Bases for Hope in Spinal Cord Injury Research

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In 1995, when Christopher Reeve was injured, he asked me whether there would be therapies that could restore function in spinal cord injury (SCI). At that time, I said that I believed so. This belief was based on the following research findings. A drug called methylprednisolone (MP) had been shown to improve neurological recovery when given <8 hours after spinal cord injury, the first “neuroprotective” therapy. Another drug called GM1 or monosialic ganglioside apparently improved locomotor recovery in patients when started 48 hours after injury and continued to 6-8 weeks. Schwab, et al. (1991) had shown that the antibody IN-1 binds to a myelin-associated growth-inhibitory protein and stimulates regeneration in spinal-injured rats. Reier, et al. (1993) found that fetal tissue transplants survived in injured spinal cords, suggesting that these cells. Kawaguchi, et al. (1994) reported that careful opposition of sharply cut neonatal spinal cords allowed regeneration and functional recovery in rats. Tuszynski, et al. (1994) genetically modified fibroblasts to express neurotrophins, transplanted the cells into injured spinal cords, and showed that these cells stimulated regeneration. The GABA-B receptor agonist baclofen was being given intrathecally to control severe spasticity and the tricyclic antidepressant amitryptiline was starting to be used for neuropathic pain. A drug called 4-aminopyridine had been reported to improve function in patients with chronic spinal cord injury by Hansebout (1992).
Surgical Therapies

- Stabilization & decompression
  - Stabilization
    - Anterior and posterior plates
    - Titanium cage & other vertebral fusion methods
  - Delayed decompression restore function (Bohlman)
  - Untethering spinal cord improves function
  - Adcon gel and other methods to prevent epidural scarring
- Syringomyelic cysts
  - Remove subdural adhesions
  - Restore CSF flow
  - Dural grafts to reduce incidence of re-adhesion
- Urological procedures
  - Suprapubic catheterization & ileal conduits (Mitrafanoff)
  - Stents and artificial sphincters for bladder and bowel
- Peripheral nerve bridging
  - Implanting avulsed roots or nerves into cord for
    - Muscle reinnervation
    - Reduce neuropathic pain
    - Bladder reinnervation
  - Peripheral nerve bridging
    - Bridging spinal accessory, intercostal, and ulnar nerves to phrenic, sciatic, pudendal, and other peripheral nerves
    - End-to-side anastomoses

Advances in surgical therapies have revolutionized spinal cord injury care. In the 1980’s and early 1990’s, patients with spinal fractures were placed in traction and often decompressed surgically several days or even weeks later. Plating allows immediate stabilization of the spinal fracture. Patients are now being decompressed and mobilized shortly after injury, allowing earlier rehabilitation and shortening length of stay. Bohlman, et al. showed that decompression or untethering of the chronic spinal cord injury can result in a surprising recovery even years after the initial injury. Treatment of syringomyelic cysts also has changed dramatically. Until recently, most syringomyelic cysts were treated by shunting, a procedure that results in reappearance of the cyst in 80% of cases. Green, et al showed that removing subdural adhesions, using dural grafts, and restoring cerebrospinal fluid flow around the injury site produces long term eradication of the cyst in 80% of the cases. Urological procedures have also markedly improved quality of life for some people with spinal cord injury. For example, suprapubic catheters, ileal conduits, and Mitrafanoff procedures reduce urinary tract infections and increase independence of quadriplegics. With more experience and better devices, stents and artificial sphincters are beginning to show good results. Finally, many surgeons are applying innovative nerve bridging techniques to restore function. For example, avulsed roots can be reinserted into the spinal cord. Peripheral nerves are used to bridge the injured spinal cord and to establish new peripheral pathways to restore bladder and muscle function.
Medical Therapies

• Subacute Therapies
  – Monosialic ganglioside (GM1) accelerates motor recovery (Geisler, 1999)
• Neuropathic Pain
  – Intrathecal drugs
  – Anti-epileptic drugs:
    • High-dose Neurontin (gabapentin), i.e. 2000-4000 mg/day may produce stable relief of neuropathic pain
    • Carbemazine
  – Glutamate receptor blockers:
    • Dextromethorphan
    • Oral ketamine
  – Cannabinoids
  – Opioids

• Anti-spasticity therapies
  – Bladder spasticity
    • Intravesicular ditropan
    • Intravesicular capsaicin
  – Tizanidine
    • Alpha adrenergic receptor agonist, similar to clonidine
  – Oral 4-aminopyridine
    • Reduces pain & spasticity (Hayes, et al. 1998)
    • May improve bladder, bowel, and sexual function
    • May improve motor and sensory function in a third of patients with chronic SCI.
    • 4-AP may be the first drug that reduces spasticity without causing weakness.

Medical therapy of spinal cord injury has improved significantly in the past seven years. In 1999, Geisler, et al. reported that monosialic gangliosides (GM1), started 48 hours after injury and methylprednisolone treatment, appears to accelerate neurological recovery but does not significantly improve the recovery extent at 6-12 months after injury. Several treatments for neuropathic pain are now available. Intrathecal administration of drugs, including morphine, is being used in some clinics. Several anti-epileptic drugs have shown significant beneficial effects on neuropathic pain, notably high-dose neurontin (gabapentin) and carbemazine. Glutamate receptor blockers and cannabinoids likewise have been reported to help. A novel approach to treating bladder spasticity is intravesicular drug delivery. For example, when instilled into the bladder, ditropan reduced bladder spasticity with less side effects. Capsaicin is the essence of pepper; when placed into the bladder, it is taken up by nerve fibers and depletes substance P in the spinal cord, resulting in prolonged (2-3 month) reductions of bladder spasticity. Tizanidine is an alpha adrenergic blocker (similar to clonidine) that was recently approved for treating spasticity. Finally, 4-aminopyridine (4-AP) may reduce pain and spasticity, as well as increase sensory and muscle function in people with demyelinated axons in chronic spinal cord injury. Current phase 3 trials are underway. If these trials are positive, 4-AP may be the first drug to reduce spasticity without compromising motor function.
Many new rehabilitative therapies have appeared. Functional electrical stimulation (FES) is commonly applied to activate paralyzed muscles. Implanted sacral stimulation systems are being used to activate micturation and to prevent incontinence. External (Ness) and internal hand (Freehand) stimulators are now available. Many FES devices are associated with exercise devices, i.e. handcrank and bicycles, to prevent muscle atrophy. But perhaps the most important advance in rehabilitation has been the recognition of the role of “learned non-use”. This term refers to the neural circuits turning off after long periods of inactivity. Like muscles that undergo atrophy when inactive, neural circuits may undergo atrophy also. Since people recover slowly from spinal cord injury and remain inactive for long periods of time, learned non-use may play a role in preventing functional recovery. Several recent studies have shown that learned non-use can be reversed with intensive training even after decades of paralysis. Taub, et al. found that people with hemiplegia from stroke can regain function when forced to use their paralyzed arms. Biofeedback therapy, likewise, can produce surprising gains of function. But perhaps the most impressive improvements have been seen in locomotion. Wernig and others have reported that intensive ambulation training can restore locomotion to a majority of people with incomplete spinal cord injury even though they have never walked after their injury. Robotic exercisers are being designed to facilitate such training.
Many therapies regenerate and improve recovery in animal spinal cord injury models. These include antibodies against Nogo (Schwab, et al., 2000-2003), Nogo receptor blockers (Strittmatter, et al. 2003), chondroitinase ABC which breaks down chondroitin-6-sulfate proteoglycan (Bradley, et al. 2002), and C3 rho inhibitor (McKerracher, et al. 2002) that block intracellular messengers mediating growth inhibition. Purine nucleotides such as inosine, AIT-082 (a modified guanosine analog), and adenosine stimulate axonal sprouting and stem cell proliferation. David, et al. found that vaccinating mice with spinal cord homogenates, as well as myelin components such as nogo or myelin-associated glycoproteins, stimulates regeneration and remyelination. Borgens, et al. (1989-2002) at Purdue University use electrical currents to stimulate regeneration. Many cell transplants improve functional recovery in spinal-injured animals, including activated macrophages (Schwartz, et al. 1998), olfactory ensheathing glia (Ramon-Cuetos, et al. 2002), nasal mucosa transplants (Lu, et al., 2002-2003), bone marrow stem cells (Black, et al., 2000; Barros, et al. 2003), fetal neural stem cells (Okano, et al., 1999-2003), and radial glial cells (Grumet, et al. 2003). Cheng, et al. (1996) used acidic fibroblast growth factor (FGF) to treat peripheral nerve bridged spinal cords and glial derived neurotrophic factor (GDNF) to treat contused spinal cords. Xu, et al. (2002) used combination nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) to stimulate regeneration in spinal cord. The L1 cell adhesion molecule may stimulates regeneration and improve recovery after spinal cord contusions (Roonprapunt, et al. 2003). Erythropoietin may be neuroregenerative and neuroprotective (Gorio, et al. 2002).
Injury not only disrupts axons but damage oligodendroglia in the spinal cord, causing demyelination. Many therapies remyelinate injured or demyelinated spinal cord. Scientists have long known that Schwann cells will invade into injured spinal cord from the nerve roots to remyelinate axons (Blight, et al., 1988; Blakemore, 1990). Bunge and Xu, et al. at the Miami Project (1993-2003) have used Schwann cell bridges to reconnect transected spinal cords. Endogenous stem cells produce oligodendroglial precursor cells that remyelinate the spinal cord (Blakemore, et al., 1996; Gage, et al., 1999). McDonald, et al. (1999) showed that transplanted mouse embryonic stem cells produce oligodendroglial precursors that remyelinate myelin-deficient mice as well as injured rat spinal cords. Diacrin sponsored a clinical trial transplanting porcine (pig) fetal stem cells into human spinal cords. Olfactory ensheathing glia (OEG) will also remyelinate axons, like Schwann cells. Kocsis, et al., (1999) used porcine olfactory ensheathing glia to remyelinate irradiated rat spinal cords. OEG thus may do double-duty as remyelinating and regenerating cells. Intravenous immunoglobulins is used clinically to treat demyelinating conditions including multiple sclerosis and Guillian-Barre. Rodriguez, et al. (1993-2002) discovered monoclonal antibodies that stimulate remyelination. Finally, copaxone is an approved clinical treatment for multiple sclerosis and Schwartz, et al. have reported that it improves recovery in spinal cord injury by stimulating immune responses to myelin basic protein.
Several clinical trials have been completed since 1995. The National Acute Spinal Cord Injury Study III extended the original methylprednisolone results. The trial randomized patients given a single bolus of methylprednisolone (MP) within 8 hours after injury to a 24-hour or 48-hour course of MP, or 48-hour course of tirilazad mesylate. The 24-hour course turned out to be best when given within 3 hours after injury. The 48-hour course was better in patients treated between 3-8 hours after injury. The Fidia Sygen Trial compared 800 patients that received a 24-hour course of methylprednisolone only or methylprednisolone followed by GM1 (Sygen, 100 mg/day) given daily for 6 weeks after injury. The results suggest that GM1 may accelerate recovery, particularly during the first 6 weeks but did not significant alter the final extent of recovery at 6-12 months. The University of Florida at Gainesville carried transplanted human fetal spinal cords into patients with progressive syringomyelic cysts. The cells survived and filled the cavity. The trial showed that the transplantation procedure, even with short-term immunosuppression, was safe and feasible. Finally, AIT-082 (Neotrofin) is a modified guanosine analog that can be taken orally. It was assessed in a multicenter double-blind, placebo-controlled, and randomized clinical trial. The results have not yet been published.
Several clinical trials are underway. Acorda Therapeutics is running phase 3 multicenter trials assessing the effects of 4-aminopyridine (4-AP) on people with chronic spinal cord injury; prior phase 2 trials suggest that 4-AP may improve neurological function and reduce spasticity in as many as a third of people with chronic spinal cord injury. Proneuron has started a multicenter phase 2 trial of activated macrophage transplants; a prior phase 1 trial in Tel Aviv and Brussels showed that macrophages can be collected from the blood, activated, and transplanted safely into the spinal cord of people within two weeks after spinal cord injury. Diacrin is sponsoring a clinical trial of porcine fetal neural stem cell transplants at Washington University in St. Louis and Albany Medical Center; fetal neural stem cells from pigs are transplanted to people with chronic spinal cord injury. A clinical trial at Purdue University is assessing the effects of alternating current electrical stimulation applied within 2 weeks after injury. Olfactory ensheathing glia (OEG) are being transplanted in Beijing, Lisbon, and Brisbane. In Beijing, over 350 patients have received OEG cells isolated from olfactory bulb of aborted fetuses. In Brisbane, 3 patients have received OEG transplants cultured from nasal mucosa. In Lisbon, nasal mucosa is transplanted directly into the spinal cord of people with chronic spinal cord injury. Finally, Drs. Tarcisio and Erika Barros at the University of Sao Paulo is transplanted autologous bone marrow stem cells into the spinal cords of people with chronic spinal cord injury.
Emerging Promising Therapies

- Chondroitinase
  - Chondroitin-6-sulfate proteoglycan (CSPG) inhibit axonal growth in spinal cord (Silver, et al., 1993)
  - Chondroitinase ABC (Chase ABC) is a bacterial enzyme that breaks down CSPG and stimulates regeneration (Bradbury, et al. 2002)

- Glial-derived neurotrophic factor (GDNF)
  - A growth factor produced by glia, GDNF appears to be neuroprotective (Cheng, et al. 2002) and stimulates axonal growth (Xu, et al., 2003).
  - GDNF is currently in clinical trial for Parkinson’s disease.

- Olfactory ensheathing glia (OEG)
  - These specialized cells originate in nasal mucosa, migrate in olfactory nerves to olfactory bulbs, and may explain ability of adult olfactory nerves to regenerate (Doucette, et al., 1991)

Two therapies are attracting a great deal of attention this year at the 2003 Neurotrauma and Society for Neuroscience meetings. Chondroitin-6-sulfate proteoglycans (CSPG) are extracellular matrix proteins. Secreted by reactive astrocytes, CSPG strongly inhibits axonal growth the injury site. Chondroitinase ABC (CABC) is a bacterial enzyme that breaks down CSPG. Elizabeth Bradbury and colleagues showed recently that CABC applied daily to the spinal cord will allow regeneration with improved function in rats after dorsal hemisections. Glial-derived neurotrophic factor is a growth factor produced by glial cells. Recent studies suggest that GDNF is neuroprotective (Cheng, et al., 2002) and neuroregenerative (Xu, et al., 2003). It is already in clinical trial for Parkinson’s disease. Olfactory ensheathing glial cells have also attracted much attention. Described in 1991 by Doucette, et al., these cells are made by stem cells in the nasal mucosa and migrate up the olfactory nerve into the olfactory bulb where they reside in the outer layers of the olfactory cortex. When isolated from the olfactory bulb or nasal mucosa, these cells can be transplanted into the spinal cord where they survive, migrate, and remyelinate axons. They have been reported to regenerate axons as well.
Olfactory ensheathing glia (OEG) are of particular interest because of their ability to facilitate regeneration and remyelination of the spinal cord. Reported about four years ago to improve neurological recovery in animals, OEG are being transplanted in three clinical trials being carried out in Beijing, Lisbon, and Brisbane. OEG originate from the lamina propia of the nasal mucosa, migrate up the olfactory nerve, and take up residence in the olfactory bulb. They are believed to be the reason why the olfactory nerve is the only central nervous system structure continuously regenerates in adults. OEG cells take three forms in culture. The bipolar form appears to be the migrating structure. The multipolar form appears to guide axons and express L1, laminin, and other cell adhesion molecules that are attractive to axons. The “fried egg” form may be the ensheathing form. Note that OEG cells express nestin (a primitive filament that is often seen in neural stem cells) and GFAP (a filament that is present in glial cells). They also express P75 (the low affinity neurotrophin receptor). Transplanted into the spinal cord, OEG cells generally have a bipolar form but often can be seen myelinating axons like Schwann cells.
Clinical trials of olfactory ensheathing glia (OEG) transplants are being conducted in four places around the world.

### OEG Clinical Trials

- **Lisbon (Portugal)**
  - Carlos Lima in Lisbon transplanted nasal mucosa into spinal cords of over 10 patients with chronic spinal cord injury

- **Brisbane (Australia)**
  - Tim Geraghty and Alan McKay-Sims in Brisbane cultured and transplanted 15 million OEG cells from nasal mucosa into four patients with chronic spinal cord injury

- **Beijing (China)**
  - Hongyun Huang in Beijing cultured OEG from fetal olfactory bulb and transplanted into over 300 patients with chronic spinal cord injury

- **Novosibirsk (Russia)**
  - Samuel Rabinovich has transplanted mixtures of OEG and neural stem cells into 15 patients with chronic spinal cord injury
Beijing OEG Clinical Trial

- **Subjects**
  - 171 patients
  - age 2-64 (mean 34.9) years
  - 139 male and 32 female,
  - 6 months to 18 years after injury

- **Surgery**
  - Block laminectomy
  - 500,000 fetal OEG injected above and below the injury site
  - Tight dural closure

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Hungyun Huang and colleagues recently published a paper in the Chinese Medical Journal (2003, 116:1488-91) reporting the neurological results on the first 171 patients into whom they transplanted olfactory ensheathing glial (OEG). The patients ranged from 2 to 64 years of age, were mostly male (139, female 32), and were 6 months to 18 years after injury (average 2 years after injury). The cells were cultured from olfactory bulb of aborted human fetuses. The spinal cord above and below the injury site was exposed by laminectomy. Approximately a half million cells were injected into each of two sites, above and below the injury. The table shows the average motor score, touch score, and pinprick score improvement in the patients at 4-6 weeks after transplantation for each age group. Approximately 71% of the patients were ASIA A (complete spinal cord injury). There was no significant difference of recovery between the age groups.
Other Clinical SCI Studies

- NIH Clinical Trial to assess use of supported treadmill ambulation training to reverse learned non-use
- Spinal cord L2 stimulation to activate locomotor pattern generator
  - Hermann in Tucson and Dimitrijevic in Vienna
- Experimental surgical approaches
  - Fetal stem cell transplants (Moscow, Novosibirsk, Beijing)
  - Peripheral nerve bridging to spinal cord (Brunelli in Brescia)
  - Peripheral nerve bridging to bladder and muscle (Zhang in Shanghai)
  - Bridging spinal cord injury site with peripheral nerves & growth factor cocktail (Cheng in Taiwan)
  - Untethering, peripheral nerve transplants, omentum transplant, hyperbaric oxygen, and 4-aminopyridine (Carl Kao in Ecuador)
  - Omentum transplants (U.S., Cuba, China, and Italy)
  - Shark embryonic transplants (Tijuana)

Many other clinical studies are being carried out. Weight-supported treadmill ambulation training has been reported to improve locomotor recovery in people with chronic spinal cord injury. Clinical trials to show this are underway in several European countries (Switzerland, Germany, Belgium, etc.) and the United States. The training apparently reverse “learned non-use”.

About two years ago, Hermann, et al. in Tucson, Arizona and Dimitrijevic in Vienna, Austria reported that L2 spinal cord stimulation will activate the locomotor pattern generator in humans. Such stimulation not only can produce walking activity but subthreshold activation of the locomotor pattern generator appears to facilitate voluntary locomotor activity in people with chronic spinal cord injury. Finally, a large number of controversial experimental surgical procedures are being tried in many countries outside of the United States. These include omentum transplants, bone marrow stem cell transplants, fetal stem cell transplants, peripheral nerve bridging of transected spinal cords, peripheral nerve bridging from spinal cord above the injury site to paralyzed muscles, and even shark embryo transplants.
Many clinical trials are being planned. IN-1 (the original antibody described by Martin Schwab), licensed and being developed by Novartis. Nogo receptor blockers were discovered by Stephen Strittmatter at Yale and licensed by Biogen. Moses Rodriguez at Mayo Clinic discovered IgM kappa remyelinating and regenerating antibodies; this is has been licensed by Acorda Therapeutics. Larry Benowitz from Harvard found that inosine stimulates corticospinal tract regeneration and Boston Life Sciences Inc has licensed this technology. Almudena Ramon-Cuetos in Madrid has completed monkey studies and showed that autologous olfactory ensheathing glia can be grown from adult olfactory bulbs and transplanted to spinal cord. Lisa McKerracher in Montreal discovered that C3 and other rho inhibitors can block Nogo effects. An NIH-funded stem cell center at Tulane University, headed by Darwin Prockop has announced intention to initiate a bone marrow stem cell clinical trial for spinal cord injury. Dr. Okano at Keio University has completed monkey studies of fetal neural stem cell transplants. Umbilical cord blood Phase I trials may already be beginning in several centers around the country. Several companies are working on Chondroitinase ABC, including Acorda Therapeutics. Glial derived neurotrophic factor (GDNF) is already in clinical trial for Parkinson’s disease and may be tried in SCI (Amgen). Erythropoietin is being considered now for human clinical trial (Johnson & Johnson).
One way to think about the development of spinal cord injury therapies is that we are currently in the first generation of therapies. Nearly a dozen first generation therapies are in clinical trial currently. Some of these may turn out and others will not. I believe that it is likely that one or more of these therapies will turn out to restore some function to some people. Second generation therapies will begin in the coming years and should restore more function to more people. Almost all of these therapies have been reported to improve functional recovery in animals. Clearly, there are many candidate therapeutic agents and the separation of the treatments into first and second generation therapies is just for illustration purposes. What becomes “second-generation” obviously depends on the results of the first generation clinical trials.
## Third Generation Therapies

- **Combination therapies**
  - Regenerative
    - Bridging the injury site
    - Growth factors
    - Overcoming inhibition
    - Guiding axons to target
  - Remyelinating
    - Stimulating remyelination
    - Remyelinating with Schwann, OEG, O2A, embryonic stem cells
  - Restorative
    - 4-aminopyridine
    - Biofeedback therapy
    - Forced use therapy
    - Activity-induced plasticity

- **New therapies**
  - Vaccine
    - Regenerative vaccines
    - Neuroprotective vaccines
    - Remyelinating vaccines
  - Stem cells
    - Neuronal replacement
    - Reversing atrophy
    - Replacing motoneurons
  - In vivo gene therapy
    - Gene therapy to express neurotrophins and other growth factors
    - Cell adhesion molecules to direct axonal growth
    - Ephrins and sonic hedgehog to stimulate axonal growth

Third generation therapies will probably involve combinations of regenerative, remyelinating, and restorative treatments. Some truly new therapies are being considered, including therapeutic vaccine, stem cell replacement of neuronal loss, and means of guiding axonal growth. These therapies were not even a gleam in scientists’ eyes in 1995 because nobody had thought of stimulating the animals to produce their own antibodies to stimulate neuroprotection, regeneration, and remyelination. Pluripotent stem cells were not available in 1995 and the first human stem cells were grown in culture for the first time in 1997. Finally, although the concept of gene therapy was around in 1995, the tools were not available for in vivo gene therapy. Possible genes include neurotrophins and other growth factors, cell adhesion molecules, ephrins and sonic hedgehog.
Sources of Stem Cells

- **Embryonic stem cells**
  - In vitro fertilized eggs
  - Cloned eggs
  - Parthenogenic eggs
  - Eggs from embryonic stem cells

- **Fetal stem cells**
  - Fetal neural stem cells
  - Germ cell line stem cells
  - Many other tissues of fetuses contain large numbers of stem cells.

- **Umbilical cord**
  - Neonatal blood
  - Placenta, umbilical vein

- **Adult stem cells**
  - Neural stem cells
    - Hippocampus
    - Olfactory bulb
    - Spinal cord
  - Mesenchymal stem cells
    - Bone marrow stem cells
    - Nasal mucosa stem cells
    - Peripheral blood
    - Skin and other organs
  - Enteric glia (appendix)

Replacement of cell loss may be important particularly for spinal cord injuries that involve gray matter. The cells may be lost from direct damage, secondary necrosis, apoptosis, cystic degeneration, and non-use. Stem cells may be useful for replacing the cells. There are many sources of stem cells. The best known and most extensively studied are fetal stem cells. These are cells obtained from aborted fetuses (from 6 weeks to birth). Methods of isolating and growing human embryonic stem cells were discovered in 1997 but research has been slow in the United States. Umbilical cord blood stem cells may contain large numbers of pluripotent stem cells. Adult stem cells have been discovered in many parts of the body, particularly the brain, spinal cord. Recent studies suggest that bone marrow, nasal mucosa, peripheral blood, skin, fat, and even baby teeth possess pluripotent mesenchymal stem cells. The intestines may have stem cells (enteric glia).
These are pictures of neural stem cells isolated from neonatal brain. The top left picture shows a neurosphere which is the form commonly taken by stem cells growing in serum-free media with basic fibroblast growth factor. These neurosphere stain for nestin (a primitive filament often expressed by neural stem cells) and BRDU (a stain indicative of mitosis). When a neurosphere is placed in culture with serum, the cells will begin differentiating, adhere, and grow out of the sphere.
We should keep the following principles in mind when trying to restore function in spinal cord injury. “Complete” spinal cord injury does not mean transection. Severance or transection of the spinal cord, with separation of two cut ends of the cord, is very rare. Even a little bit of tissue bridging the injury site may be sufficient to support 10% of the axons and substantial functional recovery. Many people continue to regain motor and sensory function over many years after spinal cord injury. Because some of this recovery occurs so late, it suggests the possibility that spontaneous regeneration can occur, albeit very slowly. Surviving and regenerating axons need to be myelinated. We should remember that axons need myelin to function. Spontaneous remyelination may of course occur. If not, 4-aminopyridine may be useful to detecting such axons and the need for remyelination therapy. Most scientists assume that the axons gets across the injury site and to the general vicinity of their original targets, they will connect appropriately or the brain and spinal cord is sufficiently “plastic” to accommodate the new connections. Finally, because many people with chronic spinal cord injury have not had function in their lower spinal cord for years, intensive training may be necessary to reverse learned non-use after applying regenerative and remyelination therapies.
Preparing for Recovery

- Avoid unnecessary irreversible surgical procedures, e.g.
  - Dorsal root rhizotomies, spinal cord transections
  - Surgery that sacrifice major peripheral nerves
- Prevent muscle and bone atrophy
  - Titrate anti-spasticity drugs such as baclofen so that not all spasticity is eliminated.
  - Do standing and walking exercises
  - Use functional electrical stimulation (FES) to maintain and build up muscles
- Relieve causes of continuing spinal cord damage
  - Decompression
  - Untethering cord
  - Reduce syringomyelia cysts
- Reverse learned non-use
  - Physical therapy
  - Activity-induced plasticity
    - Swimming and hydrotherapy
    - Weight supported treadmill ambulation training
  - Biofeedback therapy
  - L2 locomotor pattern generator stimulation

Most commonly asked question from people with spinal cord injury is how they can prepare for recovery. Here is what I would do. First, I would avoid unnecessary and irreversible surgery. For example, some surgeons recommend cutting of spinal roots (rhizotomies) and even the spinal cord to treat spasticity and neuropathic pain. Likewise, it would be important to avoid surgeries that sacrifice major peripheral nerves. Second, prevent muscle and bone atrophy. Titrate antispasticity drugs so that some spasticity remains. Spasticity helps maintain muscles. Do standing and walking exercises. Use functional electrical stimulation to maintain and build up muscles. Third, relieve causes of continuing spinal cord damage, including compression, tethering, and syringomyelic cysts. Finally, reverse learned non-use. Get regular physical therapy, swim, and do weight-supported ambulation training, biofeedback, and even L2 stimulation to activate the locomotor when it becomes available.
Conclusions

• In 1995, only one therapy (methylprednisolone) improved recovery when given after spinal cord injury. Several therapies showed promise in laboratory studies.
• In eight years, advances in surgical and medical therapies have revolutionized spinal cord injury care. Intensive training may improve locomotor recovery.
• Several clinical trials have shown limited results (fetal spinal cord transplants, GM1) but other ongoing trials may yield positive results (4-AP, OEG, AC currents).
• Many regenerative and remyelinating therapies that improve functional recovery in animals have started or will soon start in clinical trials.

In conclusion, I had reason to be cautiously optimistic in 1995 when Christopher Reeve asked whether there would be therapies that would restore function in people with spinal cord injury. In the past eight years, advances in surgical and medical therapy of spinal cord injury have revolutionized spinal cord injury care. Intensive ambulation training has been shown to improve locomotor recovery in people with incomplete spinal cord injury, who have not walked even many years after injury. Several clinical trial shave shown limited results (fetal spinal cord transplants, GM1) but several ongoing trials (4-AP, OEG, alternating current stimulation) may yield positive results. Many regenerative and remyelinating therapies have been reported to improve functional recovery after spinal cord injury and are awaiting clinical trials. There is thus much basis for hope in the field. It is not a matter of if therapies will be available but when.