How Can Stem Cells Provide a "Cure" for Multiple Sclerosis?

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Notes to Reader

This paper is formatted in the style of the American Psychological Association, as requested by the School of the Future Science Department.

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The West Wing (NBC)
Episode #610
Broadcast January 5, 2005

Scene: The effects of multiple sclerosis are becoming more evident on Josiah Bartlett (Martin Sheen), the President of the United States.

Presidential Aide: **"Is there a cure for MS?"**
Presidential Doctor: **"Give me 10 years and some stem cells."**

There are many illnesses for which there are no cures. A cure is "to bring about recovery from an illness, disorder, or injury."[1] Multiple Sclerosis (MS) is an illness without a cure. It wasn't until 50 years ago that science had any idea about how to diagnose MS. It wasn't until 25 years ago (the 1980s) that doctors began to use MRIs (Magnetic Resonance Imaging) to view MS lesions in the brain and spinal cord. Ten years ago, clinical trials led to drugs used as treatments for the disease. Science has come a long way, but still there is no cure. However, one question circling in the society of multiple sclerosis patients is, "Can stem cells provide a 'cure' for MS?." One of the most promising developments for a cure involves stem cells. This research has lead to the hypothesis that stem cells can repair scarred myelin and create new myelin in order to "cure" Multiple Sclerosis.

What Is MS?

According to the National Multiple Sclerosis Society, MS is a widespread disease in which the body attacks itself, also known as an autoimmune disease. Multiple Sclerosis affects over 2.5 million people worldwide and over 10,000 people a year are newly diagnosed. The majority of MS patients are women and most are diagnosed within the ages of 20 and 50. There are both national and international societies, which provide support groups, hold events such as fundraising walks, and fund research dealing with MS. Some well-known people with MS are Montel Williams, Tamia (R&B singer), Richard Cohen (Meredith Viera's husband) and J.K. Rowling's (the author of Harry Potter) mother.

MS occurs in the central nervous system, including the brain. Schapiro (1998) says the central nervous system is responsible for transmitting messages between the brain and the spinal cord. The peripheral nervous system sends messages between the spinal cord and the muscle myelin. MS causes the transmission of messages to be halted and when this happens, patients end up with a wide range of symptoms.

In MS, the body attacks itself through the destruction of something called myelin. The literal meaning of multiple sclerosis is "many scars." The myelin is destroyed by scarring. (see Figure 1). Myelin is a material made up of protein and fats, which surround and serve as a sheath for the nerve cells. The sheath protects nerve impulses as they are spread throughout the body. The myelin sheath regulates the transmission of the nerve impulses from one end of the cell to the other. Myelin serves as a protective covering much like the rubber that insulates an electrical wire. If the rubber is destroyed, then harm will be done directly to the electrical wire.

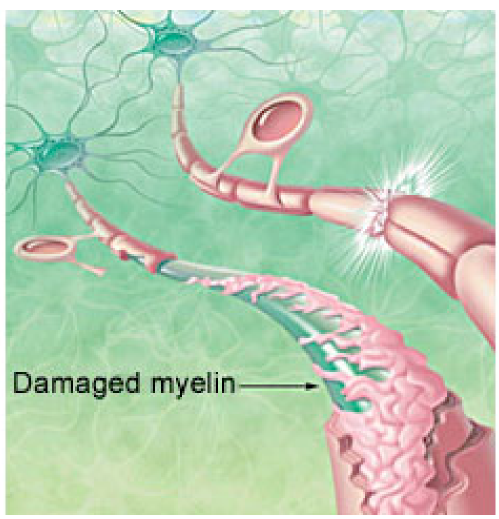

Figure 1. The myelin on the right is the healthy myelin. The myelin on the left is myelin damaged by MS.

While the myelin gets destroyed in MS, the person suffers physically as their nerves do not respond to what brain signals are telling them to do. This causes immobility in patients with MS, one of the most serious symptoms of the disease. According to occupational therapist Stephen B. Kern, MS patients may require a cane, walkers, or even a wheel chair allowing them to adapt to functions their bodies can no longer handle.

Other grave symptoms described by Holland (2002), include numbness in the legs and arms, dizziness, paralysis, speech difficulty and problems swallowing, tremors, bladder problems, sexual difficulties, cold feet and swollen ankles. These symptoms occur because myelin on nerve cells throughout the body is being destroyed. Immobility is caused by the myelin deterioration in the central nervous system. As the disease worsens, it is more difficult to control the body. In a person not affected by MS the central nervous system would send signals throughout the body. The signals tell your hand to pick up a pen or your foot to move. In an MS patient, the signals do not carry through. In many severe cases of MS, patients become bed ridden.

Two of the most problematic symptoms for MS patients are fatigue and depression (Holland, 2002). Fatigue is the most common symptom. It can come on suddenly, like a wave, during a normal day and makes it difficult for a person to continue what they are doing. Limbs can exhibit increased weakness, but will recover if rested. Fatigue may be due to the lack of strength in the limbs. Myelin deterioration causes lack of strength in limbs because signals from the central nervous system don’t always carry through to the limb. The patient becomes tired and restless. If rested, they may be able to build up the strength to continue what they were doing, or even just finish a walk down a street.

Meanwhile, depression is common in MS patients when they first find out that they’ve been diagnosed. This type of depression can progress and become a serious depression. MS patients with depression may feel “ongoing sadness, loss of interest in or enjoyment of important activities and relationships, feelings of hopelessness and despair, sometimes including suicidal thoughts, and changes in sleeping and eating patterns."[2] Depression can be due to a number of things. It can be caused by disease activity in the brain. Drugs given to Multiple Sclerosis patients can often have the side effect of depression. Depression can also be due to the fact that the patient is coping with a newly diagnosed disease. Depression can be treated with antidepressants such as Zoloft or Prozac, and counseling.

Nobody knows what causes multiple sclerosis. It is thought to be "a combination of genetic, immunological, and environmental factors."[3] The lack of a known cause has made it especially difficult to find a cure. In addition, it is difficult to diagnose multiple sclerosis. A diagnosis can include an office exam by a neurologist (a doctor specializing in the central nervous system), examining family history, testing strength and sensation, spinal cord fluid, and an MRI. Cures for MS have involved everything from snake venom to "gold chloride or silver nitrate, to electrical stimulation,"[4] but nothing has worked. Because the cause of MS is still unknown and tools for diagnosis have only come into existence in the last 25 years, the search for a cure has only just begun.

Stem Cells: The Good & The Bad

Everyone who can read a newspaper knows that there is a controversy in this country about stem cells. Stem cells have the potential to treat and even maybe cure numerous diseases. Some of these diseases consist of Parkinson's, diabetes, liver disease, spinal injuries, Alzheimer's, and even cancer.

Stem cells are often referred to as blank cells that can develop into specialized cells. There are two different types of stem cells, embryonic and adult stem cells. Embryonic stem cells come from a fetus or the umbilical cord of a newborn baby. These bring up controversial issues, such as whether it is right to destroy a human embryo or even obtain embryonic stem cells. There are a limited amount of embryos stored in freezers in infertility clinics that parents don't want, but soon scientists will need more.

Adult stem cells come from tissues in different parts of the body, including the brain and bone marrow. There does not seem to be controversy over adult stem cells, but they are specialized cells assigned to certain areas of the body so they are more limited in use.

Researchers conducting experiments with stem cells believe the benefits may actually help find the cures to a wide variety of diseases:

> "The possibility of injecting therapeutic cells systematically to achieve significant clinical benefit in multiple sclerosis-like syndromes opens new opportunities for the clinical use of stem-cell based therapies to treat [up until now] incurable diseases in humans" says Gianvito Martino, a researcher at the San Raffaele Hospital's Stem Cell Research Institute in Milan, Italy.

In 2003, Martino and nearly a dozen additional researchers at San Raffaele, conducted an experiment using stem cells on mice. The mice were injected with an animal model of MS known as Experimental Autoimmune Encephalomyelitis (EAE). EAE replicates MS by displaying similar symptoms such as disease progression, lesions and behavior. Once injected, the mice's myelin soon began to be destructed and scar. They experienced paralysis. They became mice with multiple sclerosis. This research taught us that the mice experienced the same things that an MS patient would experience, but the mice's case of MS would soon be abolished.

In "Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis, (*Nature, 422,* (pp. 688-694).)," the published paper documenting the San Raffaele research, the researchers tell the story of injecting the mice with adult neural stem cells. In this experiment, the stem cells turned into mature brain cells and made myelin regenerate throughout the central nervous system of the mice. The stem cells formed into specialized cells called oligodendrocyte progenitors (also known as "oligos"), which were the cells that needed to be recovered. (Oligos disappear as the affected myelin becomes scarred.) Thanks to the stem cells, the mice recovered from the case of EAE. The scientists' experiment made people question whether or not stem cells could provide a 'cure' for Multiple Sclerosis. There are currently drugs for temporary treatment but nothing has ever completely brought the disease to an end.

Is a "Cure" Possible?

What made the scientists think stem cells might result in a "cure?" In the Italian experiment, cultured stem cells "entered into demyelinating areas of the central nervous system and differentiated into mature brain cells."[5] In other words, the neural stem cells changed from blank cells to specialized cells. In the area where the stem cells were injected, oligodendrocyte progenitors increased. Oligodendrocytes are important because they make the myelin sheath, which serves as a protector of the nerve cells. In addition, axons, which are the extensions of nerve cells, are shielded by myelin. In the experiment, oligodendrocytes increased and axons grew new myelin. This means that the damage from the EAE was repaired.

Clinically, by observation, the mice recovered from the EAE. The scientists also measured the success of the experiment neurophysiologically. The researchers used "iron particles to magnetically label the neural stem cells" (Martino 2003). Iron particles interfere with a magnetic field and this can be easily detected with MRI. In an article in the Spring 2005 "Research Highlights" published by the National MS Society, Martino called this new procedure "radiolabeling." Through MRI, the researchers can trace the injected stem cells and see the progress the cells make.

"Thirty percent of the mice recovered, and seventy percent improved significantly"[6] after thirty days, said Martino. "The novelty of this study is the possibility to induce myelin repair in multiple areas of the brain and spinal cord by transplanting brain stem cells not only directly within the central nervous system, but also into the blood circulation."[7] This is important because MS doesn't take place in just one part of the body. It is called a multifocal disease. This has always made it difficult to find a cure. When stem cells are implanted they cannot just be put in one part of the body in order for recovery of myelin or axons to take place. The stem cells are so important because they make it so that the recovery takes place in more than one part of the body.

This progression of stem cell growth throughout the body is further supported by research done by the Italians. There is evidence to support the hypothesis that stem cell therapy can create new myelin and repair scarred myelin. “Neural stem cells can start a chain reaction that leads to myelin production,” explains Guiseppe Scotti, M.D., a professor and chairman of Neuroradiology at University at San Raffaele. “Stem cells have the potential to replace the function of damaged nerve cells,” says Scotti, “this means that the stem cells will create new myelin and repair the myelin of the scarred nerve cells.” Furthermore, researcher Martino said: “The novelty of this study is…myelin repair (occurred) in multiple areas of the brain and the spinal cord by transplanting brain stem cells not only directly within the central nervous system but also into the blood circulation.” This shows that the stem cells went to all the effected areas of the body and repaired the myelin in many diseased areas.

The Pieces of a Puzzle

Stem cells have the ability to reach multiple areas in the body. They can even go through barriers. “Stem cells reached damaged areas thanks to specific ‘adhesion molecules’ on their surface which allow them to sense danger signals, pass through the protective blood-brain barrier, and repair damaged areas,” according to the researchers Stem cells communicate with, and target, the cells damaged by MS. The stem cells and the cell membrane of the targeted cell communicate with each other. The stem cells match themselves up with specific targeted cells. It’s like a puzzle, where two pieces link together in order to complete the picture. “The route of cell transplantation was also very important. We realized that the donated cells have a key to pass through the blood brain barrier and enter into the central nervous system, said the researchers. In other words, getting across the blood-brain barrier has been one of the most difficult struggles in MS research. This was a major break through which allowed the mice to receive the stem cells in their brains. “The overall message of the work,” said researcher Angelo Luigi Vescovi, in an interview in June 2004, “is that adult neural stem cells repair multifocal brain damage caused by inflammation once systemically injected (rather than transplanted directly at the site of injury).”

Just because there is good news about myelin repair and regrowth does this mean that MS can be cured? “The research raises the hope of reversing the damage caused by the disease, but does not address the cause,” said Stephen Reingold, MS Society’s vice president for research. Reingold’s point is that the researchers do not explain how to stop the disease, just how to deal with its symptoms.

A cure usually abolishes any form or part of a disease. The scientists are ecstatic about the fact that they were successful with their experiment, but they want to be able to do it again. “We have been able to discover and detail the mechanism by which these cells selectively reach damaged areas of the brain and once there, repair the tissue,” says Martino. This means that the researchers were able to trace the procedure used for the regrowth of myelin and may be able to reproduce their results.

There were no side effects to stem cell therapy in mice the way there sometimes are with a drug therapy. The researchers explain that they may be able to “cure” the disease without any drugs. With the use of drugs side effects are very common. The researchers explain that there are no side effects when using stem cells. This is good because the side effects can often be as bad as the disease itself.

There is currently an experiment being done by the researchers at San Raffaele on marmosets (monkeys that are more like humans than mice), which include embryonic stem cell injections, and takes one step closer to research in humans. The results of this study have not yet been published.

Although there has been much positive feedback, and many articles written, on the research done at San Raffaele, and it does seem that myelin can be recovered using stem cells, there are still many obstacles along the road to a cure. "This (work) opens new hope for patients, but the way is very long and very hard," said Martino. There are many impediments to the search for a cure. Vescovi predicts that in human testing neural stem cells will not work, and embryonic stem cells will have to be used. The embryonic stem cells will be taken from the tissue of spontaneous miscarriages. Embryonic stem cells have the ability to turn into over 200 types of cells and are not specialized cells, meaning they have no specialized destination. Embryonic cells are the most versatile and because of this, probably hold the greatest hope for curing disease.

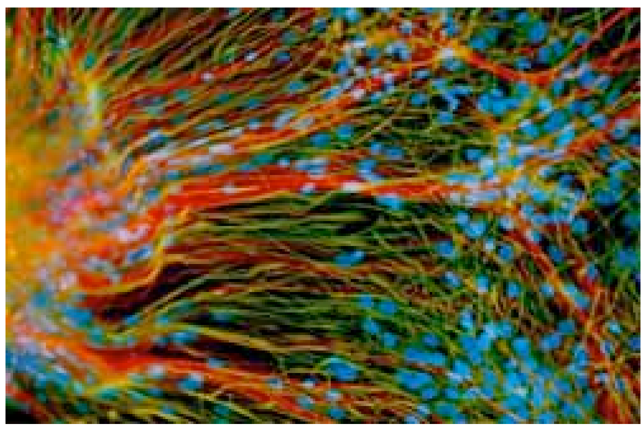

Figure 2. Made from human embryonic stem cells, neural cells grow in a lab dish and generate mature neurons (red) and glial cells (green). One type of glial cell is an oligodendrocyte. "Oligos" protect the nerve cells of the central nervous system.

Adult neural stem cells (see Figure 2 above). which were used in the mice experiment, are specialized cells. Specialized stem cells (adult neural) are assigned to certain cells in the body. They cannot go just anywhere. Once in the body, the pathway of an adult neural stem cell is set. In the Italian experiment, the stem cells went to the places where they were needed, and this was successful. But specialized cells are limited to where they can go. While the adult neural stem cells worked in this case, it does not mean that adult neural stem cells will cure other diseases.

Rejection problems also raise the issue of individualized therapy. This means that it's possible that each person may need to be screened or something may need to be done to prevent rejection. Mice do not have the same rejection problems that humans have. Human physiology is far more complex than the physiology of mice. Successful transplants often depend on acceptance of new cells. Someone's body might reject cells that are not their own, or cells that don't match with their blood type.

Currently there is no way to know whether or not the body will create just enough cells to repair the myelin, or whether it will overproduce and create an unwanted additional health problem, as in the cases of a tumor or many forms of cancer.

It's easy to say that, because of the major breakthrough in the San Raffaele experiment, it is indeed possible to cure MS with stem cell therapy. Although, with the obstacles outlined, it's also easy to say we are on the way, but we're not quite there yet. The San Raffaele experiment can be counted as one of the many stepping stones towards a cure for MS. Considering the success of new stem cell research, and the obstacles the scientists will encounter, the future is summed up best by the MS Society's vice president of research, Stephen Reingold: "This doesn't tell us (stem cell therapy) is going to work in humans, but at least it's a step forward."

Glossary

Axon – Long threadlike extension of a nerve cell that conducts electrochemical impulses away from the cell body towards other nerve cells, or towards an effector organ such as a muscle.

Glia – Connective tissue of the central nervous system, composed of cells that "service" the neurons with supportive and nutritive activities. Glial cells are far more numerous than neurons. The three types of glial cells are astrocytes, oligodendrocytes, and microglia.

Intracerebroventricularly – Administered into the brain.

Intravenously – Administered into a vein.

Line – A stem cell line is composed of a population of cells that can replicate themselves for long periods of time in vitro, meaning out of the body.

Myelin – Fatty substance that forms a sheath around the nerve fibers of vertebrates.

Oligodendrocyte – A type of glial cell which surrounds the neurons in the brain and spinal cord. They produce the insulating myelin sheath surrounding the nerve axon.

<u>Pathology</u> – Medical specialty concerned with the study of disease process and how these provoke structural and functional changes in the body.

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