

The Promise and the Reality of Stem-Cell Therapies
for Neurodegenerative Diseases

By Jonathan D. Glass, M.D.

Editor's note: Jonathan D. Glass, M.D., is leading a clinical trial testing the safety of using adult stem cells to treat patients with amyotrophic lateral sclerosis (ALS), a neurodegenerative disease that remains untreatable. This trial, along with others like it, is just the beginning of a time-intensive process necessary to determine whether stem-cell treatments are safe and effective, meaning that the benefits—if there prove to be any—outweigh the risks. But even as FDA-approved trials are underway, some people with neurodegenerative disorders are turning to dangerous, unapproved stem-cell treatments out of desperation. Dr. Glass warns that researchers must strictly adhere to the scientific process in order to convert the hope of stem-cell treatments into reality.

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Neurodegenerative diseases are maladies of the nervous system. With few exceptions, their causes and treatments are enigmatic. This category of diseases typically includes the relatively common Alzheimer's and Parkinson's diseases, rarer forms of dementia and movement abnormalities such as frontotemporal dementia and the dystonias, and motor-neuron diseases such as amyotrophic lateral sclerosis (ALS). Worldwide intensive investigation into the pathogenesis of these disorders has generated a rich theoretical landscape of potential causes for neurodegeneration, focusing mostly on genetic and environmental factors. Researchers have not identified a specific cause for any of these diseases, however, even in cases where genetic mutations are known to underlie the disease. Because scientists lack a target at which to aim therapies, drug development for neurodegenerative diseases is an inexact science at best, and the pharmacopoeia for these diseases contains few drugs with minimal effectiveness.

ALS, also known as Lou Gehrig's disease, is a case in point. A disorder affecting motor neurons of the brain and spinal cord, ALS causes weakness of limbs, difficulty with speech and swallowing, and ultimately inability to breathe. There is only one FDA-approved drug that slows the disease—and even then, it typically delays death by only three to six months. More than 100 clinical trials of other drugs have failed to show any therapeutic effect on patients with ALS, despite promising results in preclinical cell culture and animal models.

A major obstacle for ALS drug development is that we really have no idea what causes this devastating disease. And so we are left not only to guess which path to take toward therapy, but also to test therapies that, even if effective in achieving the goal of affecting that pathway, may fail because the path was a dead end to begin with. Compare this approach to drug development for cancer or infectious disease. In those cases, we can identify the “enemy” as either a tumor cell or an infectious agent. Kill the tumor cell or the bug, prevent it from coming back, and you've won! With ALS and other neurodegenerative diseases, the enemy is unknown, and so the perceived opponent may be a straw man. Even so, as dedicated clinicians and scientists, we will never give up looking for the answers that will provide effective preventive or therapeutic interventions for people with neurodegenerative diseases.

The concept of repairing or regenerating the nervous system is not new. The human nervous system has the capacity to repair itself after injury. Our bodies create new circuits and pathways to deliver electrical signals among neurons, and thus recover function. The repair process involves a variety of cell types that can clear the way for new growth, provide nutritive

trophic molecules to promote neuronal survival, and deliver tropic cues that allow neuronal processes to direct themselves to appropriate targets. Understanding and directing this enormously complex paradigm of creating and maintaining connections can be seen as the holy grail of regenerative neuroscience. Stem cells are some of the earliest tools that neuroscientists have used in this quest.

Embryonic and adult stem cells have a remarkable capacity to home in on regions of injury in the nervous system, to set up shop in those regions, and to differentiate into cell types that may replace injured elements or promote repair. Although researchers have observed the almost magical propensity of stem cells to localize in cases of stroke, brain tumors, and even spinal cord injury, they do not know the mechanism behind the localization. Even so, if stem cells could replace damaged tissues or nourish a diseased nervous system back to health, we may eventually find a way to attack previously untreatable diseases, whether or not we understand how or why the treatment works.

The Science of Stem Cells

Stem cells are immature, undifferentiated cells that can increase in number and give rise to other, more differentiated cell types. Differentiation involves development into a cell that has a specific function in a multicellular organism—for example, a heart, liver, or brain cell. Embryonic stem cells—those that are present during the earliest stages of embryonic development—have the ability to differentiate into all cell types. These cells are at the epicenter of an ethical and political controversy about “human cloning.” Non-embryonic, or adult, stem cells persist throughout life within each organ system. These stem cells, called progenitor cells, may lie dormant within a parent tissue, where they differentiate into functional cells to replace those lost to normal attrition or tissue injury.

While embryonic stem cells are undifferentiated, progenitor cells are partially differentiated along a functional pathway that is specific to their locations. For example, hematopoietic, or blood-forming, stem cells in bone marrow can develop into the various types of adult blood cells. Neuroprogenitor cells isolated from the fetal nervous system and even the adult brain can develop into both neurons and their supporting glial cells. Using a recently developed technology involving induced pluripotent stem cells (iPS cells), scientists can induce dedifferentiation of adult cells into cells that behave as embryonic stem cells, thus avoiding the

ethical, religious, and political minefield of harvesting human embryos for research or therapeutic use.

Given their capacity to regenerate and replace cells that have been damaged by disease, stem cells are considered the new frontier for treating neurodegenerative diseases. Imagine being able to replace the neurons in the cerebral cortex and hippocampus that are responsible for memory. Could we restore memory function to people who suffer from Alzheimer's disease—or even halt the disease altogether? For people with Parkinson's disease, what if we could provide a source of cells that deliver dopamine to the regions of the brain that are starved of this essential neurotransmitter? And for patients with ALS, how about introducing cells that can differentiate into motor neurons and replace those that have degenerated during the course of disease?

Importantly, cell replacement may not be necessary to provide a therapeutic outcome. Stem cells could provide a source of growth factors that could nourish the remaining neuronal populations and even stimulate intrinsic repair systems within the brain. In the case of ALS, scientists have proposed that through the use of stem cells, they could provide new glial cells that support the sick motor neurons and “nurse” them back to health by allowing them to reconnect with their target muscles, thus returning strength and preventing death. Glial cells, most notably astrocytes, provide the essential functions of removing potentially toxic substances from the areas around neurons, supplying nutrients to neurons, and buffering the neuronal environment during fluctuations of surrounding acidity, mineral concentrations, and other variables.

Extraordinary preclinical data relating to animal models of neurological diseases buttresses the idea of using stem cells as therapeutic agents for neurodegenerative diseases. One provocative example is a study in which researchers injected stem cells into rats with virus-induced spinal cord injury. The rats recovered significant neurological function, even though the majority of the surviving cells became glial support cells rather than neurons.¹

Stem-Cell Transplants for Neurodegenerative Diseases

There are few examples of scientifically based trials of cellular therapies for the treatment of neurological diseases. The most widely studied approach has been the injection of fetal dopaminergic cells into the brains of patients with Parkinson's disease. These were not stem cells, but cells derived from fetal brains or adrenal glands, delivered surgically by direct injection into the brain. The results of these studies were mixed. There was post-mortem evidence that

injected cells survived and made connections with the host nervous system. Some patients experienced clinical benefit.² However, scientists have largely abandoned this approach to treatment due to a combination of factors, including variability and shortage of tissue sources, inconsistency of clinical outcomes, and, most important, the availability of other therapeutic interventions for Parkinson's disease.

Researchers also have initiated investigations into stem-cell therapies for patients with spinal cord injuries, stroke, and ALS. These trials have been small (fewer than ten patients) and uncontrolled, meaning there were no placebo groups. There have been no reports of improvements in neurological function, although patients seemed to tolerate the surgical procedures and there were few negative outcomes.³

My group is currently involved in a phase 1 trial of injecting neural progenitor stem cells into the spinal cords of a limited number (12 to 18) of patients with ALS. This is a safety trial only, designed to determine whether the direct injection of stem cells into the spinal cord is safe enough to pursue as a possible treatment for ALS. Preclinical experiments with these cells included spinal cord injections in a rat model of ALS. In this experiment, the injected cells differentiated into neurons and glia, and they had a minor (but measurable) positive effect on the clinical course of disease.^{4,5} Using mini pigs as the experimental animal because of similarities in spinal cord anatomy, Dr. Nicholas Boulis perfected the surgical technique for applying this delicate procedure to humans.

It must be emphasized that this phase 1 trial is neither designed nor powered to investigate the therapeutic potential of the stem-cell injections. We are focused on doing no harm to patients as we pursue this potential therapy and evaluate the effects of surgery, the injected cells, and the immunosuppressive drugs in the course of the disease.

Unfortunately, the magic and promise of stem-cell therapies have fostered an industry of for-profit medical tourism. As we step carefully through the research and trials required to ensure that treatments are safe and effective, many patients have a driving need to get results fast, and they might fall prey to unproven claims. Patients with ALS and other as-yet-untreatable neurological diseases can find promises of cures just by searching the Internet. Illegitimate stem-cell clinics, which are located exclusively outside of the United States and the jurisdiction of the FDA, feed on the desperation of patients and families affected by a variety of disorders. These largely unregulated clinics are typically managed by unscrupulous physicians and

pseudoscientists, the modern equivalents of snake-oil salesmen, who see treating the untreatable as a business opportunity.

Of course, these “stem-cell” treatments that are not part of clinical trials are simply criminal. In most cases, the “therapists” do not disclose the origin and types of cells they deliver, and there is no rigorous follow-up with patients to determine whether the treatments are helpful. In the worst cases, the sellers of these treatments make claims of therapeutic success without providing any evidence either to patients or to the medical community. Consequently, legitimate scientists and clinicians cannot glean any useful information that may assist in the development of rigorously tested stem-cell therapies.

Challenges of Therapy Development

As with any new medical intervention, developers of stem-cell therapies must respect the scientific and ethical guidelines of human experimentation. We must answer the following questions before we can claim success in using stem cells to treat neurodegenerative diseases:

1. What types of stem cells should we use? Will they be different for different diseases?
2. How do we deliver the stem cells? Will delivery require direct injection into the nervous system, or can we exploit the localizing ability of stem cells and introduce them intravenously? Will these new cells make functional connections with the host cells?
3. Is it safe to inject stem cells into people with debilitating diseases? Will we make them worse?
4. Do we need to treat people with immunosuppressive drugs so their immune systems will not reject the implanted cells? What are the toxicities of these drugs, and will our patients be able to tolerate them?
5. What are the potential long-term complications of stem-cell therapies? Will the cells migrate to regions where they may do damage? Will they form tumors?

And most importantly,

6. Do stem cells actually slow progression, improve function, or speed recovery for patients with neurological diseases?

The answers to these questions should be addressed concurrently by scientific and clinical communities focused on determining whether stem-cell therapies will live up to the

hopes, expectations, and hype. To date there are no clear answers for any of these questions, and rigorous debate and experimentation continue.

In the case of ALS, there are groups applying various hypotheses regarding the pathogenesis of motor-neuron degeneration to the potential therapeutic use of neural or glial progenitor cells. Researchers are testing the delivery of cells directly into the spinal cord and brain, and there are also plans for injecting cells into the spinal fluid and allowing them to circulate along the spinal-fluid pathways. While many of these questions are being addressed in animal models of disease, we and others are moving ahead with testing the safety of the surgical procedure and the potential toxicities of using immunosuppressive drugs in debilitated patients. Only time will tell whether the introduction of stem cells into the human nervous system will create long-term improvement in the clinical course of this universally fatal disease.

No matter the disease process or the degree of desperation, we must adhere to the principle of “first do no harm.”⁶ Risks are inherent to the process of clinical investigation, but to achieve real breakthroughs, we must balance the risks with a tenacious respect for both the scientific method and human dignity. We must make sure that any human experimentation is designed and fulfilled to achieve the goals of the study. The goals may be limited—for example, whether patients with ALS will tolerate injections into the spinal cord—but the aggregation of these baby steps will lead us safely down the path toward the responsible testing of a promising new way to treat currently untreatable diseases.

The well-publicized case of Jesse Gelsinger, who died in 1999 during a gene-therapy trial for an inherited liver disease, was an unfortunate and eye-opening event for both scientists and the public.⁷ This 18-year-old boy was reportedly living a relatively normal and healthy life when he agreed to participate in the trial, in which researchers used a virus as a gene-delivery system for replacement of an abnormal, disease-causing gene. The viral infection became uncontrollable, and Gelsinger subsequently died. In retrospect, it is clear that the potential benefits of participation in the trial did not outweigh the risks, which the research team may have misrepresented. The result was not only the death of Jesse Gelsinger, but also the cessation of any further human trials of gene therapy for more than a decade.⁷

Where Are We Now, and Where Are We Going?

Stem-cell therapies for neurodegenerative diseases are still in their infancy. The first trials of stem-cell injections for patients with ALS, spinal cord injuries, and stroke are just beginning. Trials for Parkinson's disease, Alzheimer's disease, and Huntington's disease are on the near horizon. Those of us involved in these trials understand that we must be careful in our approach, as a single catastrophic outcome (as with Jesse Gelsinger) could have a chilling effect on the development of stem-cell trials worldwide.

Investigators studying the diseases that stem-cell therapies might target are obligated to learn from the work of others from different fields, so that they can adopt best practices and avoid mistakes. In addition, we must continue to look past stem cells as merely replacement therapies. The ability of stem cells to home in on areas of damage may allow scientists to use stem cells as targeting vectors to deliver drugs directly to the site of injury. Indeed, researchers are coming close to using this approach in clinical trials for targeting chemotherapy to brain tumors.⁸ Also, it appears we can engineer stem cells to produce therapeutic agents—such as growth factors and cellular transporters—that may be deficient in the brain, spinal cord, or muscles of patients with neurodegenerative diseases. Implanted stem cells can create a local factory for restoring these molecules and potentially slowing or even reversing disease. Finally, the technology for generating stem cells from a patient's own tissues may revolutionize the field of stem-cell treatments by creating personalized sources of stem cells that will eliminate the problem of immune rejection.

It is an exciting time, but we must move forward with meticulous regard for the scientific process and cautious respect for what we do not know and cannot anticipate. No one has all the answers to the myriad questions that will need to be addressed. Scientists and clinicians, with the guidance and assistance of regulatory agencies, must work together to make this hope a reality.

Jonathan D. Glass is the director of the Emory ALS Center and the division of neuromuscular diseases in the department of neurology at Emory University in Atlanta. He is widely known for his research on the pathogenesis and prevention of axonal degeneration in neurological diseases, and for his work in human and experimental neuropathology. His laboratory currently focuses on the role of axonal degeneration in animal models of ALS as well as on proteomic biomarkers of ALS in animals and in humans. Dr. Glass is also the principle investigator for the current phase 1 study of spinal cord injection of spinal cord derived neural progenitor cells for patients with ALS (funded by Neuralstem, Inc.). Dr. Glass is an active clinician who has been cited each year since 2001 as one of “America's Top Doctors” (Castle Connolly Medical) and since 2005 as one of the very few neurologists in “Atlanta’s Top Doctors” (*Atlanta Magazine*). A teacher and mentor to young physicians, he served as the director of Emory’s neurology residency program from 2001 to 2006. Dr. Glass received his undergraduate degree from Middlebury College (Vermont) and his M.D. from the University of Vermont. He trained in neurology and neuropathology at Johns Hopkins, where he was a faculty member until moving to Emory in 1996.

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