



Advances in Spinal Cord Injury Therapy

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There has been grumbling about the slow progress of spinal cord injury research. In reality, there has been remarkable progress in the field. Perhaps the best way to illustrate this is a list of therapies that I couldn't have predicted in my wildest dreams a mere seven years ago and movements of several other therapies either into or close to clinical trial since 1995.

New Therapies Developed since 1995

- **Stem cells.** In 1995, stem cells weren't even in the horizon. We did not know that there were neural stem cells in adult brain and spinal cord, pluripotent stem cells in many tissues of our body. We did not know that it would be possible to clone stem cells. Even embryonic stem cells were not part of our thinking because there was no easy way of culturing stem cells. Today, of course, many studies are showing that stem cell therapies can help repair tissues and replace cells that have been lost in diseases ranging from diabetes and myocardial infarcts to brain and spinal cord injury. Multiple sources of stem cells are being discovered and developed into practical sources.
- **Immunotherapy.** In 1995, we thought that all the immune system did was to kill and remove molecules and cells. Today, we

think of the immune system as an integral part of tissue repair and regeneration. The concept of vaccinating people to promote remyelination and regeneration was not even even part of our science fiction lore. Now, of course, several immune therapies (activated macrophages, activated lymphocytes, therapeutic vaccine, copaxone, and others) are being tested in animals or are already in clinical trials.

- **Nogo receptors.** In 1995, Nogo was just a yet unidentified protein that may be present in myelin, believed to be the reason why the spinal cord could not regenerate. Several other competing inhibiting proteins (such as MAG and CSPG) were candidate inhibitors. An antibody called IN-1 had been developed against Nogo but little progress had been made to develop a better a better antibody. Now, we not only have the gene for Nogo but also the gene for the Nogo receptor which turns out also to be the receptor of MAG and CSPG.

- **Intracellular messengers.** In 1995, we had no clear understanding of how and why proteins prevented axons from growing in the central nervous system. Not only did we not know what the receptors were but we had little idea of the intracellular messengers that were responsible for mediating the inhibitory effects of the receptors on axonal growth. Today, we know the major intracellular messenger systems that affect axonal growth: cAMP and rho. New therapies based on increasing cAMP (rolipram) and inhibiting rho (C3) now being tested in animals and soon in clinical trials.

- **Olfactory ensheathing glia.** In 1995, few people had even heard of OEG. They were an obscure cell present in the olfactory system and there had been some speculation that they facilitate regeneration in the olfactory nerve. Few laboratories knew how to isolate and culture these cells, or even how to identify them. Today, many laboratories have shown that these cells when transplanted to the central nervous system can support regeneration in brain and spinal cord. New and potentially practical sources of OEG have been identified, including adult olfactory bulb, fetal olfactory bulb, and adult nasal mucosa. Clinical trials have begun.

- **Anastomoses of the spinal cord.** In 1995, most people thought that it would be impossible to rejoin cut ends of the spinal cord together and obtain regeneration. In 1994, Kawaguchi had reported that it was possible to do so with neonatal rat spinal cords, however, this was considered to be impossible still with adult spinal cords. By 1996, however, Cheng, Olson, and colleagues had shown that that it was possible to use peripheral nerves to bridge the cord. Kawaguchi has made considerable progress in developing techniques to reanastomose transected adult spinal cords and will soon be reporting successful regeneration of adult rat spinal cords.

Other Therapeutic Advances since 1995

Several potential therapies that were known before 1995 have also come closer to practical application. These include:

- **Alternating Current Therapy.** In 1995, we had little idea of the mechanism underlying electrical current stimulation of axonal growth. Today, we know that such alternating currents raise cAMP levels in growth cones and may orient glial processes in the spinal cord as well. This is now in clinical trial.

- **L1 cell adhesion molecule.** In 1995, this was believed to be just a cell adhesion molecule but there is now evidence to suggest that the molecule is not only an adhesion molecule but also a receptor that turns on a number of intracellular messengers that stimulate axonal growth. It is now possible to apply the molecule in the form of a soluble fusion molecule to the spinal cord.

- **M1 antibody.** In 1995, this was recognized to be an antibody that may stimulate axonal remyelination. A human form of the antibody has now been identified and this may soon be in clinical trial.

- **4-aminopyridine.** In the late 1980's, this drug was reported to improve conduction in demyelinated axons in multiple sclerosis and spinal cord injury. Unfortunately, the drug was only available to be given intravenously. In 1995, this drug was just beginning to be given orally in clinical trials. It has side effects and there were fears that the drug causes seizures. A sustained release

formulation of the drug has been developed with potentially less side effects and can be given more conveniently. This drug has gone through extensive phase 2 clinical trials and is now undergoing phase 3 trials for both SCI and MS. If these trials show a beneficial effect, it may well be the first treatment approved by the FDA to improve function in chronic spinal cord injury.

- **Schwann cell transplants.** In 1995, only a few laboratories had the capability of isolating and growing large number of Schwann cells for transplantation purposes. Today, it is possible to isolate and grow large numbers of these cells from a short segment of peripheral nerve, making clinical trials of this cell transplant possible. This therapy is beginning clinical trial in multiple sclerosis and possibly in spinal cord injury aswell.

- **Porcine stem cell transplants.** In 1995, the concept of transplanting animal cells into the spinal cord was still very controversial. There were several companies investing in the creation of transgenic pigs that had cells that were more immunologically compatable for transplantation in humans. Porcine xenografts have now been carried out in well over 100 people with stroke, Parkinson's disease, and even spinal cord injury by Diacrin.

- **Fetal cell transplants.** In 1995, there was considerable skepticism about the possibility of fetal or any other kind of cell transplants to the spinal cord of humans. While there had been several reports that fetal cells were being transplanted into human spinal cord in Russia and some early attempts to do so in people with Parkinson's disease, there had not been any attempts to do so in the United States or Western Europe. Today, however, we know that it is not only feasible but safe to carry out such transplants, although much still remains to be done to demonstrate that such transplantsimprove function.

- **Weight-supported ambulation training.** Many animal studies have suggested that treadmill training of animals after spinal cord injury can restore locomotor function in animals. In 1995, several reports from Anton Wernig and colleagues in Germany suggesting that intensive weight-supported ambulation training on treadmills can remarkably restore locomtor function in

people who had never walked after spinal cord injury. Many clinics have confirmed that many people may benefit from such training, years or even decades after spinal cord injury. In the meantime, work from Taub and colleagues have suggested strongly that the central nervous system turns off neural circuits that are not being used and that intensive repetitive training can result in activity-induced recovery. Such training is now being considered and implemented in many rehabilitation centers. So, in summary, basic animal research has contributed significantly to opening many therapeutic options for spinal cord injury. I have not mentioned many additional therapies that are just now being developed now. It is critical that this pipeline of therapies be maintained. Clinical trials must be carried in conjunction with animal studies. The two must go in parallel because clinical work provides important ideas for animal studies and vice versa.

Some people have, in understandable frustration, advocated stopping animal studies in order to pursue clinical trials. They should understand that stopping animal studies will sound the death knell for therapeutic development in spinal cord injury. It is not only short-sighted but ultimately selfish to call for an end to animal studies now. We can advocate for clinical trials without being negative about animals studies. In the same way, it is very difficult for me to accept the view that we must somehow treat spinal cord injury as a zero-sum game where we must be satisfied with the current funding. No other field does this. Can you imagine people in the AIDS field calling for the cessation of basic science as the first AIDS treatments went into clinical trial?