The Story of ALS

Amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease, is a progressive, fatal disease that attacks nerve cells and pathways in the brain and spinal cord causing the body's motor neurons to waste away. ALS is an extraordinarily costly disease, in both monetary and in human terms – it kills about one of every 1000 adults without warning or cause.

In a bewildering attack on the motor neurons of the brain and spinal cord, ALS shatters a patient's health and well-being, often in very short order. Its origins are not well understood and effective treatments have remained maddeningly elusive. What is known is that ALS causes progressive muscle weakness, incoordination and difficulty breathing, speaking and swallowing. The median survival time following diagnosis is three years.

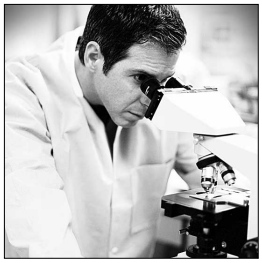
In addition to the physical and psychological costs borne by patients, ALS exacts a heavy toll on the patient's family. They may feel isolation, frustration and despair. Most struggle to find good medical care. Many have a hard time obtaining accurate, comprehensive information to guide them through the maze of questions and choices they will face in the course of their loved one's battle with the disease.

These formidable challenges notwithstanding, now is a time of unprecedented hope for those who suffer from ALS. With the advent of molecular genetics and cellular biology, medical science is acquiring the tools – for the first time – to unlock the mysteries of this heartbreaking disease. Armed with a clearer understanding of the basic biology of ALS, basic and clinical researchers working together will be able to make progress on the interventions that slow, arrest and ultimately prevent this disorder.

California has two of the nineteen ALS Association Certified Centers in the country located in San Francisco – the ALS Treatment and Research Center at UCSF directed by Dr. Catherine Lomen-Hoerth and the Forbes Norris ALS Research Center at California Pacific Medical Center directed by Dr. Robert Miller. These Centers provide a unique program of research coupled with a multidisciplinary, team approach to advanced, aggressive and compassionate medical care tailored to each ALS patient's specific needs.

The Science of ALS: The Current State of Knowledge

ALS is a neurodegenerative disease that usually attacks both upper and lower motor neurons and causes their degeneration throughout the brain and spinal cord. Most often striking adults between the ages of 45 and 65, it can occur as early as the teens or very late in life. Painless weakness in a hand is the most common first symptom that brings an ALS patient into the physician's office, and occurs in about half of all cases. Other first symptoms are slurring of speech and difficulty walking. ALS is inexorably progressive. Death is most often the result of respiratory insufficiency, pulmonary infection, or complications of immobility.



Only five to 10 percent of all ALS cases are inherited through family lines. The rest arise spontaneously and mysteriously, making seemingly random attacks on previously healthy adults. Therein lies one of the most frightening aspects of the disease; it can strike anyone, anytime. No individual or family is immune.

The biological mechanisms that cause ALS are only partially understood. The only known cause for ALS is a mutation of a specific gene – the SOD-1 gene. This mutation is believed to make a defective protein that is toxic to motor nerve cells. However, the SOD-1 mutation appears to account for only 1 to 2 percent of all ALS cases, or 20 percent of inherited cases. In the remainder of cases, scientists expect to find multiple causes for ALS.

Physicians have limited choices for testing ALS, and the options that exist have all come into use within the last 10 years. Studies have suggested that patients' length of survival and quality of life are benefited by night-time breathing assistance early in the course of their disease, and by aggressive application of alternate feeding options to assure good nutrition once swallowing becomes difficult. The only drug approved by the FDA for treatment for ALS is riluzole, which in clinical trials has shown slight benefit in modestly increasing survival times.

No current ALS treatment is expected to prevent the devastating outcome of the disease. The interventions available simply attempt to provide relief to patients and improve quality of life as the syndrome's progression is modestly slowed.

Future Possibilities

Armed with ever-better understanding of the cellular and molecular events that lead to ALS, scientists are making progress on experimental treatments. Obvious targets are the development of more potent antioxidants than the currently available vitamins, and more effective glutamate inhibitors than riluzole. The major current thrust of the biotechnology industry toward treatment of ALS focuses on neurotrophic factors and other naturally occurring proteins within the central nervous system. These proteins normally have a role in inhibiting genetically programmed cell death in all of us.

Great promise lies in the detection of cellular and molecular events that are not yet recognized. A dedicated team of clinical and basic scientists will be able to identify new molecular mechanisms and the subsets of patients that are affected by each. Then, the collaboration of biotechnology firms will allow rapid development and testing of treatments not even considered at present. Through functional genomics and gene chip technology, computers are being harnessed to discover differences between the ways genes function in patients with ALS and unaffected people as well as to conduct high-speed searches through thousands of chemicals and proteins as possible interventions for ALS. Ultimately, molecular biology and biotechnology will be able to exploit the potential of neuronal stem cells (the formative cells within the central nervous system that give rise to all other cells) to develop into functionally mature neurons that replenish those lost.

Stem Cell Research and ALS

Since the discovery that embryonic stem cells have the unique ability to generate all cell types of the nervous system when provided the appropriate cues, much research has been done to explore the potential of these cells as a therapy for ALS. Investigators have now discovered the appropriate cues to differentiate embryonic stem cells, in laboratory dishes, into motor neurons, the neuronal cell type affected in the disease. Now the challenge remains to transplant these motor neurons to replace the dying cells in humans and to encourage them to make the appropriate connections.

Unlike some of the other neurodegenerative diseases where the lesions are more focal (as in Parkinson's disease) and the task of neuron replacement appears to be less daunting, motor neurons have an exquisite property as their axons extend up to a meter in length. These long processes connect the cell with the muscle and enable communication and transport of important nutrients between the cell body and muscle. Scientists are now tackling the problem by bringing stem cell experts together with developmental biologists and leaders in the field of axonal guidance, determining what cues are needed to encourage appropriate reconnection of the cell processes.

Whilst scientists recognize that the potential to generate a large number of motor neurons from stem cells is currently only possible from embryonic stem cells, work continues to try and manipulate adult stem cells to generate these motor neurons. More importantly as scientific discoveries advance in the field of ALS, it is becoming evident that it is not only the motor neuron that is at risk in the disease but important neighboring cells the astrocytes and microglia. Studies to attempt to replace these cells are ongoing and may be more feasible than motor neuron replacement. In addition, efforts to determine the cues that may stimulate endogenous stem cells to generate cells of the nervous system are underway as an important alternative approach in ALS.

Not only are stem cells being considered as replacement therapy. More likely in the immediate future, stem cells may be important vehicles that can be targeted to the damaged area and provide missing factors to help remaining cells survive, in other words they act as a "local pump". This approach, together with gene therapy is crucial in a disease where delivery of appropriate factors to the cells at risk is a challenge. In addition, stem cells provide an excellent tool for drug screening purposes.

The many avenues of stem cell biology for ALS, together with the challenges to making this a reality for therapy make this field of research an incredibly important one and one that will benefit tremendously from the increased resources and expertise focused on ALS.

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