**History of Cure Research**

Research to find a cure for spinal cord injury (SCI) may seem like a recent event. Yet scientist Theodor Schwann reported as early as 1830 that nerve cells in rabbits showed signs of regrowth or regeneration. Santiago Ramon Cajal later described, in 1890, how damaged nerves in mammals try to regenerate. The problem he found was that they lacked the ability to make proper connections. Cajal also knew that nerves in the peripheral nervous system (PNS), which are outside the brain or spinal cord, did regrow. He believed that if PNS cells were implanted into the damaged area of the spinal cord, which is part of the central nervous system (CNS) that they could make the injured nerves re-grow. Later, in the early 1900’s, scientist J.F. Tello showed nerves can regenerate but need nourishment.

Human SCI research did not make any major progress until after World War II. That is when the discovery of antibiotics and improved surgical and critical care techniques helped more individuals survive their initial SCI. Researchers then turned their focus to explore the spinal cord, its cells and how the nerves work.

During the 1960’s, Rita Levi-Montalcini and Viktor Hamburger discovered a substance that nourished nerve cells to help them grow. This was the first nerve growth factor (NGF). Many new growth factors were discovered during the next 20 years, such as brain derived neurotrophic factor (BDNF) by Yves Barde. Scientists also learned that different cells respond to different growth factors. Findings by Raisman in 1969 showed that nerves can make new connections and that the central nervous system has the capacity to reorganize. By the 1980’s, scientists had success using peripheral nerve grafts in rats to show that axons can regrow. However, Martin Schwab showed that blockers or inhibitors found in the CNS stopped this growth. Researchers’ next focus was to find ways to prevent these blockers from stopping nerve fibers’ growth.

Increased funding during the past 15 years has provided more research in the area of spinal cord injury. The ultimate goal is for an individual to regain full function. However, “cure research” technically involves all phases of care, beginning with the effective handling of the patients at the time of injury, during acute care and through rehabilitation.

**Present Areas of Cure Research**

Today, cure research focuses on four main areas: neuroprotection, regeneration, transplantation and rehabilitation.

**Neuro-protection**

*How can the damaged nerve cells at the site of the injury be protected and kept alive?*

Research results show that after the initial spinal cord injury there is a risk for further (secondary) damage. Cells at the injury site continue to die for days, even weeks, after the initial injury. The damage can affect nerve cells in the spinal cord and the nerves’ protective covering (myelin). More harm can occur when the healthy cells are actually “poisoned” by these damaged cells. Sometime the body rejects the damaged cells before they even have a chance to heal. Researchers have been studying ways to medically stabilize the patient, relieve pressure on the spinal cord and prevent scar and cyst formation. They are also looking at using multiple treatments to prevent secondary damage and late cell death.
Research in the area of neuroprotection includes the following:

- **Methylprednisolone**
  Methylprednisolone (MP) is an anti-inflammatory steroid. It was the first drug shown to reduce spinal cord damage in humans. It reduces damage to the spinal cord by preventing swelling and inflammation at the injury site. Methylprednisolone is now the American “standard of care.” It is given to most individuals within 8 hours after their spinal cord injury; however, its true benefits are still being debated. (1)

- **Interleukin-10**
  Interleukin-10 (IL-10) is a potent anti-inflammatory substance. Researchers at the Miami Project, led by John Bethea, PhD, are using IL-10 in their research with rats. Rats treated with IL-10 recovered significant use of their hind limbs during the weeks following injury. Further study is needed before this drug can be tested on humans. Researchers must first determine how long after injury IL-10 can be given and still provide therapeutic effects. Findings with animals show that more is not better. Two doses of this highly effective drug can reverse its protective benefits. This could result in greater damage. This emphasizes the importance for testing drugs on animals before doing clinical trials with human patients. More testing is needed to determine IL-10’s use in combination with other drugs, such as methylprednisolone. The use of two different anti-inflammatory drugs may be harmful or not needed. (2)

- **GM-1 Ganglioside (Sygen)**
  The drug Sygen (GM-1 ganglioside) showed it enhanced nerve growth and regeneration in injured cats. It also counteracted some of the secondary damage. The news of these results had individuals requesting immediate access to this potential “cure” for spinal cord injury rather than waiting for further research studies. A human clinical trial on the use of Sygen was undertaken. But, the results were disappointing. The company has now taken the drug off the American market. The research experience with this drug demonstrates the need to prove the effectiveness of new therapies before they are released for use throughout the country.

- **Glutamate (AMPA) Receptor Blockers**
  Glutamate is a chemical substance that works as a neurotransmitter. The cells of the nervous system release it when the spinal cord is injured. Large amounts of glutamate can kill nerve cells by causing them to fire excessively. Animal studies have shown that Glutamate receptor blockers decrease this harmful activity and further damage to the spinal cord. Human clinical trials with these receptor blockers are being performed in stroke patients. Clinical trials with spinal cord injury patients could begin within a few years.

- **4-Aminopyridine**
  The drug Fampridine-SR (also known as 4-aminopyridine or 4-AP) does not have neuroprotective effects. However, research does show it improves function in surviving spinal cord nerve cells long after the injury. One human clinical trial of 4-AP was completed and it did demonstrate functional improvements. Patients are being enrolled for future studies. (3, 4)

- **Other Neuroprotective Treatments**
  Research continues on other treatments to prevent or lessen the secondary damage caused by an SCI. These include preventing scar formation, developing improved surgical techniques to stabilize and decompress the spinal cord, and designing a more effective system to get drugs to the spinal cord.

  Some possible treatments under investigation include: Cyclohexamide, hypothermia (reducing body temperature to decrease metabolism and excitotoxicity) and opioid antagonists (i.e. Naloxone).

**Regeneration**

- **Is it possible to get nerves to grow and regenerate?**
- **Are there factors preventing spinal nerve regrowth?**
- **What can be done to promote correct “connections” on both sides of the injury?**
- **What can be done to make it easier for nerves to grow?**

Researchers are investigating many different areas for answers to these questions on spinal cord regeneration.
• **Increase Growth Factor Production**

  Damaged nerves must first grow for regeneration to occur. The neurotrophic proteins function as “growth factors.” These help prevent cell death. They also work like a “nerve fertilizer” to help neurons survive, nerves regenerate, and allow messages to flow up and down the spinal cord again.

  Scientists are studying several growth factors and how they can be used in treating spinal cord injury. Each growth factor has very specific target cells that it works on. They include NT-3 (Neurotrophin 3); BDNF (brain derived neurotrophic factor); aFGF (acidic Fibroblast Growth Factor) and NGF (nerve growth factor).

  Another area of research with growth factors is in spinal cord injuries that are not complete. Some fibers connecting the brain with spinal segments below the level of the injury may survive. The goal of this research is to increase the quality and strength of the nerve impulses in the surviving connections.

  Dr. Ira Black at the University of Medicine & Dentistry of New Jersey is using growth factors to promote regrowth of spinal cord nerve fibers. BDNF and NT-3 growth factors are being used along with neurons “grown” in the lab from bone marrow stem cells. Researchers are analyzing their use in spinal cord injured rats to define how they may improve nerve growth.

  Results from Lorne Mendell’s lab at the State University of New York, Stony Brook report that neurotrophin molecules (such as NT-3) can improve function at synapses in the spinal cord of newborn rats. The goal is to devise ways to make this finding useful in restoring function to the damaged spinal cord in adult rats and, ultimately in humans.

• **Implant glial or Schwann cell grafts**

  Schwann cells from peripheral nerves, and glial cells from the central nervous system (CNS) act as “helper cells” to protect, insulate and nourish neurons. Schwann cells and glial cells also make growth factor proteins, which support nerve function. Researchers have shown that implanting or placing these cells into the injury site can stimulate additional spinal cord regeneration. These cells also help bridge the gap in the spinal cord at the site of injury. These cells can be genetically engineered to produce additional growth factors and further improve regeneration. All of this research is now being done with animals and results show some improvements in leg movement. However, the results are not reliable enough yet to try with humans.

• **Block Inhibitory Process**

  One problem that occurs in regeneration is that certain factors keep nerve cells in the central nervous system from growing. Spinal cord tissue contains certain chemicals that stop nerve regeneration. Martin Schwab, a University of Zurich researcher, has identified one of these inhibitory chemicals as a protein called Noga-A. He discovered an inhibitor-neutralizing antibody (IN-1) that can block these inhibitors and promote growth. This process has worked in cell cultures and in animals. His researchers’ next step is to focus on preparing these antibodies for human use. (5)

• **Promote correct connections on both sides of injury**

  First, researchers must keep nerve cells alive and get them to grow. Then it is necessary for the axons to reconnect to their proper target sites. In other words, the nerves must rejoin with their companion nerves for the connection to be complete and functional. Researchers are working with different substances to guide nerve growth so nerves grow past the injury site and reconnect with the proper nerve.

  **Netrins:** Netrins are proteins produced in the brainstem, that “attract” nerve cells. They encourage nerve cells to migrate to and grow branches toward a “target.” Dr. Mark Tessier-Lavigne of Stanford University has identified netrins in several animal models and is evaluating their use with spinal cord injury. (6)

  **Neural Glues:** Neural glues are substances that can fuse together the ends of damaged nerve axons. Scientists at the Center for Paralysis Research, Purdue University, used polyethylene glycol (PEG) in guinea pigs. This neural glue helps to partially
restore nerve function immediately following spinal cord compression injury. It is thought that this helps restore nerve cell membranes disrupted by the spinal cord injury. (7)

**Fibroblasts:** Fibroblast cells, commonly found in the skin, act as a “bridge” across a spinal cord lesion. Scientists genetically engineer these fibroblast cells to produce neurotrophin-3. The cells can then stimulate regrowth. Rats showed improved leg function following implantation of these fibroblasts in research done by Dr. Marion Murray at MCP Hahneman University. (8)

- **Electrical stimulation**
  Researchers at Purdue University’s Center for Paralysis Research and Indiana University School of Medicine are using low-level electrical stimulation on paralyzed dogs. They implant a small battery pack, known as an extraspinal oscillating field stimulator (OFS), near the dog’s spine. It sends a weak electrical signal (thousandths of a volt) to the site of injury. This helps regenerate cells and guide growth in the damaged nerves. In about a third of the cases, the dogs improved significantly. The first human clinical trial of this new treatment is now underway. Patients being entered in the study must be within 18 days from the time of their injury. (9, 10, 11)

**Transplantation**

What are the effects of transplanting various cells into the injury site to promote regeneration?

- **Peripheral Nerve Transplants**
  We now know that damaged or injured peripheral nerves sometimes regenerate but cells and nerves in the spinal cord do not. Scientists are transplanting peripheral nerve cells into the site of injury. Their goal is that the transplanted nerve cells will mature and become a part of the central nervous system.

  There are several different approaches being studied related to transplantation. Drs. Cheng and Olson of the Karolinska Institute in Stockholm demonstrated recovery of leg function using transplant techniques in rats. (12, 13)

  Transplantation procedures to repair the spinal cord involve multiple steps such as:
  - creating multiple peripheral nerve bridges
  - re-routing white to gray matter
  - filling grafted area with fibrin-based tissue glue
  - adding acidic fibroblast growth factor (aFGF)
  - stabilizing the spine to prevent reinjury.

- **Fetal Central Nervous System Tissue**
  Tissue from a growing fetus contains stem cells, progenitor cells, and many substances that support growth. These can all help with regeneration. The advantage in using stem cells is they can develop into several cell types, depending on the signals they receive. Research is examining if these cells can develop and then re-establish lost circuits when transplanted into the spinal cord.

  Researchers at the Albany Medical Center, New York and Washington University in St. Louis are implanting fetal spinal cord cells from pigs into the injury site of mice and rats. Fetal neural cells from pigs are used because they grow rapidly and are “functionally identical to human fetal neural cells.” Another step is masking (hiding) the pig proteins to prevent immediate rejection. Masking is done with antibodies. It appears this eliminates the need for long-term immune-suppressing drugs. The goal of this procedure is for these cells to produce myelin. Myelin is the substance that insulates nerve cells, giving the spinal cord the ability to heal and to send electrical signals. Some paralyzed animals regained partial use of their hind limbs after treatment. In April 2001, clinical trials with humans began. It will be months before researchers know whether these transplanted cells have resulted in any spinal cord regeneration. (14, 15)

- **Stem Cells**
  Certain kinds of stem cells can produce any kind of cell in the body. This means they can make replacement cells for other body parts, including spinal cord cells. Miami Project researchers showed that they could stimulate unspecialized cells in the CNS (“stem cells”) to divide and develop into nerve and glial cells. This exciting finding has opened up new possibilities for cell line development without an ongoing need for fetal tissue donors. (16)

  Stem cells from both rodent and human tissues are being studied. One major question is what
determines whether stem cells develop into cells that help regeneration, e.g. nerve cells, or cells that make myelin, and not into cells that prevent regeneration, e.g. scar tissue. Once nerve cells can be reliably obtained from stem cells, then they must show they can grow appropriately to the type of cell lines described above.

- **Activated Macrophages**

  A highly publicized human clinical trial is taking place in Israel with individuals who have a complete spinal cord injury. The treatment involves harvesting blood cells (macrophages) from the patient’s own blood. These macrophages are first treated in a lab. They are then implanted in the individual’s spinal cord to “repair” the damaged cord. Recent results report that one patient had limited restoration of leg movement. Phase I of these human trials are also ongoing in Brussels. Patients must be enrolled within weeks of injury. (17, 18, 19, 20)

**Rehabilitation**

Rehabilitation is expected to be a crucial part of any cure treatment strategy. It is unlikely that any cure treatment will result in an individual having immediate or complete recovery of all function. The physical therapy routines and other health care practices taught during their initial rehabilitation can help them remain healthy and maintain their flexibility and muscle strength. Some research even suggests that these factors not only maximize the use of the undamaged nerves but also will be vital to recovering movement.

Traditional rehabilitation focused on making up for deficits, or “using what you’re left with.” The renewed hope for a cure has refocused interest on restoring lost function. Researchers must continue to explore rehabilitation methods that can help in recovery after injury.

Recent studies showed CNS reorganization can and does occur. Researchers believe it could be important to simulate movements, such as walking. This movement may help maintain and reinforce spinal cord and brain circuitry. Researchers from the Miami Project use Body-Weight Supported Gait training to “re-educate” the spinal cord on to walk. Miami Project researcher Blair Calancie, PhD, has been conducting research related to the Central pattern generator (CPG) in the spinal cord for stepping. (21)

- **Neuroprostheses**

  Recent interventions use new electronic technologies to “bypass” the spinal cord injury and allow direct muscle stimulation. This can help control various bodily functions, such as standing/walking, grasping and urinating. There are a number of electrical and mechanical devices that work with the nervous system to help replace a person’s lost motor and sensory functions.

  Miami Project researchers studied Functional Electrical Stimulation (FES) to determine benefits of FES-walking. They thought it could provide effective opportunities for exercise and conditioning in subjects with paraplegia. Results showed that the system was “functional” over short distances and can be used to provide greater mobility in some situations. FES also increases the opportunity for conditioning exercise, which is limited after SCI. FES walking showed much more promise as an exercise tool. The most obvious physical effect was enlarged thigh and calf muscles, but the internal benefits were more revealing. After the training, subjects could exercise for significantly longer periods during an arm-crank test before showing signs of fatigue. (22)

**Future studies:**

**A Multidisciplinary Approach**

Everyone hopes for a single “magic pill” remedy to cure spinal cord injury. However, it is more likely individuals will need a combination of therapies to return maximum function. Spinal cord researchers are now taking a more multidisciplinary approach. They are testing various combinations of therapies and treatments. What is the best combination of stem cell-derived neurons, growth factors and trophic factors to restore function after spinal injury? How can acute surgical management and rehabilitation be utilized? By closely looking at and incorporating each component, it is hoped that an ideal “cure” strategy can be found. Stay tuned!
**Additional Resources**

The following web links offer more detailed information on the research discussed in this paper. For additional information on Research and Research for the Cure, visit the SpinalCord Injury Information Network web pages at www.spinalcord.uab.edu/show.asp?durki=21783 or www.spinalcord.uab.edu/show.asp?durki=21781

1) **Prolonged treatment with methylprednisolone improves recovery in spinal cord injured patients**
   www.ninds.nih.gov/news_and_events/pressrelease_methylprednisolone_052797.htm

2) **Interleukin-10 protects the spinal cord by reducing inflammation**
   www.miamiproject.miami.edu/miami-project/Library/nl9912/nl991223.htm

3) **Fampridine (4-AP) study at UW**
   http://depts.washington.edu/rehab/sci/forum-research4AP0400.shtml

4) **Fampridine-SR (Product page)**
   www.acorda.com/pfam.htm

5) **Martin Schwab’s research group**
   www.neurozh.ch/e/groups/schwab00.htm

6) **Mechanisms of axon guidance in vertebrates**
   www.hhmi.org/research/investigators/tessierlavigne.html

7) **Neuron fusion and repair using polyethylene glycol (PEG)**
   www.vet.purdue.edu/cpr/research.html#PEG%20repair

8) **Axonal regeneration, synaptic plasticity, recovery of function**
   http://neurobio.mcphu.edu/MurrayWeb/murray.html

9) **Applied voltages and electrical stimulation**
   www.vet.purdue.edu/cpr/research.html#Electrical%20Stimulation

10) **Human trial for spinal injury treatment launched by IU, Purdue**
    www.medicine.indiana.edu/news_releases/archive_00/spinalcord_00.html

11) **Spinal cord study may offer hope for paralysis patients**

12) **Swedish researchers combine treatments to repair severed rat spinal cords**

13) **In a triumph of microsurgery**
    http://whyfiles.org/023spinal_cord/karolinska.html

14) **Porcine spinal cord cells for spinal cord injury**
    www.diacrin.com/newpage1.htm

15) **Albany med physicians first to use pig cells in spinal cord surgery**

16) **The stem cell: another promising tool**
    www.miamiproject.miami.edu/miami-project/Library/nl0111/nl011123.htm

17) **Proneuron biotechnologies**
    www.proneuron.com/index2.html

18) **Macrophage therapy**
    www.proneuron.com/MacrophageTherapy.html

19) **CNS regeneration**
    www.proneuron.com/Regeneration.html

20) **Melissa’s story**
    www.cbsnews.com/story/0,1597,296665-412,00.shtml

21) **Do the locomotion... training the spinal cord to improve gait**
    www.miamiproject.miami.edu/miami-project/Library/nl0004/nl000423.htm

22) **The Parastep® I System**
    www.sigmedics.com/AboutUs/Parastep%20Technology/parastep%20Technology.htm

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