Facts About

Amyotrophic Lateral Sclerosis

(ALS or Lou Gehrig's Disease)

MDA Muscular Dystrophy Association

Fighting Muscle Disease

Updated April 2011

Dear Friends:

Glenn Harwood

When I learned in 1994 that I had ALS, my world changed. I was in my early 50s, had a good career with the U.S. Small Business Administration, and was a husband and father. Suddenly, I faced a serious disease that would affect every aspect of my life.

I decided my best weapon in this battle would be attitude. I've met every challenge ALS has presented with an approach that's unbeatable: I can do it, I will do it. With that conviction, I have a full and rewarding life with the help of a power wheelchair, a voice synthesizer and lots of email. I've continued working, traveling and learning.

I have wonderful allies in this fight: a fantastic family, including my wife, Fran, our two children and beautiful grandchildren, who give me all the help I need and great joy and purpose. My faith in God never fails me, and helps me keep going with hope.

I've also honed my sense of humor. I carry a page of jokes with me at all times and regularly email friends across the country with "My Sunday Bulletin," a compendium of jokes I collect from my email friends. My motto is "Can't Walk or Talk But Can Always Laugh."

Another vital weapon in my arsenal is the Muscular Dystrophy Association, which offers the best doctors and health care professionals in the country. You also can count on MDA for support groups, help in finding special equipment, and support and understanding at every turn.

This MDA booklet offers an introduction to ALS, so you can begin preparing to meet the coming changes. MDA also gives each person with ALS copies of its very helpful and thorough books, ***Everyday Life with ALS: A Practical Guide*** and the ***MDA ALS Caregiver's Guide***.

From this booklet you'll learn several encouraging things about having ALS: that your diagnosis is in no way your "fault" … that many physical functions remain unaffected in ALS … and that better treatments and technological devices are constantly being tested and developed for every aspect of the disease.

It's good to know that society is far more aware of people with disabilities today, and the laws entitle you to equal employment opportunities and access to public places.

By the way, people with ALS can survive much longer than expected — in my case, more than 17 years since the earliest symptoms. I know of others who've had the disease for 15, 20 or more years.

You'll find, as I did, that the love of your family and friends will give you strength. A hopeful attitude and good sense of humor will keep ALS in perspective, as only one part of your life.

And remember: MDA and all its resources are there to help you and your family. You're not alone.

Glenn Harwood
Crofton, Maryland

MDA's ALS Division

MDA is a world leader in fighting ALS. If you've recently received an ALS diagnosis, this booklet will help you understand the disorder, while guiding you to the many services MDA provides.

Since the early 1950s, when Eleanor Gehrig served as a national volunteer leader of MDA, the Association has led the effort to assist those affected by the disorder that takes its name from her husband, baseball great Lou Gehrig, who died of ALS in 1941.

MDA's ALS Division offers the most comprehensive range of services of any voluntary health agency in the nation, and leads the search for better treatments and a cure through its aggressive worldwide research program. Since 1950, the Association has invested more than $290 million in its ALS program.

"MDA is Here to Help You" on page 15 describes in more detail MDA's ALS Division program, which includes MDA/ALS research and clinical centers, an ALS website and several publications geared to those affected by ALS. We invite you to contact your nearest MDA office for help at each step of the way.

Augie and Lynne Nieto

Augie's Quest and ALS TDI

Augie's Quest (www.augiesquest.org) is an MDA research initiative aggressively focused on finding ALS treatments and a cure.

Fitness pioneer Augie Nieto and his wife, Lynne, serve as co-chairs of MDA's ALS Division. Nieto, of Corona del Mar, Calif., received a diagnosis of ALS in March 2005.

MDA'S Augie's Quest has funded several research programs that have accelerated the development of therapeutic agents for ALS.

Foremost among these is the partnership between MDA and the ALS Therapy Development Institute (ALS TDI) in Cambridge, Mass. (www.als.net). As of early 2011, Augie's Quest has awarded more than $23.4 million to ALS TDI.

ALS TDI has screened more than 100 molecules to determine whether they affect the progression of ALS. Institute scientists have identified a molecule that increases body weight, delays progression and prolongs survival in an animal model of ALS. Other molecules are under investigation, and the Institute is working to bring the lead molecule to clinical testing.

As a part of its research, ALS TDI published a seminal paper explaining how to best test potential therapeutics for ALS in the SOD1 research mouse model of ALS. These careful practices will improve the reliability of all future ALS research.

What Is Amyotrophic Lateral Sclerosis?

ALS is a disease of the parts of the nervous system that control voluntary muscle movement.

The word "amyotrophic" comes from Greek roots that mean "without nourishment to muscles" and refers to the loss of signals nerve cells normally send to muscle cells. "Lateral" means "to the side" and refers to the location of the damage in the spinal cord. "Sclerosis" means "hardened" and refers to the hardened nature of the spinal cord in advanced ALS.

In the United States, ALS also is called Lou Gehrig's disease, named for the Yankees baseball player who died of it in 1941. In Britain and elsewhere in the world, ALS is often called motor neuron disease in reference to the cells that are lost in this disorder.

ALS can strike people of any age, though it usually occurs in late middle age.

What happens to someone with ALS?

In ALS, nerve cells that control muscle cells are gradually lost. In most cases, the cause is unknown. As these motor neurons are lost, the muscles they control become weak and then nonfunctional. Eventually, the person with ALS is paralyzed.

Without assistive technologies such as mechanical ventilation and feeding tubes, the average life expectancy is three to five years after an ALS diagnosis.

About 4 to 10 percent of those with the disease live more than 10 years, and some survive for decades, such as British physicist Stephen Hawking, who has had ALS since the 1960s and is still able to practice his profession.

Modern technology has allowed people with ALS to compensate to some degree for almost every loss of function, making it possible even for those with almost no muscle function to continue to breathe, communicate, eat, travel and use a computer.

It's important to note that the involuntary muscles, such as those of the heartbeat, gastrointestinal tract, bowel and bladder, and those that regulate sexual functions are not directly affected in ALS. (However, prolonged inability to move and other effects of ALS can have some indirect impact.) Hearing, vision and touch generally remain normal.

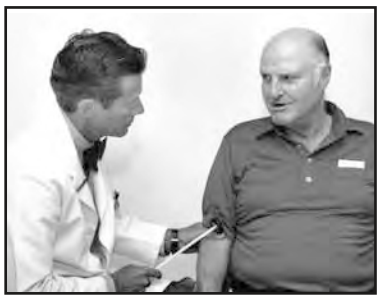
Pain is not a direct consequence of the disorder, although moderate pain can certainly occur as a result of immobility and its various complications.

Mild cognitive impairment is not uncommon, but severe cognitive impairment, known as "dementia," occurs in only about 3 to 5 percent of cases. Some with ALS may experience involuntary laughing or crying spells that are unrelated to their emotional state. Called involuntary emotional expression disorder, or pseudobulbar affect, this symptom can be treated with medication. (For more on these cognitive and emotional symptoms, see "Emotional and intellectual life," page 9.)

What happens to the nervous system in ALS?

Muscle-controlling nerve cells, or motor neurons, are divided into two types: upper and lower. The upper motor neurons are located on the surface of the brain and exert control over the lower motor neurons, which are in the brainstem and the spinal cord. (See illustration on page 6.)

The lower motor neurons are directly attached to muscles through "wires" called axons. Bundles of these axons leave the spinal cord and extend out to the muscles. It's these bundles that doctors are referring to when they talk about the "nerves."



Diagnosis is based on medical history, physical examination and exclusion of disorders that may mimic ALS.

MDA's ALS centers offer a team approach to treatment.

The function of lower motor neurons is straightforward. They send "go" signals to muscles. When these cells gradually die in ALS, muscles atrophy (shrink) and become progressively weaker and eventually unable to contract, resulting in paralysis.

The lower motor neurons that control most of the muscles in the body are in the spinal cord. Those that control the muscles of speaking, swallowing and facial expression are in the brainstem. They're sometimes called bulbar motor neurons, because the part of the brainstem that houses them has a bulblike shape. The term bulbar involvement means that the muscles of the face, mouth and throat are affected by the disease.

The upper motor neurons have more complex functions. It's harder to study them, and not as much is understood about them, although new techniques are changing that.

These cells seem to exert complex control over the lower motor neurons that allow movements to be smooth, directed and varied in intensity. (For instance, they're part of an elaborate system that allows a person to aim a hand at a glass of water, pick it up, estimate its weight, and use the right amount of force to lift it to his or her mouth, all while thinking about something else.) When upper motor neurons are lost and lower motor neurons remain, movements are still possible but can become tight (spastic) and less precise.

In ALS, a combination of these effects is usually seen because both upper and lower motor neurons are dying. People with ALS can have weak and atrophied muscles with tightness (spasticity). Muscle twitches (called fasciculations) and cramps are common; they occur because degenerating nerves become irritable.

Who gets ALS?

ALS usually strikes in late middle age (the average age of onset in the United States and Europe is between 56 and 63) or later, although ALS also affects younger adults and even children, as well as very elderly people. Some genetic forms of ALS have their onset in youth.

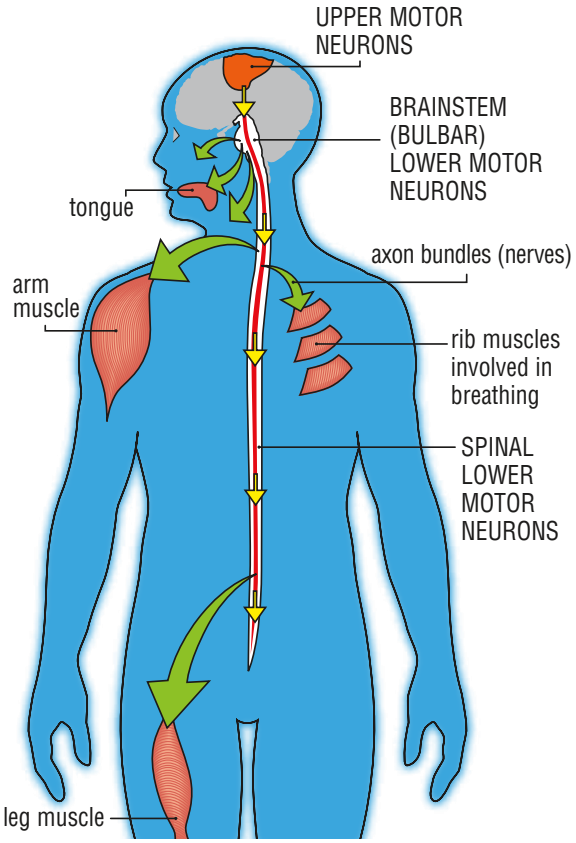
Men are somewhat more likely to develop ALS than are women. Studies suggest an overall ratio of about 1.5 men to every woman who develops the disorder in Western countries. In younger-onset patients, there seems to be a greater male predominance.

Genetic factors are involved in the cause of ALS, and the disease can run in families (see "Does It Run in the Family?" page 13). ALS is "familial" (that is, there is more than one case in a family) about 5 to 10 percent of the time. The other 90 to 95 percent of the time, it is "sporadic" (that is, there is no family history of the disease).

For years, experts have tried to find factors common to people who develop ALS, such as environmental toxins, occupational hazards, places of work or residence, and so forth. So far, the evidence for such risk factors and triggers has been frustratingly unclear, although a recent finding of an association between developing ALS and having served in the Gulf War in the early 1990s has indicated one of the strongest of these proposed risk factors. (For more on causes of ALS, see "What causes ALS?" page 10.)

How is ALS diagnosed?

ALS usually announces itself with persistent weakness or tightness in an arm or leg, making it difficult to use the affected limb; or in the muscles controlling speech or swallowing, leading to difficulty with these functions. At this stage, it isn't unusual for people to ignore these prob-



Upper motor neurons normally send signals to lower motor neurons, which send signals to muscles. In ALS, both upper and lower motor neurons degenerate.

lems or to consult a physician who is relatively unconcerned.

However, the disease — if it's truly ALS — continues to progress. It generally spreads from one part of the body to another, almost always in parts adjacent to each other, so that eventually the problem can no longer be ignored or treated with exercise or a cane.

It's at this point that the patient is usually referred by a general practitioner to a neurologist, who will then consider ALS among many other possibilities.

A thorough medical and family history and physical examination are the starting points of a neurologic work-up. The person will undergo simple, in-office tests of muscle and nerve function.

If ALS is still being considered at this point, the next step is usually an electromyogram, or EMG. This test measures the signals that run between nerves and muscles and the electrical activity inside muscles to see if there's a pattern consistent with ALS. If there is, more tests likely will be ordered.

Additional tests may include imaging of the spinal cord and brain, usually by MRI (magnetic resonance imaging) scan, and sometimes a test of the fluid surrounding the spinal cord (spinal tap or lumbar puncture), which is performed by putting a needle into the back between two lower vertebrae.

Blood tests to exclude disorders that mimic ALS also are performed. In some instances, a muscle biopsy, which involves taking a small sample of muscle under local anesthesia, is performed.

With the exception of genetic testing that can reveal the source of the disorder in a small percentage of cases, the diagnosis of ALS is mostly a "rule-out" procedure. This means ALS is diagnosed after all other possibilities have been ruled out by specific tests.

Among the conditions that resemble ALS are some forms of muscular dystrophy, the neurologic conditions known as spinal-bulbar muscular atrophy and adult-onset spinal muscular atrophy, the nerve-to-muscle transmission disorder known as myasthenia gravis, and various causes of compression of the spinal cord or brainstem, such as tumors and malformations.

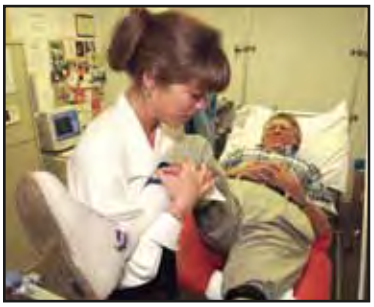
If your condition has been diagnosed as ALS outside a major medical center or without extensive testing, it may be worth getting a second opinion. MDA-supported clinics and MDA/ALS centers are staffed by professionals who are highly skilled at diagnosing ALS and the conditions that resemble it.

What can be done about ALS?

Although ALS research is proceeding at an unprecedented pace, only one medication has been found to be somewhat effective against the disease and is approved by the U.S. Food and Drug Administration (FDA) as an ALS treatment. That medication, riluzole (brand name Rilutek), has a modest effect in prolonging survival.

In 2010, the FDA approved the drug Nuedexta for the treatment of uncon-

Supportive braces can improve function.



Physical therapy can help with mobility.

Speech-generating devices help maintain communication.

trolled expression of emotion related to brain changes in ALS. This condition, also known as pseudobulbar affect, involves laughing and crying spells unrelated to mood.

Several other medications are now in clinical trials (See "MDA's Search for Treatments & Cures" page 14.)

MDA clinics and centers use a team approach to patient care that mobilizes a variety of health care professionals, all of whom aim to alleviate symptoms, maintain function and independence, prolong life and offer guidance for those with ALS and their families.

In-depth information and advice about coping with ALS can be found in MDA's book ***Everyday Life with ALS*** and ***The MDA ALS Caregiver's Guide***. Both are available free online (www.als.mda.org) and in print at your local MDA office.

In ALS, when it comes to technology, durable medical equipment and health-enhancing strategies like feeding tubes, the key is to "stay ahead of the game." Investigate and obtain these important aides before you need them, to increase the chances that you will fully benefit from them.

Preserving hand function

Special grips for writing implements and eating utensils, devices that fit over keys to make them easier to turn, zipper pulls and button hooks can help make weakening hands more functional.

Eyegaze technology provides an alternative to using the hands to access the Internet, write, use a communication device and even drive a power wheelchair.

A professional therapist associated with your MDA clinic or MDA/ALS center can help you with these devices.

Preserving mobility

Today's technology allows for mobility for almost everyone, no matter how few muscles remain functional. Physical and occupational therapists at your MDA clinic can help you identify the equipment that's best for each stage of the disorder.

In the early stages, a cane or a supportive brace (orthosis) may be all that's needed. An ankle-foot orthosis, or AFO, can keep the foot from dropping with each step and causing tripping while walking. Later, additional devices may be useful, such as walkers, manual wheelchairs and power wheelchairs.

As mobility becomes more difficult, a power wheelchair is usually highly desirable. A "tilt-in-space" type allows the seat to be positioned at a variety of angles, which relieves pressure and helps prevent skin breakdown. Some models allow the user to be brought into a standing position, which is generally good for circulation, bowel and bladder function, and bone preservation, as well as providing the psychological benefits of standing.

Careful planning for the type of wheelchair needed and desired, and a thorough knowledge of insurance matters in relation to wheelchairs, is important. Your MDA clinic or center often has a wheelchair specialist who can consult with you on these matters.

Custom-fitted power wheelchairs can take many weeks or months to obtain, so plan ahead. Your physician or physical therapist may raise the issue of a power wheelchair before you think you're ready, but this is to avoid long delays between the time the chair is needed and the time it may arrive.

Preserving communication

For many with ALS, speaking ability may be lost as weakness increases in the muscles in the mouth and throat that control speech and in the muscles that help generate the pressure that moves air over the vocal cords. This happens earlier in the bulbar-onset form of the disease than it does in the limb-onset form.

Noninvasive ventilation can help maintain respiratory function.

Regular measuring of respiratory muscle strength is an important part of ALS care.

For this reason, speech therapists, or speech-language pathologists, are vital members of the ALS care team.

Early in the disease process, while speech is still normal or nearly so, speech therapists may suggest that a person with ALS record his or her speech. A number of commonly used phrases can be programmed into a computer, or perhaps the person would like to talk about his or her life for future listening by friends and family.

Later, the therapist can teach the person with ALS special techniques for conserving energy and making speech understood as well as possible. In some cases, a dentist can make a device called a palatal lift that can help compensate for certain types of weakness in the roof of the mouth.

Later still, the therapist can help the person with ALS learn to use a communication device (there are a variety on the market) that can substitute for speech. Some therapists recommend learning the required skills long before they're needed, preferably while good hand function remains and energy levels are fairly high.

Getting enough to eat and drink

As the muscles involved in chewing, moving food toward the back of the mouth, and swallowing weaken in ALS, eating and drinking become less pleasurable and more hazardous and time-consuming.

The most serious problems are outright choking — obstruction of windpipe by a piece of food — and aspiration, which means inhaling food or liquid into the lungs instead of routing it down the esophagus into the stomach. Normally, the throat muscles protect us from aspirating food or drink, but they may lose their ability to do so as ALS advances.

Speech-language pathologists or therapists are also specialists in swallowing, since these functions involve the same muscles as speech. Some therapists specialize more in speech and others more in swallowing. Your MDA clinic can refer you to a therapist who can help you address swallowing problems as they arise.

Swallowing problems can cause weight loss, and that's not a good thing. In ALS, there is a clear link between weight and survival. Studies show that people who are slightly overweight at the time of diagnosis, and people who maintain their weight through the course of the disease, live longer than those who start out thinner or lose weight as ALS progresses.

Early solutions to swallowing problems involve changing the consistency of food and liquids — usually thickening the liquids and avoiding large pieces of food — as well as changing swallowing techniques.

Later, if swallowing becomes hazardous and eating takes a great deal of time and energy, the therapist and physician may recommend inserting a feeding tube (also called a gastrostomy tube) that allows food to be delivered directly into the stomach. The term "gastrostomy" refers to making a small incision in the stomach. You may hear a feeding tube referred to as a "PEG," which stands for "percutaneous endoscopic gastrostomy;" or a "RIG" tube, which stands for "radiologically inserted gastrostomy." These terms describe the procedures used when the tube is first inserted.

If still able to swallow some foods or liquids safely, people with ALS can continue to eat and drink by mouth after placement of a feeding tube. The tube can be used to supplement calories so that weight is not lost. This can be a relief to those who can't take in enough calories by mouth because they get too tired or are afraid of choking, but who still want to enjoy the taste of food.

Maintaining respiratory function

Perhaps the most serious medical complication in ALS is the gradual deterioration

Some people with ALS choose tracheostomy-delivered (invasive) ventilation.

of the muscles involved in breathing. The diaphragm is an arched muscle located just beneath the lungs that moves up and down and allows air to come in and move out. The intercostals are muscles between the ribs that contract and relax and also assist with air movement.

As these muscles weaken, the act of breathing, which is entirely automatic for most people, becomes conscious and energy-consuming.

At or before this stage of ALS, the neurologist will probably bring in a pulmonologist and/or respiratory therapist. These professionals are usually available in or near each MDA clinic or MDA/ALS center.

The physician may recommend that you consider using noninvasive ventilation to compensate for weakening muscles. In noninvasive ventilation, no incisions are made.

Noninvasive ventilation comes in many forms, but usually consists of two basic elements — an interface (such as a mask or nose inserts), and air delivered under pressure by a small, portable machine. Often, these machines provide a higher pressure for inhalation and a lower pressure for exhalation; this is called a bilevel positive airway pressure device, or BiPAP (BiPAP is a registered brand of Philips Respironics). There are other types of noninvasive ventilators as well, and professionals at the clinic will help you choose the device and interface that best meets your needs.

Noninvasive ventilation can be used as needed, and pressures, masks and other aspects of the device can be changed as desired.

Another form of breathing support, known as invasive ventilation, delivers air through a hole in the trachea, or windpipe. The surgical creation of this hole is called a tracheostomy, and the tube through which the air is delivered is called a tracheostomy (trach) tube.

Invasive ventilation is thought by most doctors to be a more reliable means of delivering air to the lungs when ALS is advanced and the respiratory and throat muscles are almost entirely nonfunctional.

Decisions about invasive ventilation aren't easy to make. Professionals at the MDA clinic are there to help you.

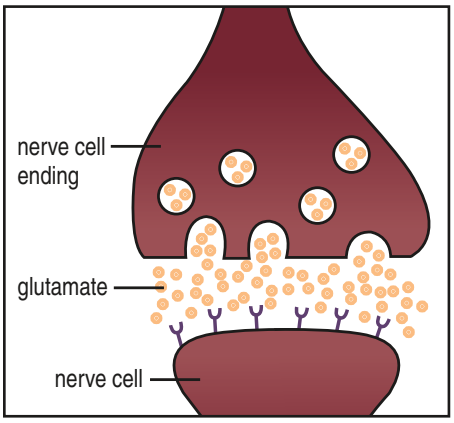
Another aspect of respiratory care that's important in ALS is assisted coughing. As the coughing muscles weaken, it becomes harder and harder to clear mucus from the airways. An assisted coughing device, which pushes air into the airway through a mask and then quickly reverses air flow, can help clear the airways and prevent infection. Your doctor also may recommend other methods to assist with coughing and clearance of secretions from the airways.

Emotional and intellectual life

Although ALS shortens life, it doesn't have to destroy it. Once the shock of the early stages of the disease have passed, many people with ALS report that they have rich emotional lives with family and friends, careers and interests, and a healthy sense of perspective and humor.

However, one "emotional" symptom of ALS that some people experience may be related purely to the physiology of the disease. Known as pseudobulbar affect, or involuntary emotional expression disorder, it involves prolonged laughing or crying spells out of proportion or inappropriate to the situation of the moment.

Some experts in neurophysiology believe this symptom arises from the loss of motor neurons in the top part of the brain that normally moderate the activity of the bulbar motor neurons in the brainstem.



Glutamate carries signals between neurons (nerve cells), and there may be too much of it in ALS.

These motor neurons activate muscles in the face and throat involved in laughing and crying. Without the influence of the upper brain neurons, more "primitive" parts of the brain may take over, experts believe, leading to physical expressions of emotion that adults normally inhibit. The "pseudo" in the term refers to the fact that the location of the problem isn't in the bulbar neurons themselves but in their loss of connection to neurons elsewhere in the brain.

Antidepressants are sometimes prescribed, and a medication called Nuedexta, developed specifically to combat this problem, was approved in 2010.

Mild cognitive impairment is fairly common in ALS, though not universal. Most people who have cognitive changes have mild problems, such as difficulty paying attention in conversations, trouble concentrating or finding words, and difficulty shifting attention from one thing to another. Severe cognitive impairment, known as "dementia," occurs in only about 3 to 5 percent of cases.

ALS is tough to handle alone. Many people with ALS and their families find support groups or Internet chat groups useful. MDA's support groups provide important help for spouses and other caregivers, whose job can be very demanding; ask at your clinic or local MDA office about one in your area.

Relief of symptoms

While researchers continue efforts to identify compounds that slow or stop motor neuron degeneration in ALS, physicians can prescribe medications to treat troublesome symptoms during the course of the disease. These include drugs to ease cramps and muscle twitches, help in handling saliva, reduce anxiety and depression, treat constipation, help with sleep problems, and alleviate pain associated with prolonged immobility and joint displacements.

What causes ALS?

Years ago, it was widely believed that there might be one cause to explain all cases of ALS. Today, doctors and scientists know that can't be the case. Together, they're working to identify the multiple causes of the disorder.

The 1993 finding of the SOD1 gene mutation that underlies some cases of ALS (see "Does It Run in the Family?" page 13) opened a window into ALS.

Even though very few ALS patients have flawed SOD1 genes, their disease (familial ALS) looks similar to sporadic ALS, the form that isn't caused by the SOD1 gene mutation. Scientists have concluded that the two types of ALS involve common biochemical and physical changes in the motor neurons.

Several clues to ALS causation have emerged since the early 1990s, and most experts believe these clues are linked to each other. The following possible causes are being studied by ALS specialists.

Free radicals

Free radicals are molecules that carry electrical charges that make them unstable and liable to damage cellular structures. They're a normal part of cellular life, and cells are usually able to neutralize most of them and keep their numbers in check. But in ALS, free radicals may build to toxic levels and damage cells, through an attack process called oxidative stress.

Excess glutamate

Glutamate is a common chemical in the nervous system, which neurons use to send signals to other neurons. But, like many things, glutamate has to be present in the right amount to work: Too

little leads to a lack of signaling, too much to the death of the nerve cells that receive the signal.

Evidence from studies of people with ALS points to an overabundance of glutamate in the nervous system. This may result from inadequate transport of glutamate away from nerve cells after it has finished its signaling work.

Experiments suggest a defect also could lie in excess production or release of glutamate by the sending cells, or it could result from defects in glutamate receptors on the receiving cells.

Buildup of neurofilaments

Proteins known as neurofilaments form the scaffolding that helps nerve cells hold their shape. In ALS, these neurofilaments tend to clump up near the body of the cell instead of moving down the "tail" (axon) of the cell. This may be causing a cellular traffic jam, and preventing nutrients and other vital materials from moving up and down the axon.

Defects in mitochondria

Of all the working parts of a cell, the energy-producing mitochondria are arguably the most crucial — especially for high-energy cells like motor neurons. They're also among the most complex and most studied parts of the cell.

Mitochondria have their own genetic material (DNA). It bears some resemblance to the cell's other DNA, which is organized into chromosomes in the cell nucleus.

But mitochondrial DNA is organized differently, packaged into microscopic rings of genetic material that lack many of the protections against damage that chromosomes in the nucleus possess.

For this reason, and because processes inside the mitochondria produce dangerous free radicals (see page 10), mitochondrial DNA is always in danger of being damaged. Some amount of damage occurs as part of the aging process, but in ALS, there may be more damage to mitochondria than the average aging cell sustains.

Cell suicide

Most cells have a built-in "suicide" program known as programmed cell death, or apoptosis. Under some circumstances, programmed cell death is normal. But in ALS and other degenerative diseases, it's possible that the cell death program is activated inappropriately.

Immune system abnormalities

Many disorders that affect the nervous system are autoimmune in nature, meaning they occur when the body's immune system mistakenly attacks its own tissues. Microglia, immune system cells found in the nervous system, appear to play a role in ALS. None of the treatments used for other autoimmune diseases has been effective against ALS.

Viruses and other infectious agents

For decades, scientists have guessed that viruses may play a role in ALS and other disorders that involve degeneration of nerve cells. So far, there's no proof of a viral trigger.

The HIV (human immunodeficiency) virus, which causes AIDS (acquired immunodeficiency syndrome), can cause an ALS-like syndrome that improves with treatment with antiviral drugs. Most ALS patients aren't HIV-positive, but the connection bolsters the idea that other viruses could also inflict motor neuron damage.

In 2011, scientists found evidence that a virus called HERV-K might be inappropriately active in some cases of ALS. This intriguing observation requires further study.

Toxins

The heavy metals lead, mercury and arsenic, although they can be toxic to the nervous system, haven't been shown to be causative agents in ALS.

Lead can damage upper and lower motor neurons, but, in the United States, exposure to lead has been monitored and limited for most people for several decades. In some circumstances, it may be worth testing for these exposures.

Prolonged contact with agricultural chemicals, such as pesticides, may be an ALS trigger in some cases.

The association of ALS with service in the Gulf War of 1990-91 may yield some clues. Some studies suggest that service in the military in general is a risk factor, in which case a broad range of factors will need investigation.

There are almost certainly genetic risk factors that may influence whether someone will develop ALS in the presence of a second or third circumstance.

A high incidence of ALS on the island of Guam has led to the idea that the cycad seed, ingested on the island, could be an ALS trigger.

Genes

In addition to those genes that can lead directly to ALS (see "Does It Run in the Family?" on page 13), there almost certainly are genetic risk factors that may influence whether someone will develop ALS in the presence of a second or third circumstance (for example, exposure to a certain virus or environmental substance).

Does It Run in the Family?

ALS is "familial" — that is, there is a family history of the disease — about 5 to 10 percent of the time. Several genes associated with ALS have been identified. Some, when flawed, cause the disease directly. Others influence susceptibility to the disease.

The SOD1 gene

In 1993, MDA-supported researchers identified a gene on chromosome 21 that, when flawed (mutated), causes ALS.

Mutations in this SOD1 gene account for some 10 to 20 percent of familial ALS cases and also perhaps 1 to 3 percent of cases with no family history. (Since ALS can be a very late-onset disease, some people with SOD1 mutations probably die from other causes without ever developing ALS, so absence of a family history in ALS can be misleading.)

SOD1 mutations usually lead to ALS that's inherited in an autosomal dominant pattern, which means the flaw isn't on a sex chromosome (it's on an autosome) and that it takes a flaw in only one of a person's two SOD1 genes to cause disease. (For more information about inheritance patterns, see the MDA publication "Facts About Genetics and Neuromuscular Diseases.")

SOD1-related ALS sometimes assumes an autosomal recessive inheritance pattern, meaning that two mutated genes — one from each parent — are required before symptoms appear.

Family members can be tested for several genetic mutations known to cause ALS.

Other ALS-causing genes

Some 15 genes, in addition to the SOD1 gene can, when mutated, cause ALS.

Three that are receiving a great deal of attention are the TDP43 gene on chromosome 1, the FUS gene on chromosome 16 and the FIG4 gene on chromosome 6.

In 2008, investigators found that a particular variant of a gene called PON1 on chromosome 7 is more common in people with ALS than in people without the disease.

In 2010, researchers found that expansions in the gene for the ataxin 2 protein, located on chromosome 12, are significantly correlated with an increased risk of developing ALS.

Genetic testing and counseling

DNA testing for mutations in the SOD1 gene, the FUS gene, the FIG4 gene and the TDP43 gene, as well as a gene for the angiogenin protein, are readily available from Athena Diagnostics, a large commercial laboratory in Worcester, Mass. Mutations in additional genes, such as the senataxin gene, the VAPB gene and the alsin gene, are available at specialized laboratories.

Physicians and genetic counselors at MDA clinics and ALS centers can guide you with respect to seeking and interpreting genetic tests for ALS.

MDA's Search for Treatments and Cures

The biotechnology and pharmaceutical industries have built on the basic science research funded by MDA to bring experimental treatments for ALS into clinical trials in people with this disease.

Some of the drugs and strategies being tested in people with ALS are:

- **arimoclomol**
  This experimental compound, developed by CytRx, is a small molecule designed to stimulate a natural cell-repair pathway in people with the SOD1-related familial form of ALS.
- **dexpramipexole**
  This experimental drug, in development by Biogen Idec, may have neuroprotective properties.
- **SB-509**
  Developed by Sangamo BioSciences, this experimental agent is designed to stimulate production of a potentially beneficial protein called vascular endothelial growth factor.
- **ceftriaxone**
  Already approved to treat bacterial infections, this drug is being tested for its ability to reduce toxic glutamate accumulations from the area around nerve cells.
- **NP001**
  This experimental compound, in development by Neuraltus Pharmaceuticals, is designed to switch immune system cells from "attack" mode to "protective" mode in ALS.
- **ISIS-SOD1-Rx**
  This experimental compound, in development by Isis Pharmaceuticals with support from MDA, is designed to block toxic SOD1 protein molecules in people with the SOD1-related form of familial ALS.
- **neural stem cells**
  These stem cells, developed by Neuralstem, are on a path toward becoming nervous system cells; they're being injected into the spinal cord in people with ALS.

Although not yet in clinical trials, the experimental drug **ALSTDI-00846**, developed by the MDA-supported ALS Therapy Development Institute, has shown benefit in mice with an ALS-like disease. It blocks a key pathway involved in activation of the immune system.

The MDA website (als.mda.org) is constantly updated with the latest research information in ALS.

On the cover:
Scott, pictured with his wife Carol, received a diagnosis of ALS in 2008. Scott was a professional boxer and retired from the sport in 1983. He worked as a ringside commentator for ESPN, and in 2010 he was inducted into the Minnesota Boxing Hall of Fame.

MDA Is Here to Help You

The Muscular Dystrophy Association offers a vast array of services to help you and your family deal with ALS.

The staff at your local MDA office is there to assist you in many ways:

- nationwide network of clinics staffed by top neuromuscular disease specialists, including a number of clinics designated as MDA/ALS centers
- help with locating durable medical equipment through its national equipment program
- financial assistance with repairs or modifications to all types of durable medical equipment
- annual occupational, physical, respiratory or speech therapy consultations
- annual flu shots
- support groups for people with ALS and their families
- online support services through the e-community *my*MDA and through *my*MuscleTeam, a program that helps recruit and coordinate in-home help

MDA's public health education program helps you stay abreast of research news, medical findings and disability information through magazines, publications, educational speakers, seminars, videos and newsletters.

MDA's ALS Division website at als.mda.org contains thousands of pages of valuable information, including ALS research and care, clinical trials and past magazine articles.

Individuals affected by ALS who are registered with MDA automatically receive two award-winning publications — the MDA/ALS Newsmagazine and Quest magazine. These provide detailed articles about research findings, medical and day-to-day care, helpful products and devices, social and family issues, and much more.

Two books — ***The MDA ALS Caregiver's Guide*** and ***Everyday Life with ALS: A Practical Guide*** — also are offered free to anyone with ALS who's registered with MDA. Other MDA publications can be found at als.mda.org/publications; many booklets also are available in Spanish. MDA offers a booklet and video on respiratory issues, and a book of recipes for easy swallowing. Ask your local office for "MDA Services for the Individual, Family and Community" and for help with obtaining copies of other publications.

If you have any questions about ALS, someone at MDA will help you find the answer. To reach your local MDA office, call (800) 572-1717, or go to the MDA website (mda.org) and enter your ZIP code in the locator box.

MDA's Purpose and Programs

The Muscular Dystrophy Association fights neuromuscular diseases through an unparalleled worldwide research effort. The following diseases are included in MDA's program:

Muscular Dystrophies

Myotonic dystrophy *(Steinert disease)*
Duchenne muscular dystrophy
Becker muscular dystrophy
Limb-girdle muscular dystrophy
Facioscapulohumeral muscular dystrophy
Congenital muscular dystrophy
Oculopharyngeal muscular dystrophy
Distal muscular dystrophy
Emery-Dreifuss muscular dystrophy

Motor Neuron Diseases

Amyotrophic lateral sclerosis *(ALS)*
Infantile progressive spinal muscular atrophy *(Type 1, Werdnig-Hoffmann disease)*
Intermediate spinal muscular atrophy *(Type 2)*
Juvenile spinal muscular atrophy *(Type 3, Kugelberg-Welander disease)*
Adult spinal muscular atrophy *(Type 4)*
Spinal-bulbar muscular atrophy (*Kennedy disease)*

Inflammatory Myopathies

Polymyositis
Dermatomyositis
Inclusion-body myositis

Diseases of Neuromuscular Junction

Myasthenia gravis
Lambert-Eaton (myasthenic) syndrome
Congenital myasthenic syndromes

Diseases of Peripheral Nerve

Charcot-Marie-Tooth disease
Friedreich's ataxia
Dejerine-Sottas disease

Metabolic Diseases of Muscle

Phosphorylase deficiency *(McArdle disease)*
Acid maltase deficiency *(Pompe disease)*
Phosphofructokinase deficiency *(Tarui disease)*
Debrancher enzyme deficiency *(Cori or Forbes disease)*
Mitochondrial myopathy
Carnitine deficiency
Carnitine palmityl transferase deficiency
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Myoadenylate deaminase deficiency

Myopathies Due to Endocrine Abnormalities

Hyperthyroid myopathy
Hypothyroid myopathy

Other Myopathies

Myotonia congenita
Paramyotonia congenita
Central core disease
Nemaline myopathy
Myotubular myopathy
Periodic paralysis

MDA Muscular Dystrophy Association
Fighting Muscle Disease

MDA's ALS Division website, als.mda.org, is constantly updated with the latest research news and information about ALS. Follow MDA on Facebook, Twitter and YouTube.

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