

The Uphill Battle Against Spinal Cord Injury

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In 1989, rookie Mike Utlely started for the Detroit Lions. In 1991 Utlely fractured his 6th and 7th cervical vertebra and was told he would never walk again.

Thousands of Americans like Mike Utlely experience spinal cord injury (SCI) each year. In the United States alone, there are an estimated 500,000 patients with SCI. Roughly 50% of these cases result from motor vehicle accidents, while the rest are caused mostly by sports-related accidents, falls, and violence (1).

Recovery from SCI has improved significantly in recent decades. During World War II, the life expectancy of SCI patients was only a few months. The “wait and see” attitude of the past has been replaced by billions of dollars of annual research and dozens of clinical trials. Now, patients can expect to live for an average of almost thirty years post-injury.

Spinal cord injuries are classified by their location and effects. Contusion injuries are the most common, affecting 40% of those suffering SCI, and are therefore the focus of a majority of animal models in research (1). Contusions are injuries to the spinal cord tissue by trauma, resulting in centralized bruising, necrosis and hematomyelia, or excessive bleeding into the cord. Such injuries are progressive and can develop into syringomyelia, characterized by the presence of growing fluid-filled cysts in the spinal cord, which can destroy the center of the cord and lead to pain, loss of bladder and bowel control, spasticity, and muscle atrophy.

After enduring a contusion injury, the spinal cord experiences three phases of response: acute, secondary, and then chronic injury. In the initial few days after the injury, the cord remains in the acute phase. Tissue and vasculature are damaged upon injury, and necrosis, or cell death, occurs predominantly in the outer grey matter (rather than the inner portion of the cord, which is comprised of white matter). Immediately, affected nerve cells experience a rush of action potentials accompanied by significant increases in intracellular sodium and calcium cations. Spinal shock is induced, as well as hemorrhaging, cord compression, and localized loss of circulation – all of which, unfortunately, exacerbate the initial injury (2). Despite the severity of these complications, their onsets occur within minutes post-injury, when medical intervention could not feasibly be administered.

Therefore, scientists have focused interventional therapy on the prevention of the deleterious effects sustained through the later secondary and chronic phases. During the course of these phases, gradual cell death and lysis occur, and glutamate is produced in toxic quantities. Edema is also seen, as well as invasion of the injured region by inflammatory cells. Apoptosis, or cell death, continues throughout the evolution of the injury, and inhibitory molecules abound, preventing immediate regeneration. Scarring, demyelination, cyst formation, alteration of neural circuitry, and chronic pain can all occur (3).

Complete recovery from spinal cord injury is still a distant vision, but efforts are being made to promote recovery and scientists have been slowly developing therapies. Glutamate toxicity can be combated through the use of glutamate receptor antagonists, and edema reduction has been attributed to the use of steroids, notably methylprednisolone (MP). When administered within eight hours of injury, studies have shown that treatment with MP helps to reduce edema and inhibit inflammation. Lowering the temperature of the cord to about 5°C, e.g. with cooled saline, has also shown promise in inflammation reduction (4). However, the benefit of MP is debated; recent research attacks the supposed benefit of MP, asserting that currently recommended doses of MP adversely affects the body, contributing to secondary clinical complications such as acute myopathy, or muscle impairment (5).

Few scientists, however, dispute the inevitability of transplanting some sort of neural cell into the site of spinal cord injury to enhance recovery. Three types of cells that show promise are human neural stem cells (hNSCs), schwann cells, and olfactory ensheathing cells. hNSCs were implanted into the injured region of mice spinal cords, and positive results were seen. Locomotion recovery and enhanced remyelination were noticed. Further, the stem cells were observed to differentiate into neurons which aligned with existing, intact neurons in the mice, showing promise that implanted hNSCs can form neurons that may replace damaged connections (6).

Neurons are comprised of different parts, two of which are the axons and dendrites; collectively, these extensions are known as neurites. The growth of these neurites corresponds with the growth and maturity of the neurons; in other words, functional neurons contain neuritic processes. However, proteins found in the spinal cord after injury inhibit these processes; to permit neurite growth, scientists have injected antibodies, specifically IN-1, to neutralize neurite growth inhibitory proteins. In one experiment, controlled incisions were made in the mid-thoracic regions of adult rats to simulate SCI. During the spinal cord surgery, hybridoma cells known to secrete abundant quantities of IN-1 antibody were injected into the microsurgical lesions. Results showed significant axonal regrowth (7).

Contusion injuries not only cause direct nerve cell damage, but also impair the myelinating cells that are necessary for synaptic transmission. Since the ensheathing myelin is necessary for electrical conduction of stimuli, scientists have attempted to implant cells, such as olfactory ensheathing cells, into the spinal cord at the site of injury. Olfactory ensheathing cells have been chosen due to their ability to aid in axon growth as well as their proven ability to thrive in the central nervous system, specifically in the spinal cord. Scientists have harvested these cells from the olfactory mucosa of individual human noses and re-implanted them into the damaged area of the spinal cord. Experiments have been performed in which olfactory ensheathing cells were inserted into lesions introduced into the thoracic regions of adult rat spinal cords. When compared to identically-lesioned rats treated with control cells, treated rats recovered much more fully. Behavioral monitoring indicated that treated rats displayed better reflexes and more coordinated hind limb movement, both of which depend on the spinal cord being intact and functional. This therapy is currently being applied in a Phase I clinical trial on paraplegic humans (8). Another experiment involving transplantation of these cells into the site of spinal cord injury offered similarly encouraging results; rats in the experimental group, which were treated with the ensheathing cells, on average regained breathing and motor control, while untreated rats remained paralyzed and dependent on ventilator support (9).

Another cell widely used for implantation studies is the Schwann cell. Like olfactory ensheathing cells, Schwann cells also contribute to remyelination of demyelinated neurons. Neurons that have been remyelinated by Schwann cells have been seen to conduct impulses (10), so these cells have been extensively studied and injected along with various other compounds in attempts to maximize post-SCI recovery (11). One such study involves treatment of injury with both Schwann cells and cyclic adenosine monophosphate, or cAMP; the effectiveness of cAMP in promoting neuronal regeneration has been verified (12). After SCI, levels of cAMP decline throughout the spinal cord region. Since cAMP is typically degraded by the enzyme phosphodiesterase, an inhibitor of this enzyme was administered post-injury. As expected, cAMP levels remained elevated. Increased remyelination was noticed, and immunocytochemical results verified the growth of neurons through the site of lesion (13).

Currently, research focuses on a method of controlling the delivery of these cells; previous studies involving the transplantation of olfactory ensheathing cells in porous capsules showed behavioral and histological improvement, but not to the degree as was seen when cells were directly implanted. Reasons for SCI repair with these cells is not fully understood; regardless, successful preliminary results have allowed early clinical testing to further explore the possible restorative ability of the implantation of olfactory ensheathing cells into injured spinal cords of paraplegic humans (8).

Further studies continue in order to optimize implantation times and methods and determine the safest and most effective implantation region. Work is also being done to explore the possibility of possibly co-transplanting ensheathing cells with stem cells or even genetically engineered cells into the spinal cord.

Implantation of cells holds promise in the future of recovery from SCI, but so far only limited positive results have been seen. Some scientists have tested the idea of implanting cells into the spinal cord with the cells seeded on a polymer scaffold. These scaffolds are being designed to mimic the structure of the cord; for example, the inner dimension resembles the inner portion of the cord (the gray matter). Further, the outer layer simulates the surrounding white matter of the cord; the white matter analog in synthetic polymers contains axially-directed pores to help guide regenerating axons through the site of injury. Scaffolds have been fabricated with biocompatible, degradable materials, such as poly-L-glycolic acid, commonly known as PLGA. (14) Behavioral and immunocytochemical data from one such experiment involving the delivery of murine neural stem cells on such PLGA scaffolds showed significant improvement in treated rats, relative to the negligible improvements noted in untreated, control rats. The scaffold is believed to alleviate scarring and cyst formation, preventing further secondary damage to the cord. Some evidence was also seen regarding the regeneration of cord fibers through the injury epicenter region (15).

Another topic of interest involves the use of electrical stimulation to regain lost neural function. Voltage gradients naturally occur in humans, aiding in the development of the nervous system. Experimentation into applying artificial voltage gradients across cells has proven fruitful. Experimentation into applying artificial voltage gradients across cells has proven fruitful; neurite processes immediately grow along the direction of the applied electric field, and growth rates increase with increasing imposed field strength (16). Injured dogs were studied; a control group went untreated, while an experimental group received implanted electrical stimulators in their bodies. In the event of spinal cord injury, treatment would be delayed for a few hours after the injury, when individuals could finally arrive at the hospital. In order to prove that similar recovery could be induced when cells were implanted at a later time period, scientists allowed six hours to transpire between the initial injury and implantation of electrical stimulators. After regular administration of an electric field in the experimental group for three months, significant improvement in nerve structure and function was noted (17). Another study of the effect of electric fields on

SCI occurred in humans. Here, again, reaction to the treatment was favorable, and recovery and functional improvement was seen in patients who underwent the implantation of an electric field stimulator (16). No permanent negative side effects were noted from the treatment.

Whether attached to the skin or inserted sub-cutaneously, the attached electrodes of these Functional Electrical Stimulation systems stimulate neurons, sometimes leading to partial recovery, which may involve regaining motor function or improved bladder control (1). This technology allowed Christopher Reeves to use an FES bike, with computer-controlled electrodes stimulating his leg motion. FES systems also stimulated his breathing, as well as slight hand and arm movements.

Despite all of the effort and resources being applied to develop a method of spinal cord injury repair, neither implantation of cells, polymers, or application electric fields or drugs such as antibody inhibitors have led to success in the battle against spinal cord injury. However, the combined application of many of these therapies, along with new discoveries, provides hope for the future.

When the doctors told Mike Utley he would never walk again, he grew angry; he knew he had faced adversity in his life as a professional football player, and he refused to believe that this particular adversity could defeat him. One month post-injury, he created the Mike Utley Foundation to assist those recovering from SCI, primarily raising funds to promote SCI research. After eight years of rigorous, continuous physical therapy, Utley took his first steps since the injury.



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