

# **Amyotrophic Lateral Sclerosis (ALS)**

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## **INTRODUCTION**

### **Description**

Amyotrophic lateral sclerosis (ALS) is also known as Lou Gehrig's Disease, which was one of baseball's greatest players. He earned the title "Iron Horse" for his record of 2,130 consecutive games. His outstanding record was ended by ALS.

ALS is a rapidly progressive neuromuscular disease caused by the destruction of nerve cells in the brain and spinal cord. This causes loss of nervous control of the voluntary muscles, resulting in the degeneration and atrophy of the muscles. Eventually the respiratory muscles are affected which leads to death from an inability to breath.

### **Symptoms**

ALS symptoms vary from one person to another according to which group of muscles is affected by the disease. Tripping, dropping things, abnormal fatigue in the arms and/or legs, slurred speech, difficulty in talking loudly, uncontrollable bouts of laughing or crying, and muscle cramps and twitches are all symptoms of ALS. ALS usually starts first in the hands and will cause problems in dressing, bathing, or other simple tasks. It may progress to more on one side of the body and generally proceeds up the arm or leg. If it starts in the feet, walking will become difficult. ALS can also start in the throat, causing difficulty with swallowing.

People afflicted with ALS do not lose their ability to see, hear, touch, smell, or taste. The bladder and muscles of the person's eyes are not affected, nor are sexual drive and function. The disease does not affect the person's mind.

### **Epidemiology**

Men make up the majority of those who contract ALS, although women also get the disease. Race, ethnicity, or socioeconomic boundaries make no difference as to who will come down with ALS. Most of those who get the disease are usually between the ages of 40 and 70, but people in their 20s and 30s can also get it. In most societies, there is an incidence of five in every 100,000 people. (Harrison 1998) (Onion 1998)

### **Course**

The rate of progression of the symptoms of ALS varies for each person. The average life expectancy for a newly diagnosed person is 2 to 5 years, although improved medical care is resulting in persons living longer. ALS frequently takes its toll before being diagnosed, causing the people who have the disease to be significantly debilitated before they learn they have it.

## Causes

There are three types of ALS: sporadic, familial, and Guamanian. The most common form is sporadic. A small number of cases are inherited genetic disorders (familial). A large number of cases, however, occur in Guam and other Pacific territories.

The familial type of ALS is caused by a genetic defect in superoxide dismutase, an antioxidant enzyme that continuously removes the highly toxic free radical, superoxide. The causes of sporadic and Guamanian ALS are unknown. Several hypothesis have been proposed including:

- Glutamate toxicity
- Oxidative stress
- Mitochondrial dysfunction
- Autoimmune disease
- Infectious disease
- Toxic chemical exposure
- Heavy metals such as lead, mercury, aluminum, and manganese
- Calcium and magnesium deficiency
- Carbohydrate metabolism
- Growth factor deficiency

### *Glutamate Toxicity*

Glutamate is the main excitatory neurotransmitter in the brain. It has been calculated that glutamate is responsible for 75% of excitatory neural transmissions. Glutamate is unique in that it can produce such marked stimulation that neurons die. It has been proposed that the neuronal damage following ischemia (deficiency of blood, for example after a stroke) is due to the action of glutamate, rather than to a lack of oxygen. (Ganong 1995)

ALS is highly linked with glutamate. One proposed mechanism is a defective glutamate transport system that permits neurotoxic levels to build up. (Onion 1998) A recent study published in the Journal Brain Research Bulletin showed significant elevations (by about 70%) of plasma levels of glutamate in ALS patients as compared to controls. (Plaitakis and Constantakakis 1993)

### *Oxidative stress*

Oxidative stress refers to a shift in the ratio of oxidants to antioxidants in the body. Free radicals are molecules that have an unpaired electron: a highly unstable state. Most free radicals react with molecules that contain oxygen to form reactive oxygen species, such as nitric oxide (NO), superoxide (O<sub>2</sub><sup>-</sup>), and hydroxyl (OH<sup>-</sup>). Free radical damage is associated with many degenerative conditions, including neurological disorders. (Ronzio 1985) (Jenner 1994)

Antioxidants inhibit oxidation by free radicals. There are many types of antioxidants, including:

- Detoxification enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione transferase.
- Proteins such as glutathione reductase, glucose 6-phosphate dehydrogenase, albumin, transferrin, ceruloplasmin, and metallothionein.

- Vitamins such as beta carotene, carotenoids, vitamin C, and vitamin E.
- Nutritional supplements including coenzyme Q10, uric acid, cysteine, glutathione, lipoic acid, citric and malic acid, bilirubin, biliverdin, histidine, conjugated linoleic acid and melatonin.

Inflammation represents a major source of oxidants. Inflammation is often caused by bacterial or viral infections, toxic exposure and trauma. The continuous production of reactive oxidant species during chronic inflammation may deplete the store of antioxidants eventually resulting in a spiral from health to disease. (Ronzio 1985)

### ***Mitochondrial dysfunction***

Mitochondria are the power-generating units of the cell and are most developed where energy-requiring processes take place (for example, in muscles). The outer membrane of the mitochondria is studded with oxidative enzymes that provide raw materials for the reactions occurring inside. In the interior, the citric acid cycle converts carbohydrates into energy releasing carbon dioxide. The energy produced by this reaction is used to form the high-energy phosphate compound ATP (adenosine triphosphate) in a process called oxidative phosphorylation. ATP is the principal energy source for both plants and animals. Mitochondrial DNA is transmitted solely from the mother. (Ganong 1995)

Mitochondrial dysfunction has been linked to neurodegenerative diseases. (Beal 1999) (Beal 1996) Defects in mitochondrial DNA have also been proposed as a causative mechanism in sporadic ALS. (Beal 2000) (Manfredi and Beal 2000) (Murphy, Fiskum et al. 1999)

One study explored the role of mitochondrial dysfunction by transferring mitochondrial DNA from ALS subjects to normal human neuroblastoma cells (embryonic cells that form nervous tissue) with their mitochondrial DNA removed. The resulting hybrid cells exhibited abnormal electron transport chain functioning, increases in free radical scavenging enzyme activity, perturbed calcium homeostasis, and altered mitochondrial structure.

The title “Iron Horse” given to Lou Gehrig is quite appropriate in a biochemical sense. The energy forming process of oxidative phosphorylation relies heavily upon transferring electrons between several iron molecules that form the electron transport chain. The oxidative phosphorylation process also requires coenzyme Q, NAD (nicotinamide or niacinamide adenine dinucleotide) and FAD (flavin adenine dinucleotide). Niacin (vitamin B3) is used to form NAD or Riboflavin (vitamin B2) is used to form FAD.

### ***Autoimmune disease***

Autoimmunity may play a role in ALS. In this disease, the immune system becomes confused and begins attacking tissues in the body. Under normal conditions, the body’s immune system produces proteins called immunoglobulins which attach to their target antigen. An antigen is a substance that produces an immune response and is usually something foreign to the body. The immunoglobulins attach to and surround the target antigen forming an antigen-antibody complex. This complex is then ingested by phagocytes such as macrophages in a process called phagocytosis.

In autoimmune disease, antibodies are produced that attach to the tissues of the body, instead of foreign substances. The following are examples of diseases with an autoimmune basis:

- In autoimmune hemolytic anemia, the body produces autoantibodies to red blood cell membrane proteins.

- In diabetes mellitus, autoantibodies are formed against insulin receptors.
- Grave's disease is associated with autoantibodies to thyroid stimulating hormone (TSH) receptors.
- Pernicious anemia can be caused when autoantibodies are formed against intrinsic factor which is needed for vitamin B12 absorption.

Researches have proposed that ALS may have an autoimmune basis. The following are the basis for their hypothesis:

- Analyses of ALS patient sera have identified circulating antibodies secreted by denervated muscle. These antibodies inhibit the stimulation of the sprouting of axons, the long arms of neurons which conduct nervous impulses to other neurons throughout the body. (Onion 1998)
- Researchers have found an immunoglobulin that affects the conductance of neuronal voltage-activated calcium channels which may induce an excessive release of glutamate from nerve endings. (Onion 1998)
- Several studies of ALS patients found the presence of antibodies that interact with motor neurons. (Niebroj-Dobosz, Jamrozik et al. 1999) (Pestronk, Adams et al. 1988; Pestronk, Cornblath et al. 1988; Pestronk, Adams et al. 1989)
- Immune complexes have been found in spinal cords of patients with ALS.

It has been proposed that T cells, activated microglia, and immunoglobulin G (IgG) within the spinal cord lesions may be the primary event that leads to tissue destruction in ALS.

The increased prevalence in Guam is associated with a decreased delayed hypersensitivity. The secondary response, which occurs with the second exposure to the antigen, is normally quicker and usually produces more antibodies than the primary response. The major reason for the enhanced secondary response is the formation of B memory cells during the primary response. (Onion 1998)

In a recent study, a family history of thyroid disease was present in 19% of ALS patients, and an additional 21% of patients described family members with other possible autoimmune disorders. In 19% of the patients with ALS, either past or present thyroid disease was documented. Eleven of 47 additional patients with ALS had significant elevations of microsomal and/or thyroglobulin antibody levels. (Appel, Stockton-Appel et al. 1986)

### ***Infectious disease***

Amyotrophic lateral sclerosis was once thought to be caused by persistent viral infection. (Salazar-Gruesso and Roos 1995) This hypothesis fell out of favor when researchers could not isolate a single causative agent. Recently, however, many researchers are reconsidering infectious agents, particularly since many neurodegenerative disorders are associated with chronic infections, particularly latent viruses. Support for the continued investigation of infectious agents in ALS include:

- It is well-known that excess free radical activity is associated with chronic infection. (Racek, Holecek et al. 2001)
- Both Lyme disease and poliomyelitis have chronic states that resemble the symptoms of ALS. (Garcia-Moreno, Izquierdo et al. 1997)

- HIV infection is associated with a variety of neurological problems. (Cruz Martinez, Lara et al. 1989) (Dalakas and Pezeshkpour 1988)
- Tertiary syphilis affects the nervous system (neurosyphilis) causing tabes dorsalis, a syndrome marked by degeneration of the posterior columns and posterior roots and ganglion of the spinal cord.

### ***Toxic Chemical Exposure***

People with a history of exposure to agricultural chemicals, including fertilizers and pesticides used in gardening and lawn care, may be at twice the risk for developing ALS. (McGuire, Longstreth et al. 1997) (Baker 1996)

Chemicals foreign to the body are called xenobiotics. They include toluene, xylene, hexanes, benzene, trichloroethane, styrene, phylates and pesticides. Most xenobiotics are lipophilic, which means that they are attracted to the fats (lipids) which comprise cell membranes. Since the brain is full of lipids, xenobiotics are able to rapidly diffuse across cell membranes into the brain and cause neurological symptoms.

Many pesticides are specifically designed as neurotoxins (toxins that affect the nervous system.) Pesticides are generally odorless and can cause progressive symptoms weeks after an exposure. (Ames, Steenland et al. 1995) (Keifer and Mahurin 1997) (Prazmo 1978)

Xenobiotics are removed from the body by a process called detoxification, which takes place in two phases. Phase I takes place inside the cell and changes the toxic chemicals into less toxic forms by means of the chemical processes of oxidation, reduction and hydrolysis. Phase II detoxification then attaches molecules such as glutathione, methionine and sulfur compounds in a process called conjugation. The body is then able to excrete these modified toxins in stool, urine or sweat.

The process of detoxification requires several nutritional cofactors including magnesium, zinc and manganese. The glutathione, methionine and sulfur molecules used in conjugation are used up in the process. As the detoxification pathways become overloaded any further toxic challenge, however slight, can cause symptoms. This is often referred to as chemical sensitivity.

Chemically sensitive people experience symptoms to a variety of chemical insults. Caffeine (the active component of coffee), aspirin and acetaminophen (Tylenol) are often used to assess the functional capacity of the detoxification system. Alcohol is metabolized in Phase I by aldehyde dehydrogenase. Gasoline fumes, deodorizers, rubber, and solvents are sources of benzene. Trichloroethylene, if blocked from the normal Phase I pathway, will form a toxic secondary metabolite called chloral hydrate, the so-called “Mickey Finn”, which causes disorientation and dizziness.

Toxic chemical exposure may be one reason why there is a higher incidence of ALS diagnosed in soldiers that participated in Operation Desert Storm. On April 6, 2000, the Associated Press reported that the Veterans Administration announced a year-long study to determine whether there is a higher incidence of Lou Gehrig's disease (amyotrophic lateral sclerosis or ALS) among the veterans of the Gulf War. At least 28 Gulf veterans have been diagnosed with this deadly disease. Researchers are interested in locating other veterans diagnosed with ALS or other motor neuron diseases that were actively serving duty between August 2, 1990 and July 31, 1991, regardless of location. Those who did not go to the gulf area will serve as part of the control group. Eligible veterans may call 1-877-342-5257 (Smith, Gray et al. 2000)

## ***Heavy metals***

Because there are high numbers of ALS patients in Guam, Western New Guinea, and Japan, there is a theory that ALS might be caused by environmental problems. These areas have large amounts of heavy metals such as lead, mercury, and aluminum. These metals can poison the body and cause ALS symptoms. (Adams, Ziegler et al. 1983) (Armon, Kurland et al. 1991) (Conradi, Ronnevi et al. 1976)

### **Lead**

Lead was used as an additive to gasoline and in many paints. Absorption of lead is enhanced by dietary deficiencies in calcium, iron, and zinc. Lead toxicity is most likely related to its affinity for cell membranes and mitochondria, where it interferes with several important enzymes.

In adults, systemic lead poisoning causes abdominal and joint pain, fatigue, anemia, and neurologic symptoms including headaches, irritability, peripheral motor neuropathy, short-term memory loss and an inability to concentrate. Chronic subclinical lead exposure affects the kidneys causing interstitial nephritis, renal tubular damage (with tubular inclusion bodies), hyperuricemia (with an increased risk of gout), and a decline in glomerular filtration rate and chronic renal failure.

An article published in the journal *Neurology* suggests that there may be an association between ALS in men and exposure to lead vapor. (Armon, Kurland et al. 1991)

### **Mercury**

Mercury exposure is thought to occur from ingestion of contaminated fish, particularly tuna and swordfish, which can concentrate methyl mercury at high levels; inhalation of mercury vapor from dental amalgams; and possibly from drinking water contaminated by toxic waste sites.

Chronic mercury exposure produces a characteristic intention tremor and a constellation of findings including excitability, memory loss, insomnia, timidity, and sometimes delirium. The neurotoxicity resulting from organic mercury exposure is characterized by paresthesia (an abnormal touch sensation often in the absence of external stimulus); impaired peripheral vision, hearing, taste, and smell; slurred speech; unsteadiness of gait and limbs; muscle weakness; irritability; memory loss; and depression. Dentists with occupational exposure to mercury score below normal on neurobehavioral tests of motor speed, visual scanning, verbal and visual memory, and visual-motor coordination. (Harrison 1998)

Amyotrophic lateral sclerosis was diagnosed in one patient after accidental injection of mercury. (Schwarz, Husstedt et al. 1996)

It is well known that the selenium decreases the toxicity of mercury in the human body. After measuring the mercury and selenium content in the hair of 13 ALS cases, one study concluded that mercury with low content of selenium might be one of the environmental factors involved in producing ALS. (Mano, Takayanagi et al. 1989; Mano, Takayanagi et al. 1990) (Khare, Ehmann et al. 1990)

### **Aluminum**

High levels of aluminum are found in the delicate threads running through the cytoplasm of nerve cells (neurofibrillary tangles) in the cerebral cortex and hippocampus of patients with Alzheimer's disease. High levels of aluminum has also been found in the drinking water and soil of areas with an unusually high incidence of Alzheimer's disease. (Harrison 1998)

Aluminum and calcium deposits were found in the neurons of patients with amyotrophic lateral sclerosis of Guam. (Garruto, Swyt et al. 1985)

### **Manganese**

Manganese toxicity can cause a Parkinson-like syndrome within 1 to 2 years, including gait disorders; postural instability, a masked, expressionless face; tremor; and psychiatric symptoms.

Manganese is emitted from the tail pipes of motor vehicles. (Aschner 2000) Occupational exposure can occur in miners, dry-battery manufacturers and arc welders. (Harrison 1998)

A recent study showed that the nitrated manganese-superoxide dismutase level was strikingly elevated in amyotrophic lateral sclerosis patients. The authors also proposed that nitration of manganese superoxide dismutase in cerebrospinal fluids is a marker for oxidative stress in neurodegenerative diseases. (Aoyama, Matsubara et al. 2000)

### ***Calcium and Magnesium Deficiency***

It is proposed that chronic environment deficiencies of calcium and magnesium may result in increased intestinal absorption of toxic metals and lead to the mobilization of calcium and metals from the bone and deposition of these elements in nervous tissue. This hypothesis, called metal-induced calcifying degeneration of CNS, has been supported by experimental studies using several animal species. (Van den Bergh, Swerts et al. 1977)

Low calcium/magnesium intake with excess amounts of aluminum and manganese are associated with the incidence of amyotrophic lateral sclerosis (ALS) in the Western Pacific. The authors conclude that the high incidence of ALS in the Western Pacific may be due to calcium/magnesium metabolism dysfunction resulting in excess deposition of aluminum. (Yasui, Yase et al. 1991; Yasui, Yase et al. 1991)

### ***Carbohydrate Metabolism***

Over the last 30 years glucose intolerance has been reported in a significant percentage of patients with amyotrophic lateral sclerosis (ALS). Currently, a controversy exists in determining whether the carbohydrate abnormality is disease-specific or secondary to decreased glucose utilization due to muscle atrophy. One study showed that the glucose infusion rate, an estimate of in vivo insulin sensitivity, was significantly diminished in ALS patients compared to both normal and disease controls which suggests that ALS may be associated with a dysfunction in carbohydrate metabolism. (Reyes, Perurena et al. 1984) (Nagano, Tsubaki et al. 1979) (Van den Bergh, Swerts et al. 1977)

### ***Growth factor deficiency***

A lack of trophic (growth) factors support has been hypothesized as a probable cause of ALS. Several growth factors have been identified, including insulin-like growth factor 1 (IGF-I), nerve growth factor (NGF), Leukemia inhibitory factor (LIF), and ciliary neurotrophic factor (CNF). More specific information can be found about these growth factors in the New Drug Section.

## **Differential Diagnosis**

Because the course of ALS is fatal within 3-5 years, a careful differential diagnosis is needed. The following should be considered (Harrison 1998):

- Physical causes such as compression of the cervical spinal cord
- Infectious diseases such as Lyme disease, post poliomyelitis, HIV infection
- Enzyme disorders in superoxide dismutase, hexosaminidase A, and alpha-glucosidase
- Other neurologic diseases such as Pick's disease and Kennedy's syndrome
- Endocrine disorders including Diabetic amyotrophy and Thyrotoxicosis.

### *Physical Causes*

#### **Compression of the cervical spinal cord**

A MRI of the head and cervical spine is usually ordered for patients with lower neurological disease to rule out compression of the spinal cord and impingement along the spinal nerves.

### *Infectious diseases*

#### **Lyme disease**

The second and third stages of Lyme disease are associated with neurological changes that may cause an axonal, lower motor neuropathy. Lyme disease is caused by the bacterial spirochete (*Borrelia burgdorferi*) spread by a deer tick (*Ixodes dammini*). The first stage of Lyme disease presents with fever, enlarged lymph glands and a characteristic bulls-eye pattern around the bite. (Hansel, Ackerl et al. 1995)

#### **Post poliomyelitis**

Polio is an enterovirus, a genus that preferentially inhabits the intestinal tract. Reactivation of a central nervous system polio infection (post-poliomyelitis) may cause a delayed deterioration of motor neurons and muscular atrophy including difficulty in swallowing (dysphagia) from bulbar involvement. Bulbar involvement indicates there is a malfunction in the medulla oblongata, a structure important for collections of nerve cells lying anterior to the cerebellum (Onion 1998) (Roos, Viola et al. 1980)

#### **HIV Infection**

HIV infection is associated with extreme immune system dysfunction. HIV-1 proteins Tat and gp120 have been implicated in the pathogenesis of dementia associated with HIV infection. (Jain, Parsons et al. 2000)

#### **Neurosyphilis**

Tertiary syphilis is seen 3-4 years after the primary infection with the spirochete *Treponema pallidum*. It is often seen in AIDS patients. Tertiary syphilis usually presents with hypersensitivity reactions since few organisms are present. Tabes dorsalis is associated motor and sensory losses in the lower extremities which causes difficulties in coordination.

### *Enzyme disorders*

#### **Superoxide dismutase (SOD)**

Familial ALS is an autosomal dominant genetic disorder. It is caused by a defect on the gene encoding superoxide dismutase on chromosome 21 (SOD1).

## **Hexosaminidase A**

Tay-Sachs disease and Sandhoff's disease are autosomal recessive genetic disorders resulting from a deficiency of hexosaminidase and the accumulation in lysosomes (small bodies in cells involved in the process of intracellular digestion) of GM2 gangliosides, particularly in the central nervous system. Motor weakness, progressive ataxia and lower motor neuron symptoms predominate in the adult form. The patients often report clumsiness in childhood and motor weakness in adolescence. The diagnosis is established by visualizing cytoplasmic bodies by electron microscopy or by detecting reduced hexosaminidase-A activity in white blood cells. (Eisen and Hudson 1987) (Harrison 1998)

## **Alpha-glucosidase**

Accumulation of glycogen in lysosomes in Pompe's disease is due to deficiency of a specific enzyme, alpha-glucosidase. The juvenile form is characterized by progressive proximal muscle weakness, including impairment of respiratory function. (Harrison 1998)

## ***Other Neurological Diseases***

### **Pick's disease**

Pick's disease exhibits a progressive atrophy of the frontal and temporal lobes of the brain. Swollen neurons called Pick cells and argentophilic (attracted to silver) neuronal inclusions known as Pick bodies affect the frontal and temporal cortical regions.

### **Kennedy's syndrome**

Kennedy's syndrome is an X-linked, lower motor neuron disorder in which progressive weakness and wasting of limb and bulbar muscles begins in males in adult life. Kennedy's syndrome is associated with androgen (testosterone) insensitivity manifested by excessive growth of the male breasts (gynecomastia) and reduced fertility.

## ***Endocrine Disorders***

### **Diabetic amyotrophy**

Neuropathy is a common clinical manifestation associated with diabetes. The most common presentation is that of peripheral polyneuropathy which is also referred to as "stocking and glove neuropathy" due to numbness and paresthesia of the hands and feet. Diabetic amyotrophy presents with progressive muscle wasting, usually of the pelvic girdle and large muscles in the upper leg. Anorexia and depression may accompany amyotrophy.

### **Thyrotoxicosis**

Thyrotoxicosis refers to the effects of excessive quantities of thyroid hormones in tissues found in patients with severe hyperthyroidism and Graves disease. Symptoms include feeling hot and sweaty, palpitations, frequent diarrhea from impaired digestion of fats, and a prominent essential tremor.

## **Assessment**

Neurologists use clinical tests such as blood testing, electromyograms (EMG), magnetic resonance imaging (MRI), CT scans, and nerve biopsies to establish a profile when diagnosing ALS. These profiles will eliminate other possibilities as to what the person might be suffering from. The following labs should be considered in the diagnosis of ALS:

- Lyme disease serology
- HIV testing
- Autoimmune panel.
- Thyroid panel, including TSH, T3 and T4
- Hormone panel, including testosterone, DHEA and pregnenolone
- Hexosaminidase A in urine is warranted when adult Tay-Sachs is suspected.
- Vitamin B12 levels are also useful.

After the diagnosis of ALS has been confirmed, additional lab tests can be used to identify the predominant etiology and thus direct appropriate treatment. Additional labs would include:

- A Comprehensive Detoxification Profile
- Oxidative Stress Analysis
- Mineral analysis, including Calcium, Magnesium, Copper and Zinc
- Toxin analysis, including heavy metals and chemicals
- Amino acid analysis

## **Treatment**

Many things can be done to improve or maintain the lifestyle of a person who is suffering from the disease. First, the patient should continue his or her usual daily activities, stopping just before getting tired. Physicians often recommend specific exercises, such as breathing exercises and/or exercises to strengthen the muscles that are not affected with the disease. Foot braces, hand splints, or wheelchairs, combined with exercise, will enable the patient to remain as independent as possible for as long as possible.

Counseling can be of help to ease the mental anguish brought on by this disease. Family counseling can also be helpful to the person with ALS as well as the family.

One of the side effects of this disease is uncontrolled muscle contractions or spasms. Physical therapy cannot restore normal muscle function, but may help in preventing painful contractions of the muscles and in maintaining normal muscle strength and function. The physical therapist should show family members how to perform these exercises so they can help maintain this therapy for the person with ALS.

Speech therapy may also be helpful in maintaining the person's ability to speak. Swallowing therapy is important as well, to assist with the problems of swallowing and drinking. This treatment helps prevent choking. It is recommended that the patient adopt a new head posture and positioning of the tongue. The patient should also change the consistency of the food to aid swallowing accordingly as the disease progresses.

Occupational therapy is also important. The therapist will come to the person's home and recommend where to move furniture to make it easier for the patient to move around her house. The therapist will also place kitchen appliances in areas where making meals will be easier. The occupational therapist will also bring devices that will help the person in making the telephone, computer, and other devices easier to use.

When the ability to breathe decreases, a respiratory therapist is needed to measure the breathing capacity. These tests should take place on a regular basis. To make breathing easier, the patient

should not lie down immediately after eating. The patient should not eat large meals, because they can increase abdominal pressure and prevent the diaphragm from expanding. When sleeping, the head should be elevated 15 to 30 degrees to keep the abdominal organs away from the diaphragm. When breathing capacity falls below 70%, noninvasive respiratory assistance should be provided. This involves a nasal mask connected to a mechanical ventilator. When the breathing capacity falls below 50%, a permanent hook-up to a ventilator should be considered.

## **Medications**

Various medications can be given to the patient as ALS progresses.

### ***Baclofen (Lioresal)***

Baclofen (Lioresal) is used to relieve stiffness in the limbs and throat. Patients with seizure disorder or impaired renal function should use caution. Serious adverse reactions include somnolence and stupor, cardiovascular collapse, seizures, and respiratory depression. Common adverse effects include headaches, dizziness, blurred vision, slurred speech, rash, weight gain, pruritus, constipation, and increased perspiration. Excessive dosing may lead to weakness. Baclofen may interact with alcohol, antipsychotics, MAOIs, narcotics, antipsychotics, tricyclic antidepressants, oral hypoglycemics, or insulin.

### ***Tizanidine (Zanaflex)***

Tizanidine (Zanaflex) is a centrally acting muscle relaxant. Zanaflex may interact with alcohol (to increase somnolence, stupor) and oral contraceptives (to decrease its clearance.) Zanaflex can increase hypotensive effects when administered concurrently with diuretics. Elderly patients and patients with impaired renal function should use caution. Serious reactions include hallucinations, severe bradycardia, and liver toxicity. Common adverse effects include dryness of mouth, somnolence and sedation, dizziness, malaise, constipation, increased spasms, and hypotension.

### ***Tricyclic antidepressants***

Tricyclic antidepressants may be used to control the production of excess saliva.

### ***Riluzole***

Riluzole, the only FDA-approved drug to treat ALS, reduces the presynaptic release of glutamate. Riluzole is metabolized in the liver. It is contraindicated with active liver disease or elevated liver function tests (SGPT or ALT and GTT.) Theophylline and caffeine may affect rate of elimination. Riluzole treatment may be associated with mild blood pressure elevation. (Scelsa and Khan 2000)

Unfortunately Riluzole, although described in medical journals as an effective treatment for ALS, provides almost no benefit and is associated with significant side effects in most patients. One journal noted "It is often said that the benefits of riluzole are marginal but the side effects are major." One writer commented that "Clearly, riluzole does succeed at one important task. It allows treating physicians to end the day assured that they did something for the ALS patients they were treating since a prescription was written – an obligation was thus fulfilled." (Rowland 1996; Ludolph and Riepe 1999; Perlmutter 2000)

## **New Drug Research**

Several new drugs are being studied for treatment of ALS. These include: (Hurko O 2000)

- NMDA receptor antagonists Mimantine and Dexamethorphan
- Growth factors such as Insulin-like growth factor-I, Nerve growth factor, ILukemia inhibiting factor, Ciliary growth factor, Pigment epithelium-derived factor, Neurturin and Transforming growth factor-beta
- TR500, a glutathione-repleting agent
- Deprenyl, a selective monoamine oxidase B inhibitor
- Pimozide, a voltage-dependent calcium channel blocker
- Gabapentin, an anti-seizure drug made from GABA

### ***NMDA receptor antagonists***

#### **Memantine**

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has been approved for use in the treatment of dementia in Germany for over ten years. NMDA receptor antagonists have therapeutic potential in numerous central nervous system (CNS) disorders. Memantine does not have the side effects common to other NMDA receptor antagonists such as dizocilpine. (Jain, Parsons et al. 2000) (Parsons, Danysz et al. 1999)

#### **Dexamethorphan**

Dexamethorphan is an N-methyl-D-aspartate receptor antagonist that is being explored for use in ALS. Preliminary studies, however, did not find positive effect. (Askmark, Aquilonius et al. 1993)

### ***Growth factors***

#### **Insulin-like growth factor I**

Some authors have reported decreased insulin-like growth factor 1 (IGF-1) in patients with ALS. (Eisen and Krieger 1993) (Torres-Aleman, Barrios et al. 1998) (Dore, Krieger et al. 1996)

Insulin-like growth factor-I (IGF-I) receptors are present in the spinal cord where they mediate signal transduction via tyrosine kinase. IGF-I was found to prevent the loss of choline acetyltransferase activity in embryonic spinal cord cultures, as well as to reduce the programmed cell death of motor neurons in vivo during normal development or following axotomy or spinal transection. Clinical trials of recombinant human IGF-I have been initiated for patients with amyotrophic lateral sclerosis. (Lewis, Neff et al. 1993)

One study examined the cost effectiveness of treatment with recombinant insulin-like growth factor 1 (rhIGF-I) in patients with ALS. They conclude that treatment with rhIGF-I is most cost effective in ALS patients who are either in earlier stages of the disease or progressing rapidly. The cost effectiveness of rhIGF-I therapy compares favorably with treatments for other chronic progressive diseases. (Ackerman, Sullivan et al. 1999)

A double-blind, placebo-controlled, randomized study of 266 patients was conducted at eight centers in North America. The authors concluded that recombinant human insulin-like growth factor-I slowed the progression of functional impairment and the decline in health-related quality of life in patients with ALS with no medically important adverse effects. (Lai, Felice et al. 1997) (Lange, Felice et al. 1996)

An European placebo-controlled trial of insulin-like growth factor-I in amyotrophic lateral sclerosis, however, showed no significant difference between treatment groups. (Borasio, Robberecht et al. 1998)

### **Nerve growth factor**

A moderate reduction in beta-NGF (nerve growth factor) levels was seen in the serum of patients with ALS and multiple sclerosis. There was a statistically significant reduction in the patients who were carriers of Parkinson's disease and Huntington's chorea. (Lorigados, Pavon et al. 1998)

### **Leukemia inhibitory factor**

Leukemia inhibitory factor (LIF) was named after its effect on hemopoietic (blood-forming) cells. Studies have demonstrated a powerful effect of LIF in the survival of both motor and sensory neurons, while reducing denervation induced muscle atrophy. LIF will also stimulate muscle regeneration in vivo when applied exogenously after injury. A human recombinant form of LIF (AM424), entered human clinical trials during 1998. (Kurek, Radford et al. 1998)

### **Ciliary neurotrophic factor**

Ciliary neurotrophic factor is currently in clinical trials for the potential treatment of motor neuron disease or amyotrophic lateral sclerosis. (Lindsay 1994)

### **Pigment epithelium-derived factor**

Pigment epithelium-derived factor (PEDF), a natural substance produced by the body, was located for the first time in the spinal cord and skeletal muscles of humans, monkeys, and rats. Previously, scientists believed that PEDF was found only in the pigmented layer of cells beneath the retina. Using slices of rat spinal cords kept alive in culture, PEDF showed a dramatic ability to protect cells from the toxic effects of threohydroxyaspartate (THA), a chemical that mimics the effects ALS, causing slow death of motor neurons. The PEDF-treated sections showed a near-normal neuron count compared with untreated cultures. According to Dr. Ralph Kuncel, who led the Johns Hopkins research team, protection of the spinal cord nerves in culture by PEDF was nearly complete. He went on to state that "...If we had this same level of protection in patients with ALS, they'd experience slight muscle weakness at most." The effectiveness of PEDF will be tested next on transgenic mouse models.

### **Neurturin**

The same research team recently reported in the May issue of *Molecular and Cellular Neuroscience* on another natural compound known as neurturin, a neurotrophic substance that will stimulate regeneration of damaged nerve cells. Neurotrophic factors including PEDF and neurturin are believed to protect healthy cells from the damaging effects of glutamate, a neurotransmitter that gluts the spaces between motor nerve cells causing over-stimulation and contributing to the progression of the disease. Although riluzole mildly restrains the immediate release of glutamate, it provides minimal protection to motor neurons as do PEDF and neurturin. The researchers predict the development of an "ALS cocktail," drug combinations containing neurotrophic factors, "each working at a different point in the process." (Bilak, Shifrin et al. 1999)

### **TGF-beta**

In an commentary published in the November issue of the journal *Nature Neuroscience*, authors Richard J Miller and Clifton W Ragsdale of the University of Chicago discuss the function of transforming growth factor-beta, or TGF-beta in the programmed death, or apoptosis, of nerve cells. TGF-beta is part of a family of growth factors by the same name that are involved in many biological functions in all of the body's tissues, such as embryonic development, reproduction and wound healing. (Miller and Ragsdale 2000)

In a study reported in the same in the same issue, chick embryos were immunized to neutralize the three forms of TGF-beta during the restricted period of embryonic development in which 50% of the neurons that have formed experience apoptosis. Neuron death was halted in all of the cells that were destined to die, which included central nervous system motor neurons and peripheral nervous system autonomic neurons. It is possible that TGF-beta works only on those neurons that will die, acting in a way that permits rather than instructs the cells to die. In other circumstances TGF-betas may enhance neuron survival. The researchers, led by Kerstin Krieglstein of the University of Saarland at Homburg, Germany conclude that TGF-beta could function as a molecular switch, which determines the life and death of neurons. (Krieglstein, Richter et al. 2000)

The authors of the commentary state that the findings may have important implication for diseases such as amyotrophic lateral sclerosis (ALS) which is characterized by the death of motoneurons and may involved programmed cell death. Spinal cord trauma may involve neuron death by apoptosis as well. The removal of TGF-betas may be able to reduce the death of neurons and prevent some of the disability associated with this and other conditions.

### ***TR500***

TR500, a glutathione-repleting agent, is being studied for use in ALS. (Hurko and Walsh 2000)

### ***Deprenyl***

Deprenyl (Eldepryl, Selegiline hydrochloride), a selective monoamine oxidase B inhibitor, is effective in Parkinson's disease, and can slow the cognitive deterioration in Alzheimer's disease. Studies of it's use in ALS however did not show any significant improvement. (Lange, Murphy et al. 1998) (Kuhn and Muller 1996)

### ***Pimozide***

Pimozide is a voltage-dependent calcium channel blocker that is being explored for use in ALS. One study showed a significant decrease of the index of progression of the disease in pimozide treated patients as compared to selegiline and vitamin E. In a randomized trial of 44 patients diagnosed as either definite or possible ALS, were treated with 1 mg per day of pimozide for 3-12 months. Statistical analysis showed a significant decrease of the index of progression of the disease in pimozide treated patients as compared to the others. (Szcudlik, Tomik et al. 1998)

### ***Gabapentin***

Gabapentin (Neurontin) is derived from gamma-aminobutyric acid (GABA). Gabapentin prevents seizures in a wide variety of models in animals, including generalized tonic-clonic and partial seizures. In vitro, gabapentin modulates the action of the GABA synthetic enzyme, glutamic acid decarboxylase (GAD) and the glutamate synthesizing enzyme, branched-chain amino acid transaminase. Results with human and rat brain NMR spectroscopy indicate that gabapentin increases GABA synthesis. In vitro, gabapentin reduces the release of several mono-amine neurotransmitters. (Taylor 1997; Taylor, Gee et al. 1998)

Unfortunately Gabapentin was found to provide no evidence of a beneficial effect on disease progression or symptoms in patients with ALS in a Phase III randomized double-blind placebo trial. (Miller, Moore et al. 2001)

## DIET

People suffering with ALS should avoid eating processed foods (foods with preservatives and artificial ingredients) and only eat fresh, natural foods.

Fresh fruits and vegetables are good because they provide vitamins and antioxidant substances. Meat, fish, eggs, and cheese, which contain protein which is used to build muscle should also be consumed. Nutrient-dense foods should be eaten. These are foods a person can eat much less of to get the adequate amount of nutrition; thus, the patient does not have to waste a lot of energy eating. Foods containing fiber are also good to eat because they prevent constipation.

### *Monosodium glutamate*

Dietary intake of glutamate is associated with an increased risk of ALS. (Nelson, Matkin et al. 2000) Glutamate is found in monosodium glutamate (MSG) which occurs naturally in many foods. The following foods should be avoided:

Table1: Monosodium Glutamate Content in Food

High	Roquefort cheese, Parmesan cheese, Soy Sauce
Medium	Walnuts, Fresh tomato juice, Grape juice Peas, Mushrooms, Broccoli, Tomatoes, Oysters, Corn, Potatoes
Low	Chicken, Fish (Mackerel), Beef Eggs, Cow's Milk

High            over 1000 mg/100g

Medium        100-1000 mg/100g

Low            1-99 mg/100g

Source: MSG Facts <http://www.msginfo.com>

### *Aspartate*

Aspartate, another potent neurotoxin, should also be avoided in chronic neurologic disease. Aspartate is found in artificial sweeteners such as Aspartame and NutriSweet.

## NUTRITIONAL SUPPLEMENTS

Most of the research on nutritional supplements for ALS focuses on several areas:

- Protection against glutamate toxicity with vitamin B12 and SAMe
- Antioxidants including glutathione, superoxide dismutase, zinc and copper, N-acetylcysteine, vitamin C, vitamin E, and alpha-lipoic acid
- Protection and regeneration of neurons with vitamin B12, Essential Fatty Acids, Acetyl-L-carnitine, Pregnenolone and DHEA, Genistein
- Improving mitochondrial function with coenzyme Q10 and creatine
- Growth stimulation with Human growth hormone and Testosterone.

- Mineral deficiencies of magnesium, calcium and Vitamin D
- Miscellaneous supplements including ginseng, branched-chain amino acids, Hydergine, Vinpocetine, and trimethylglycine.

## **Protection against glutamate toxicity**

One cause of brain cell death is glutamate toxicity. Brain cells use glutamate as a neurotransmitter, but unfortunately glutamate is a double-edged sword in that it can also kill aging brain cells. The release of glutamate from the synapses is the usual means by which neurons communicate with each other. Effective communication means controlled release of glutamate at the right time to the right cells. However, when glutamate is released in excessive amounts, intercellular communication ceases. It is like replacing radio signals with x-rays. The flood of glutamate onto the receiving neurons drives them into hyperactivity and the excessive activity leads to cellular degradation.

### ***Methylcobalamin and SAME***

It may be possible to protect brain cells against glutamate toxicity by taking methylcobalamin (vitamin B12) supplements. In a study published in the *European Journal of Pharmacology*, it was shown that chronic exposure of rat cortical neurons to methylcobalamin protected against glutamate-, aspartate-, and nitroprusside- induced neurotoxicity. This study also showed that S-adenosyl-methionine (SAME) protected against neurotoxicity. (Akaike, Tamura et al. 1993)

In a study published in *Investigational Ophthalmology Visual Sciences*, a combination of methylcobalamin and SAME was used to protect against retinal brain cell toxicity caused by glutamate and nitroprusside. The mechanism by which methylcobalamin protected against neurotoxicity was postulated by the researchers to be enhancement of brain cell methylation. The scientists who conducted these studies emphasized that chronic exposure of methylcobalamin was necessary to protect against neurotoxicity. (Kikuchi, Kashii et al. 1997)

Based on its unique mechanisms of action, methylcobalamin could be effective in slowing the progression of diseases such as ALS. Since methylcobalamin is not a drug, there is little economic incentive to conduct expensive clinical studies. It may be a long time before we know just how effective this vitamin B12 analog is in slowing the progression of ALS. This indicates that for methylcobalamin to be effective in protecting against neurological disease, daily supplementation may be required. An appropriate dose for an ALS patient to take would be 20 to 60 mg a day taken sublingually.

## **Antioxidants**

Free radicals are molecules that have an unpaired electron, a highly unstable state. Most free radicals react with molecules that contain oxygen to form reactive oxygen species, such as nitric oxide (NO), superoxide (O<sub>2</sub><sup>-</sup>), and hydroxyl (OH<sup>-</sup>). Free radical damage is associated with many degenerative conditions, including neurological disorders. (Ronzio 1985) (Jenner 1994)

Antioxidants inhibit oxidation by free radicals. The term “oxidative stress” refers to the balance of free radicals to antioxidants. Antioxidants include detoxification enzymes, such as superoxide dismutase; vitamins including beta carotene and other carotenoids; vitamins C and E; and nutritional supplements such as coenzyme Q10, cysteine, glutathione, lipoic acid, and melatonin.

In a study published in *Neurochemical Research*, several parameters indicative of oxidative stress were evaluated in blood from individuals with the sporadic form of amyotrophic lateral sclerosis

(SALS) and were compared to healthy controls. Plasma levels of 2-thiobarbituric-reactive substances (TBARS), products of lipid peroxidation, were significantly higher ( $p < 0.03$ ) in the SALS patients compared to controls. The ratio TBARS/alpha-tocopherol was 47% higher in the SALS individuals than in controls. (Oteiza, Uchitel et al. 1997)

Evidence suggests that free radicals in the brain may play a role in the development of age-related neuronal impairments. The increase in the concentration of the pro-inflammatory cytokine (cells which regulate immune responses), interleukin-1 beta (which can cause fever, induce synthesis of acute phase proteins, and initiate metabolic wasting), in aged brain tissue, may also be a contributory factor. This study analyzed changes in enzymatic and non-enzymatic antioxidant levels, in parallel with interleukin-1 beta concentration, in cortical brain tissue prepared from young and aged rats. Results showed an age-related increase in the activity of superoxide dismutase. An age-related decrease in the concentrations of vitamin E and C was also shown. These observations, coupled with age-related increases in lipid peroxidation and interleukin-1 beta concentration show a compromised antioxidant defense in cortex of aged rats. These negative changes were not observed in cortical tissue prepared from rats fed on a diet supplemented with vitamin E and C for 12 weeks. (O'Donnell and Lynch 1998)

### ***Glutathione***

Glutathione, an antioxidant and molecule used to conjugate toxins in the body, may be beneficial for ALS. A decrease in total glutathione concentrations in the substantia nigra has been observed in preclinical stages, at a time at which other biochemical changes are not yet detectable. (Schulz, Lindenau et al. 2000)

One study showed that estradiol, a naturally occurring estrogen that has been produced semi-synthetically, protects spinal motor neurons from excitotoxic insults in vitro, and may have application as a treatment for ALS. The dose of estradiols required for motor neuron protection was greatly reduced by co-administration with glutathione. (Nakamizo, Urushitani et al. 2000) A study of the role of estrogen in ALS, however, found that there was no difference in survival in those patients taking estrogen compared to those not on the medication. (Rudnicki 1999)

### ***Superoxide dismutase***

The genetic form of ALS is autosomal dominant with a defect on SOD1, the gene encoding superoxide dismutase. Superoxide is an oxygen molecule with an extra electron. Superoxide dismutase, or SOD, is an antioxidant enzyme that adds hydrogen to the superoxide molecule to convert it into stable oxygen plus hydrogen peroxide ( $H_2O_2$ ). (Robberecht 2000)

There is evidence that the point mutations in superoxide dismutase, which are associated with amyotrophic lateral sclerosis, may contribute to mitochondrial dysfunction. (Beal 1999) A recent study showed that treatment with superoxide dismutase improves neuromuscular dysfunction and morphological changes in wobbler mouse motor neuron disease. (Ikeda, Kinoshita et al. 1995)

Superoxide dismutase is under Phase One scientific investigation for its use in ALS. (Hurko and Walsh 2000) (Kinoshita and Ikeda 1998)

### ***Zinc and Copper***

Zinc supplementation should be considered in addition to superoxide dismutase. A recent study showed that the loss of zinc from SOD was sufficient to induce apoptosis (programmed cell death) in cultured motor neurons. When replete with zinc, SOD was not toxic. Both protected motor neurons from growth factor withdrawal. (Estevez, Crow et al. 1999)

Mitochondrial superoxide dismutase requires manganese, while the cytoplasmic (cellular) form requires copper and zinc. Patients with familial ALS possess a defective gene that decreases cytoplasmic SOD by 40%. (Ronzio 1985)

### *N-acetylcysteine*

N-acetyl-L-cysteine (NAC) is an antioxidant agent that reduces free radical damage.

In a study at Massachusetts General Hospital and Harvard Medical School, N-acetyl-L-cysteine (NAC) was used as preventative treatment in transgenic mice with a superoxide dismutase mutation. NAC supplementation resulted in significantly prolonged survival and delayed onset of motor impairment when compared to control mice. The authors encouraged further research and clinical trials for ALS treatment with NAC. (Andreassen, Dedeoglu et al. 2000)

One study published in the Journal of Neuroscience (USA) studied the effects of N-acetyl-L-cysteine (NAC) on mice with mutation that caused lower motoneuron degeneration with associated skeletal muscle atrophy (wobbler mice). This mutation shares some of the clinical features of amyotrophic lateral sclerosis (ALS). Litters of wobbler mice were given a 1% solution of the glutathione precursor NAC in their drinking water for a period of 9 weeks. Functional and neurological examination of these animals revealed that wobbler mice treated with NAC exhibited (1) a significant reduction in motor neuron loss and elevated glutathione peroxidase levels within the cervical spinal cord, (2) increased axon caliber in the medial facial nerve, (3) increased muscle mass and muscle fiber area in the triceps and flexor carpi ulnaris muscles, and (4) increased functional efficiency of the forelimbs, as compared with untreated wobbler littermates. These data suggest that reactive oxygen species may be involved in the degeneration of motor neurons in wobbler mice and demonstrate that oral administration of NAC effectively reduces the degree of motor degeneration in wobbler mice. (Henderson, Javaheri et al. 1996)

Another study published in the Journal Neurology Science (Netherlands) described how 36 patients with sporadic amyotrophic lateral sclerosis were treated with an array of antioxidants in addition to their prescription medications. Their customary prescription sequence was N-acetylcysteine (NAC); vitamins C and E; N-acetylmethionine (NAM); and dithiothreitol (DTT) or its isomer dithioerythritol (DTE). Patients with a history of heavy exposure to metal were also given meso 2,3-dimercaptosuccinic acid (DMSA). NAC, NAM, DTT, and DTE were administered by subcutaneous injection or by mouth or by both routes, the other vitamins and DMSA by mouth alone. Comparison of survival in the treated group and in a cohort of untreated historical controls, disclosed a median survival of 3.4 years (95% confidence interval: 3.0-4.2) in the treated and of 2.8 (95% confidence interval 2.2-3.1) years in the control patients. This difference may be explained by self-selection of the highly motivated treated group and by its initial survival of diagnosis for an average of 8.5 months before onset of treatment. The authors conclude that antioxidants neither seem to harm ALS patients, nor do they seem to prolong survival. (Vyth, Timmer et al. 1996)

### *Vitamin C*

A recent paper has proposed that vitamin C deficiency may be the underlying mechanism for the development of ALS. Three mechanisms were proposed. First, superoxide radicals are a common substrate for both superoxide dismutase and ascorbate. Second, brain-cell ascorbate release is coupled with glutamate uptake. Third, there is evidence supporting the vitamin C deficient (scurvy) guinea pig as a model for amyotrophic lateral sclerosis. (Kok 1997)

Vitamin C also plays an important role in the transmission of signals between neurons. Glutamate and aspartate (Vitamin C) are the two main excitatory neurotransmitters in the brain with glutamate

being responsible for 75% of it. One possible hypothesis would be that excessive reliance on glutamate may be due to a deficiency of vitamin C. (Ganong 1995)

To help protect against respiratory dysfunction, 600 mg of N-acetylcysteine (NAC) and 1000 mg of vitamin C, 3 times a day, are suggested.

### ***Vitamin E***

Vitamin E is a potent antioxidant. Deficiency is associated with progressive neurologic deterioration. Several studies in the 1940s described improvement in ALS patients when supplemented with alpha-tocopherol, the natural form of Vitamin E. (Werbach 1996) (Wechsler 1940) (Rosenberger 1941)

A recent study in *Neuroscience Letters* reported remarkably low levels of alpha-tocopherol quinone in the cerebrospinal fluid of patients with sporadic amyotrophic lateral sclerosis. (Tohgi, Abe et al. 1996)

The authors of one paper on vitamin E stated that “dietary supplementation with vitamin E delays onset of clinical disease and slows progression in the transgenic mice model but does not prolong survival.” (Gurney, Cutting et al. 1996)

One author notes that vitamin E is beneficial only for some patients with ALS and recommends further investigation. (Reider and Paulson 1997)

### ***Alpha-lipoic acid***

Alpha-lipoic acid is a potent antioxidant that is especially effective in preventing diabetic neuropathy. (Reljanovic, Reichel et al. 1999) (Ziegler, Hanefeld et al. 1995) (Klein 1975)

Alpha-lipoic acid has been shown to stimulate nerve growth factor synthesis and secretion in mouse astroglial cells. Astrocytes are cells which support the structure of the nervous tissue. (Murase, Hattori et al. 1993)

Therefore, a dose of 250 mg 3 times a day of alpha-lipoic acid to protect the neurons affected by ALS is suggested.

## **Protect and regenerate neurons**

### ***Vitamin B12, methylcobalamin***

High doses of methylcobalamin have been used to treat degenerative neurological diseases in rodents and humans. People with amyotrophic lateral sclerosis (Lou Gehrig's disease) took 25 mg a day of methylcobalamin for a month. In this disease, the neurons that control muscle movements deteriorate. The double-blind, controlled study showed that methylcobalamin improved muscle response after a month of treatment. (Kaji R 1998)

A study published in the journal *Internal Medicine* investigated the daily administration of 60 mg of methylcobalamin to patients with chronic progressive MS, a disease that has a poor prognosis and widespread demyelination in the central nervous system. Although motor disability did not improve, there were clinical improvements in visual and auditory MS-related disabilities. The scientists stated that methylcobalamin might be an effective adjunct to immunosuppressive treatment for chronic progressive MS. This again suggests a potential benefit, but no clinical

studies on ALS patients using methylcobalamin have been conducted. (Kira, Tobimatsu et al. 1994)

The effects of methylcobalamin were studied on an animal model of muscular dystrophy. This study published in *Neuroscience Letters*, looked at the degeneration of axon motor terminals. In mice receiving methylcobalamin, nerve sprouts were more frequently observed and regeneration of motor nerve terminals occurred in sites that had previously been in a degenerating state. (Yamazaki, Oda et al. 1994)

In a study published in the *Journal of Neurological Science*, scientists postulated that methylcobalamin could up-regulate protein synthesis and help regenerate nerves. The scientists showed that very high doses of methylcobalamin produced nerve regeneration in laboratory rats. The scientists stated that ultra-high doses of methylcobalamin might be of clinical use for patients with peripheral neuropathies. The human equivalent dose to duplicate this study would be about 40 mg of sublingually administered methylcobalamin. (Watanabe, Kaji et al. 1994)

In humans, a subacute degeneration of the brain and spinal cord can occur by the demyelination of nerve sheaths caused by a folic acid or vitamin B12 deficiency. In a study published in the *Journal of Inherited Metabolic Diseases*, it was shown that some people have genetic defects that preclude them from naturally producing methylcobalamin. The scientists stated that a deficiency of methylcobalamin directly caused demyelination disease in people with this inborn defect that prevents the natural synthesis of methylcobalamin. (Unknown 1993)

An early study published in the Russian journal *Farmakol Toksikol* showed that the daily administration of methylcobalamin in rats markedly activated the regeneration of mechanically damaged axons of motor neurons. (Mikhailov and Avakumov 1983)

An even more pronounced effect was observed in laboratory rats whose sciatic nerves were mechanically crushed. Two studies published in the Japanese journal *Nippon Yakurigaku Zasshi* showed that the administration of methylcobalamin caused significant increases in the in vivo incorporation of the amino acid leucine into the crushed sciatic nerve. This resulted in a stimulating effect on protein synthesis repair and neural regeneration. (Yamatsu, Kaneko et al. 1976; Yamatsu, Yamanishi et al. 1976)

### ***Acetyl-L-carnitine***

Acetyl-L-carnitine has produced dramatic results in protecting neurons in a wide range of disease states. Alzheimer's disease and amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) also respond to higher doses of acetyl-l-carnitine combined with other neuroprotective supplements.

One study of exercise tests in six ALS patients and six matched untrained controls indicated that the exercise-induced increase in plasma free fatty acids, beta-hydroxybutyrate, esterified carnitine, and muscle esterified carnitine was significantly retarded in ALS patients. (Sanjak, Paulson et al. 1987)

It is therefore suggested that ALS patients take 3000 mg a day of acetyl-L-carnitine.

### ***Essential Fatty Acids***

Neuronal damage can be caused by degeneration of the myelin sheath, a fatty layer that wraps the signal-moving neuronal fibers. Omega-3 and omega-6 fatty acids may help to repair the myelin sheath required for proper neuron conduction.

### ***Pregnenolone and DHEA***

New studies show pregnenolone to be a specific memory-enhancing hormone. Pregnenolone maintains the “program” brain cells need to store and retrieve short-term memories. As stores of pregnenolone (and DHEA) are depleted with advancing age, we see a marked and often dramatic decline in the neuronal synchronization required for optimal mental function. (Faloon 1996)

DHEA is a hormone primarily made in the adrenal glands. Production peaks around the age of 25-30 and then drops by 85-90% by the age of 70. DHEA has been associated with the ability to stay thin, make muscle, improve memory, resist stress, and produce a sense of “well-being”.

Since pregnenolone and DHEA are involved in the regulation of neurologic function, supplementation with 50 mg 3 times a day of pregnenolone, and/or 25 mg 2 to 3 times a day of DHEA should be considered.

### ***Genistein***

The phytoestrogen genistein, found in soy products, may also help the survival rate in ALS patients, according to research results in the journal *Biochemical and Biophysical Research Communications*.

Researchers at the Hughes Institute in Minnesota studied the effects of genistein on male and female mice with familial ALS. The researchers propose that the higher incidence of the disease and earlier onset in the male mice could be related to the presence of estrogen in females. Results of the study indicated that the genistein provided neuroprotective effects that were both estrogen-dependent and independent. Genistein warrants further study as a preventive agent against conditions such as ALS and stroke. Because there are insufficient research studies on humans, a physician must be consulted for dosage and prophylactic effectiveness. (Trieu and Uckun 1999)

### ***Progesterone***

Progesterone is synthesized in the peripheral nervous system in glial cells, which comprise the supporting structure of the nervous system. Studies have shown that progesterone stimulates neuron growth, accelerates the maturation of the regenerating axons, and enhances the remyelination of nerve fibers. The progesterone-induced myelination is probably mediated by progesterone receptors, as it is impaired by mifepristone (RU486), a progesterone antagonist. (Koenig, Gong et al. 2000)

## **Improve mitochondrial function**

### ***CoQ10***

In a study published in the *Proceedings of the National Academy of Sciences*, when CoQ10 was administered to rats genetically bred to develop ALS, a significant increase in survival time was observed. After only 2 months of coQ10 supplementation, mitochondrial energy expenditure in the brain increased by 29% compared to the group not getting coQ10. The human equivalent dose of coQ10 to achieve these results was 100-200 mg a day. The conclusion by the scientists was: “CoQ10 can exert neuroprotective effects that might be useful in the treatment of neurodegenerative diseases.” (Matthews, Yang et al. 1998)

This study documented that orally supplemented CoQ10 specifically enhanced metabolic energy levels of brain cells. While this effect in the brain has been previously postulated, this study provides hard-core evidence. Based on the types of brain cell injury that CoQ10 protected against,

the scientists suggested that it might be useful in the prevention or treatment of Huntington's and amyotrophic lateral sclerosis. It was noted that while vitamin E delays the onset of ALS disease in mice, it does not increase survival time. CoQ10 was suggested as a more effective treatment strategy for neurodegenerative disease than vitamin E because survival time was increased in mice treated with CoQ10.

About 95% of cellular energy are produced from structures in the cell called mitochondria. The mitochondria have been described as the cell's "energy powerhouse" and the diseases of aging are increasingly being referred to as "mitochondrial disorders". When coenzyme Q10 is orally administered, it is incorporated into the mitochondria of cells throughout the body where it facilitates and regulates the oxidation of fats and sugars into energy.

CoQ10 levels decrease with aging. Depletion is caused by reduced synthesis of CoQ10 in the body, along with increased oxidation of CoQ10 in the mitochondria. CoQ10 deficit results in the inactivation of enzymes needed for mitochondrial energy production, whereas supplementation with CoQ10 preserves mitochondrial function.

Further studies at Massachusetts General Hospital demonstrated that CoQ10 could protect against striatal lesions produced by both malonate and 3-nitropropionic acid. It extended survival in a transgenic mouse model of amyotrophic lateral sclerosis. (Beal 1999) One study of 30 patients with ALS, however, found that serum CoQ10 levels were unrelated with the risk of ALS. (Molina, de Bustos et al. 2000)

Based on this very preliminary research, ALS patients might want to take 100 mg of an oil-based coenzyme Q10 supplement 3 times a day. CoQ10 absorbs best when taken with fat, so oil-based supplements of CoQ10 can markedly improve systemic absorption.

### *Creatine*

A study published in the journal *Nature Medicine* found the amino acid creatine more effective than riluzole in extending the survival of mice with an ALS-type disease. The scientists reported that with 1% creatine administration, survival was extended by 13 days, and with 2% administration of creatine, survival doubled to 26 days. These scientists note that riluzole alone extends survival rate by 13 days (in mice). The supplemented creatine protected the mice from the loss of motor neurons and improved movement. This study proposed that creatine could help reverse the effects of ALS at the cellular level. This is done by stabilizing the enzymes in the mitochondria, the "powerhouses" of the cell that store energy, thus slowing the cell death process. (Klivenyi, Ferrante et al. 1999)

After taking creatine, patients with muscular dystrophy also showed a 10% increase in strength, according to a study in Neurology. (Walter, Lochmuller et al. 2000)

"Creatine is well tolerated" explains Leon Charash, M.D., who chairs the medical advisory committee of the Muscular Dystrophy Association. "Harnessing its apparent ability to buffer and stabilize the production and transportation of energy within cells could yield important health benefits for people with ALS and other progressive diseases."

Recent evidence has demonstrated a neuroprotective effect of creatine monohydrate supplementation in animal models of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and after ischemia. A low total and phosphocreatine concentration has been reported in human skeletal muscle from aged individuals and those with neuromuscular disorders. (Tarnopolsky 2000)

A study in the journal *Neurochemistry* showed that creatine significantly increased longevity and motor performance of transgenic mice with a superoxide dismutase mutation. Creatine also significantly attenuated the increases in glutamate measured with spectroscopy at 75 days of age, but had no effect at 115 days of age. The authors concluded that the beneficial effect of creatine might be due to an improved function of the glutamate transporter, which has a high demand for energy and is susceptible to oxidative stress. (Andreassen, Jenkins et al. 2001)

Another study found that oral administration of creatine produced a dose-dependent improvement in motor performance and extended survival in G93A transgenic mice. It also protected mice from loss of both motor neurons and substantia nigra neurons at 120 days of age. (Klivenyi, Ferrante et al. 1999)

Creatine monohydrate (10 g daily for 5 days to 5 g daily for 5 days) was administered to patients with neuromuscular disease in a pilot study (n = 81), followed by a single-blinded study (n = 21). Body weight, handgrip, dorsiflexion, and knee extensor strength were measured before and after treatment. Creatine administration increased all measured indices in both studies. The authors conclude that short-term creatine monohydrate increased high-intensity strength significantly in patients with neuromuscular disease. (Tarnopolsky and Martin 1999)

## **Mineral Deficiency**

### ***Magnesium***

Magnesium and glycine play an important role in NMDA (N-methyl-D-aspartate) receptors, which is a type of glutamate receptor. NMDA receptors permit passage of relatively large amounts of calcium ions. First, glycine binds to it to facilitate its function. Second, the channel is blocked (closed) by a magnesium ion. The channel becomes unblocked when the membrane becomes partially depolarized. (Ganong 1995)

### ***Vitamin D***

Two studies have shown a deficiency of vitamin D in patients with ALS along with decreased intestinal absorption of calcium and a reduction in bone mass (osteopenia). (Sato, Honda et al. 1997) (Yanagihara, Garruto et al. 1984)

## **Growth Stimulation**

### ***Human growth hormone***

Growth hormone has multiple functions in the body, including maintenance of lean body mass, mobilization of fat, counteracting insulin, enhancing immunity, lowering blood pressure and improving cholesterol levels, increasing energy, and even improving vision. (Dean 2000)

Growth hormone received the Food and Drug Administration's imprimatur in 1996 for use in adults with GH deficiency due to pituitary or hypothalamic disease, injury, surgery or radiation therapy. This now allows doctors to prescribe growth hormone as an anti-aging treatment for adults with low levels of IGF-1, which indicates a failure of the pituitary gland to produce adequate amounts of growth hormone.

Innovative drug therapies for ALS also might include 10 to 20 mg a day of Hydergine, 40 mg a day of vinpocetine, and testosterone and human growth hormone replacement therapy.

## ***Testosterone***

The link between testosterone and ALS has been proposed, but discounted in research conducted in the 1980s. Testosterone was explored because of the male-to-female ratio of the disease, the age of onset, and the sparing of neurons of cranial nerves III, IV, and VI that coincidentally lack androgen receptors. The hypothesis is that ALS may be due to a loss of androgen receptors that results in an inability to respond to a variety of insults including axonal damage. (Weiner 1980) The hypothesis was discounted by a study in which four men with ALS were treated with 200 mg of testosterone weekly. Lab tests indicated the expected degree of suppression of pituitary luteinizing hormone and follicle-stimulating hormone production. These data suggest that testosterone's (androgen) interaction with its receptors in the hypothalamic-pituitary axis is normal in patients with ALS. (Jones, Yu et al. 1982)

Testosterone is an anabolic steroid. It stimulates the body to grow. Testosterone is responsible for the development of masculine characteristics. The role of testosterone in amyotrophic lateral sclerosis is unclear, but the evidence presented clearly indicates that it may have a role in some patients.

## **Miscellaneous**

### ***Thiamin***

Several studies have proposed that a deficiency of thiamin (Vitamin B1) may be associated with amyotrophic lateral sclerosis. Thiamin and its esters are present in axonal membranes, and electrical stimulation of nerves effects the hydrolysis and release of thiamin diphosphate and triphosphate. Thiamin deficiency causes dry beriberi, a neurologic disease characterized by “burning” feet, peripheral neuropathy, and Wernicke-Korsakoff syndrome that causes the neurological problems common in alcoholism (staggering gait, confusion, problems with coordination, etc). The histological lesion of thiamin deficiency is a non-inflammatory degeneration of myelin sheaths.

A study published in the journal *Archive Neurology* measured free thiamin and thiamin monophosphate levels in plasma and cerebral spinal fluid of patients with amyotrophic lateral sclerosis (ALS), alcoholics, and controls. In plasma of patients with ALS as well as in plasma and CSF of alcoholics, both thiamin and thiamin monophosphate concentrations were decreased. In CSF of patients with ALS, however, thiamin monophosphate values decreased much more than thiamin levels. The selective impairment of thiamin monophosphate production by nerve cells is likely to result from the reduction of the activity of thiamin pyrophosphatase, an enzyme synthesized and highly concentrated in the Golgi complex, a component of the cell where complex molecules such as proteins are synthesized and packaged for use in the body. Thiamin pyrophosphatase is known to diminish in ALS as well as in experimental motor neuronal degeneration or axotomy. Thus, the Thiamin to Thiamin monophosphate ratio could be taken as an index of the impairment of neuronal protein synthesis in ALS.(Poloni, Patrini et al. 1982)

In a follow-up study, thiamine and thiamine monophosphate levels were measured in the CSF of patients with typical sporadic ALS (50 cases), in other motor neuron diseases (MND) (14 cases) and in patients with upper and/or lower motor neuron lesions of varying origin (disseminated sclerosis, polyneuropathy, spondylotic myelopathy). The Thiamin to Thiamin monophosphate ratio was greater than or equal to 1 in a high percentage of patients with typical sporadic ALS (94%), in 35.7% of cases with other MND, while it was below 1 in the all other patients. The decrease of Thiamin monophosphate with the inversion of the Thiamin to Thiamin monophosphate ratio is a finding highly specific to typical sporadic ALS. (Poloni, Mazzarello et al. 1986)

More recent research measured the enzymes involved in thiamin synthesis: thiamin-pyrophosphatase (TPPase) and thiamin-monophosphatase (TMPase) in brain tissue obtained at autopsy from amyotrophic lateral sclerosis (ALS) and parkinsonism-dementia (PD) patients from Guam and from Guamanian patients who died from other diseases (controls). TPPase content, chemically determined at pH 9.0, was found to be significantly reduced in the frontal cortex of ALS and PD patients compared to controls. TMPase content, on the contrary, was unchanged. (Laforenza, Patrini et al. 1992)

### ***Ginseng***

Ginseng (*Panax quinquefolium*) was given to transgenic mice with a defect in SOD1-G93A. Compared to controls there was a prolongation in onset of signs of motor impairment and survival. These experiments lend support to the use of ginseng root in ALS. (Jiang, DeSilva et al. 2000)

### ***Branched-chain amino acids***

Nutritional supplements called branched-chain amino acids can slow weight loss and muscle decline. There is, however, controversy in using branched-chain amino acids with ALS patients. One research group, however, reported higher than usual normal mortality rates, which caused the cessation of the clinical trial. (Anonymous 1993)

### ***Hydergine***

Hydergine is a drug approved by the FDA for persons “over sixty who manifest signs and symptoms of an idiopathic decline in mental capacity.” Studies have shown that it increases stores of the universal energy molecule, adenosine triphosphate (ATP), stabilizes the intracellular messenger molecule cyclic adenosine monophosphate (cAMP) content of nerve cells, improves utilization of glucose in the brain, and enhances cerebral microcirculation. (Dean 1999)

A recent study published in *European Neuropsychopharmacology*, showed that Hydergine causes an increase of superoxide dismutase (SOD) and catalase in the brain. SOD and catalase are the body’s natural antioxidants and are among the most effective free radical scavengers. (Sozmen, Kanit et al. 1998)

What was interesting about this study is that Hydergine was administered for only 20 days, but its effects in the brains of the lab rats were dramatic. Hydergine specifically increased catalase levels in the brain, as well as SOD in the hippocampus and in the corpus striatum regions. Those regions of the brain suffer severe oxidative damage from hydrogen peroxide and other free-radical generating agents. Orally ingested SOD and catalase have not proven efficacious because these antioxidant enzymes are broken down in the stomach, so scientists have concentrated on ways of prompting the body to produce its own cellular SOD and catalase. This study showed that Hydergine could increase brain levels of SOD and catalase after only short-term administration. (Faloon 1998)

### ***Vinpocetine***

Vinpocetine is produced by slightly altering the Vincamine molecule, an alkaloid extracted from the Periwinkle plant, *Vinca minor*. Vinpocetine has been shown to enhance cerebral metabolism and selectively vasodilate cerebral arteries. Vinpocetine has also been shown to enhance oxygen and glucose uptake from blood by brain neurons, and to increase neuronal ATP bio-energy production, even under hypoxic (low oxygen) conditions. (Vamosi, Molnar et al. 1976) (Solti, Iskum et al. 1976) (Szobor and Klein 1976) (Biro, Karpati et al. 1976)

Recent studies demonstrate that vinpocetine offers significant and direct protection against neurological damage caused by aging. The molecular evidence indicates that the neuroprotective action of vinpocetine is related to its ability to maintain brain cell electrical conductivity and to protect against damage caused by excessive intracellular release of calcium. Vinpocetine also has been documented to partially protect against excitotoxicity induced by a wide range of glutamate-related neurotoxins. (Faloon 1998)

### ***TMG (trimethylglycine)***

Re-methylation nutrients such as folic acid and TMG (trimethylglycine) are being studied as possible therapies to treat Alzheimer's disease, and the same mechanism of action might have a beneficial effect against ALS.

### ***Sphingolin***

Sphingolin, from Ecological Formulas, is an extract of bovine myelin sheath and is a rich source of myelin protective proteins. Use of this product may benefit those with myelin diseases such as multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS -Lou Gehrig's Disease)

## **Anecdotal Evidence**

Nutritionist Carmen Fusco reports that, while under her care for ALS, Senator Jacob Javits seemed to improve enough to reduce his hospital admissions. He recommended the following nutrients: octocosenol as it occurs in raw wheat germ oil; high doses of pantothenic acid (vitamin B5, the "stress vitamin"); and DMG sublingual. Fusco also has used the branch-chain amino acids and sublingual vitamin B12. Dr. Benjamin Frank recommended the coenzyme form of the B vitamins, which were administered intramuscularly by injection.

## **SUMMARY**

Physical, occupational and speech therapies are important to the patient with ALS to make it easier to live their lives. Wheelchairs, foot braces, and other devices that can make it easier to use the telephone and computer are helpful in making the patient as independent as possible.

Certain medications may be prescribed as the disease progresses. These include bacofen to relieve stiffness in limbs and throat; tizanidine as a muscle relaxant; riluzole to reduce the presynaptic release of glutamate; and Hydergine to increase brain levels of SOD and catalase.

## **Therapeutic Approach**

A great number of natural supplements may be helpful for patients with amyotrophic lateral sclerosis. There are over twenty listed in this article! Careful history and laboratory testing will help guide the choice of which supplements are most important. In addition, there are many products that are formulated with high amounts of antioxidants. A basic protocol might include the following:

- A high-quality multiple which contains plenty of antioxidants
- Reduced glutathione, 250-500 mg per day
- Methylcobalamin, 20 mg, 2 to 3 times a day
- Vitamin B1 (Thiamin), 100 mg per day

- Acetyl-L-carnitine, 3000 mg a day
- Creatine, 5 grams a day on an empty stomach.

Other supplements can of course be added based on the individual patient. SAME may be more indicated in clients that are emotionally distressed. N Acetyl cysteine is indicated if there is significant mucous congestion. Alpha lipoic acid is particularly useful for detoxification and associated liver disorders. Essential fatty acids may be indicated if the hair, skin and nails are dry and brittle. Extra magnesium is helpful for constipation. A hormone lab test is a simple and effective way to determine which hormones may be useful.

It should also be noted that the protocol will dramatically change depending upon the underlying cause. For instance, chronic viral infections need specific treatment. Chelation therapy may be useful for heavy metal toxicity. Detoxification of toxic chemicals and pesticides is beyond the scope of this article.

Of particular interest should be the type and quantity of carbohydrates in the patients diet. It is not uncommon to find people that eat little else but simple carbohydrates (breads, pasta, donuts, sugar, beer, etc.) Subclinical disorders such as Syndrome X (insulin resistance) should be considered. In these cases a switch to complex carbohydrates and protein can be accomplished with a suitable Green drink and Whey protein powder, along with proper diet counseling.

Despite the dire prediction of the conventional medical establishment, hope still remains for these predictions of a quick demise are based on patients with severe problems that have not tried any nutritional supplements. Simple dietary changes and nutritional supplements can often result in dramatic health improvements when a true nutrient deficiency is the underlying cause.

## List of Supplements

The supplements that may be beneficial to ALS patients are:

### *Protection against glutamate toxicity*

- Methylcobalamin, 20 mg, 2 to 3 times a day.
- SAME, 600-1800 mg per day (should be taken with folic acid, B12, and B6)

### *Antioxidants*

- Glutathione, 250-500 mg per day
- Superoxide dismutase
- Zinc, 30 mg with 5 mg copper, with food.
- N-acetylcysteine (NAC), 600 mg 3 times a day
- Vitamin C, 1000 mg 3 times a day.
- Vitamin E, 800 units 3 times a day.
- Alpha-lipoic acid, 250 mg 2 to three times a day.

### *Protect and regenerate neurons*

- Vitamin B12, methylcobalamin (see above)
- Acetyl-L-carnitine, 3000 mg a day

- Essential Fatty Acids containing both omega-3 and omega-6 fatty acids
- Pregnenolone, 50 mg 3 times a day.
- DHEA, 25 mg 3 times a day.
- Genistein, in a standardized soy isoflavone formula, 100 mg daily

### ***Improve mitochondrial function***

- Coenzyme Q10, 100 mg 3 times a day
- Creatine, 5 grams a day on an empty stomach.

### ***Minerals***

- Magnesium, 500 mg a day, particularly if the patient is constipated
- Calcium, 250 mg a day
- Vitamin D, 200 iu per day.

### ***Growth Stimulation***

- Human Growth hormone
- Testosterone

### ***Miscellaneous***

- Thiamin (Vitamin B1), 100 mg per day
- Ginseng
- Branched-chain amino acids, 1200 to 2400 mg daily
- Hydergine
- Vinpocetine, up to 30 mg daily
- DMG, 250 mg daily
- TMG, up to 2500 mg (should be taken with folic acid, B12, and B6)
- Sphingolin by Ecological Formulas, two capsules daily.

### **For more information.**

Contact the ALS Association National Office, 21021 Ventura Blvd., Suite 321, Woodland Hills, CA 91364; (818) 340-7500; patient hotline: (800) 782-4747; e-mail, [alsinfo@alsa-national.org](mailto:alsinfo@alsa-national.org). This association is a nonprofit, voluntary, national health organization committed solely to the fight against ALS through research, patient support, information, advocacy, and public awareness.

Contact the Family Caregiver Alliance, 690 Market Street, Suite 600, San Francisco, CA 94104; (415) 434-3388; Web site <http://www.caregiver.org>; e-mail, [info@caregiver.org](mailto:info@caregiver.org). The Family Caregiver Alliance supports and assists caregivers of brain-impaired adults through education, research, services, and advocacy.

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