, and vinpocetine (periwinkle).

Diagnosis, Treatment, and Prevention Overview

Many people are familiar with the the dramatic strokes portrayed in movies. While these are clearly a medical emergency, most strokes are much less dramatic. In fact, the symptoms of most strokes are so mild that they are often dismissed as unimportant. The critical time for strokes is immediately after they occur.

- The symptoms of thrombotic strokes include nausea and dizziness; sudden, severe headaches; weakness, numbness; paralysis, particularly to one side of the body; partial or total loss of sight in one eye.
- Diagnostic procedures for thrombotic strokes include ultrasound, CT scan, and MRI.
- Treatment of thrombotic strokes consists of medication, natural supplements, and surgical interventions, based on the underlying cause. Controlling hypertension is essential prevention in the occurrence of ischemic strokes.

- Silent strokes commonly occur after thrombotic strokes and may cause damage weeks or months after the initial stroke.

Ischemic stroke is a medical emergency. Time to treatment of this “brain attack” is important, as what is done once in the emergency room.

- **Tissue plasminogen activator** is of great importance immediately after a stroke has occured to help dissolve blod clots before they thrombose.
- **Heparin** is sometimes used in critical care settings, and should be requested by stroke victims.
- **Warfarin** is the drug of choice to prevent strokes. Unfortunately it has a large number of contraindications and drug interactions with many commonly used medications.
- **Low-dose aspirin** is widely recommended to help thin the blood and prevent strokes. One tablet a day with a heavy meal is recommended. The Life Extension Foundation recommends Healthprin, which contains 81 mg of enterically coated aspirin. One tablet per day is recommended for it’s anti-clotting and anti-inflammatory effects.
- **Ticlopidine** may be recommended as a substitute for aspirin.
- **Mevacor**, a statin drug (HMG-reductase inhibitor), is being investigated for use in reducing the risk of stroke primarily because of its effect on cholesterol.

The following innovative drug strategies should be considered in stroke prevention, treatment and rehabilitation.

- **Hydergine**, an antioxidant medication that protects brain cells, may be given in an acute situation. The recommended dosage is 10 mg given sublingually and 10 mg administered orally. Because the FDA has not approved Hydergine for this purpose, the patient or patient’s advocate should request that the medication be given.
- **Piracetam**, a nootropic medication, may be useful in the prevention of thrombotic strokes because it appears to protect brain cells from injury during the stroke event. The recommended dosage for piracetam is 4800 mg a day, administered orally.
- **Nimodipine** is a prescription medication that dramatically increases cerebral blood flow by acting as a calcium channel blocker. Nimodipine may be of clinical benefit in acute stroke. The recommended dose is 30 mg three times a day, although up to 60 mg four times a day have been used in studies.
- **Aminoguanidine**, a medication that prevents glycosylation of proteins and helps prevent mental decline in the elderly, may be useful in preventing thrombotic strokes. The recommended dose is 300 mg once a day with food. This dose should not be exceeded.

An aggressive program for stroke prevention begins by addressing the known risk factors for stroke:

- The risk factors for ischemic strokes are hypertension, arteriosclerosis, and blood that has a propensity to clot abnormally inside vessels. Blood components that increase the risk of abnormal arterial clotting include elevated levels of LDL cholesterol, homocysteine, C-reactive protein and/or fibrinogen. Drug and alcohol abuse, age, gender, and race are also factors.

Conventional medicine often recommends several drugs to cover some of these risk factors, including anti-hyertensives, cholesterol-lowering drugs (statins), and anti-coagulants, such as

Coumadin and aspirin. Each of these drugs has side effects and may interact with each other, particularly with Coumadin. Bleeding is of primary concern with anticoagulant therapy as it dramatically increases the risk of hemorrhagic stroke (see the Hemorrhagic Stroke protocol).

Summary

Natural supplements can be used as an adjunct to conventional drugs. Proper testing is required to monitor the effectiveness of both drug and nutritional supplement programs. Recommended blood tests include total cholesterol, HDL, LDL, triglycerides, glucose, prothrombin time homocysteine, C-reactive protein, and fibrinogen. Further, use optimal levels, instead of the standard reference ranges, for these lab tests. The primary objective of using the following nutrients is to help restore function to injured brain cells.

1. **CDP Choline** has been shown to be effective and is currently in clinical trials in the United States for treating strokes. CDP Choline Caps contain 250 mg of pharmateutical grade cytidine-5'-diphosphocholine. One capsule a day is recommended for healthy people over the age of 40. Those with neurological impairnemt should take 2 capsules daily under the care of a physician.
2. **Ginkgo biloba** has been shown to be very effective as an antioxidant and in treating cerebrovascular deficiency, including stroke.
3. **Essential Fatty Acids**, including alpha linolenic acid (ALA) and docosahexaenoic acid (DHA) from fish oils. Super GLA/DHA provides high potency anti-inflammatory fatty acids.
4. **Vitamin C** is recommended as a daily supplement for healthy people and may also be of benefit in stroke. 1,000 to 4,000 mg of high-quality vitamin C may be taken a daily.
5. **Vitamin E** is an antioxidant and blood-thinner. The recommended dose for most people is 400-500 IU of alpha tocopherol, 210 mg of gamma tocopoherol and at least 50 mg of the tocotrienols. Vitamin E should be used with caution with warfarin as it thins the blood.
6. **Alpha-lipoic acid** may also be considered. Alpha lipoic acid should be taken with vitamin B12, as it may cause a worsening of symptoms in those with a vitamin B12 deficiency.
7. **Minerals**, including calcium, magnesium, potassium and selenium should be considered based on the results of serum electrolytes (although serum levels may not represent mineral stores in the body). Thiazide and loop diuretics deplete potassium and coffee increases it excretion. Magnesium is needed for the absorption of potassium.
8. **Vitamin B6, Vitamin B12, Folic acid and Trimethylglycine** should be considered if homocysteine levels are elevated. See the Homocysteine and Hypertension protocols for more information.
9. **SAMe** may be considered, particularly if there is related depression. The recommended total daily dose is 400 mg to 1600 mg. It is best taken without food, unless GI upset occurs. Refrigeration is recommended.
10. **Policosanol** has been shown to have a dramatic effect on lowering cholesterol, reducing platelet aggregration and decreasing the size of experimentally induced thrombus. The ideal cholesterol range is between 180 and 200 mg/dl. The average person uses 10 mg a day to achieve optimal cholesterol levels. Some people may only need 5 mg a day, while others may

require 20 mg a day. Cholesterol levels should be monitored regularly as levels below 150 may be dangerous.

11. **Garlic extract**, 1500 to 6000 mg daily, may help lower cholesterol levels.
12. **Melatonin** readily crosses the blood-brain barrier and may help protect against further free radical–induced brain cell injury. Melatonin is to be taken before bed as a sleep-enhancer.
13. **DHEA and Testosterone** may be helpful in stroke patients. A comprehensive hormone panel is recommended to guide treatment.
14. **Arginine, Vitamin B2, Vitamin B3, and folic acid** may be considered as a way to naturally increase nitric oxide synthesis. Arginine should be used with caution in diabetics, and those with psychosis.
15. **Carnosine** may be useful in protecting the brain from neurological damage.
16. **Vinpocetine** has been shown to have a positive effect on brain metabolism and may be of benefit in stroke recovery. Two 5 mg tablets are recommended three times daily.
17. **Theanine**, an amino acid found in green tea, produces a tranquilizing effect on the brain by increasing production of GABA, an inhibitory neurotransmitter. Theanine may also prevent ischemic damage to neurons. Up to four 100 mg capsules can be taken daily.
18. **Dietary measures** to lower stroke risk includes high amounts of fresh fruits and vegetables every day and several servings of fish per week.

For more information

Contact the National Institute of Neurological Disorders and Stroke, (800) 352-9424.

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