Acute, Subacute, and Chronic Spinal Cord Injury

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Last Updated: January 9, 2002

There is much confusion about the terms acute, subacute, and chronic spinal cord injury. This is understandable because there is no standard definition of these terms. Here, I would like to define the phases, what appears to be happening in the spinal cord during each phase, and the appearance of the spinal cord in each phase.

**Acute Phase**

The acute phase of spinal cord injury refers to the immediate post-injury period when there is continuing tissue damage. For a long time, I thought of the subacute period as the time when the spinal cord is undergoing repair and regaining function while chronic spinal cord injury represents the period when there is no longer any functional change. However, the distinctions between acute, subacute, and chronic phases of injury are beginning to blur. For example, as our own little poll on these forums showed, people continue to recover over long periods of time. As many as quarter of patients continue to recover over many years. This percentage may be higher if more people undergo intensive training to reverse learned non-use.

The mechanical trauma immediately damages axons and cells at the injury site. This is called the primary injury. However, the response of the spinal cord causes three subsequent waves of cell death. Immediately after contusion of the spinal cord with a weight, the contusion site shows relatively little damage. However, over 8-24 hours, the injury site develops hemorrhagic necrosis as cells die. In necrotic cell death, the cells swell and dissolve. For many years, the acute period was considered to last 8-24 hours. In 1998, however, when four laboratories using the rat spinal contusion model that we
developed reported two delayed waves of apoptotic cell death. In apoptic cell death, the cells shrivel up. One wave takes place at 24-48 hours and involve mostly neurons in gray matter surrounding the injury site. The other is a wave of apoptosis at 1-2 weeks, spreading in degenerating white matter tracts, involving mostly oligodendroglia. There is considerable debate whether preventing these delayed waves of apoptosis improves functional recovery.

Neuroprotective therapies aim to stop or reduce the immediate responses to injury that can further damage the spinal cord. Injury induces a very rapid (within minutes) and very intense (10-fold or greater) gene responses that includes many pro-inflammatory factors. These factors, which include the pro-inflammatory cytokines TNF-alpha, interleukin 1-alpha, interleukin 1-beta, and interleukin-6, activate microglia (the resident population of cells that produce macrophages) and attract peripheral inflammatory cells (such as lymphocytes, neutrophils, and monocytes which are peripheral macrophages) to the injury site. These cells kill and clear cells.

The inflammatory response is associated with increased expression of growth factors. For example, at the same time that cytokines expression increases in the injured spinal cord, there is an increase in neurotrophin expression. Methylprednisolone (a very potent anti-inflammatory drug) markedly suppresses pro-inflammatory cytokines as well as the neurotrophin increase. There is much evidence suggesting that neurotrophins contribute to apoptosis. This role of neurotrophins was discovered by Dennis Choi’s group several years ago, a phenomenon that Dennis aptly calls "the dark side" of neurotrophins. High levels of neurotrophins, for example, will cause neurons to undergo apoptosis in tissue culture.

**Subacute Phase**

The spinal cord starts the reparative process shortly after the injury. This is apparent from the massive collections of inflammatory cells that appear at the injury site by 12-24 hours. The first inflammatory cells that appear are neutrophils, followed by lymphocytes, and then macrophages. The first two types of cells come from blood. By 48 hours, a majority of the cells at the injury site may be macrophages, big active-looking cells with myelin and other cell fragments inside them. These cells are cleaning up the dead cells and debris.

Complete or prolonged suppression of the inflammatory response to injury can impair recovery. For example, if one gives methylprednisolone (a potent anti-inflammatory steroid) too late or for too long, it reduces neurological recovery. NASCIS 2 showed a trend for poorer neurological recovery in patients when methylprednisolone was started more than 8 hours after injury. Likewise, Bethel, et al. at the Miami Project found that the anti-inflammatory cytokine IL-10 improves recovery when given shortly after injury but increased tissue damage when it was given at 3 days after injury. That is one of the reasons why methylprednisolone treatment is strictly limited to 24-48 hours after injury.

Pro-inflammatory therapies may enhance repair and recovery when started late after
injury. For example, I believe that GM-1 is pro-inflammatory; it increases expression of pro-inflammatory cytokines, as well as neurotrophins. The recently reported GM1 trial (Geisler, et al. 2001) suggests that GM1 accelerates recovery when administered from 2-120 days after injury. I think that some of the "subacute" therapies that are currently in clinical trial are also pro-inflammatory. AIT-082 may also be pro-inflammatory; it increases neurotrophin expression. Activated macrophages and vaccine-induced immune responses are pro-inflammatory. Finally, implanting cells, particularly foreign cells that might provoke an inflammatory and immune response, is intrinsically pro-inflammatory.

While neutrophils and lymphocytes eventually disappear from the spinal cord, macrophages often remain. Richard Bunge looked at human spinal cords as long as 20 years after injury and there were macrophages in the spinal cord. In rats, macrophages are abundantly present at the injury site and in degenerating white matter tracts for as long as we have looked. Given the huge number of macrophages in the spinal cord, one question that should be asked is why implantation of more macrophages do anything for the injured spinal cord.

Proneuron is currently conducting a clinical trial in which activated macrophages are being transplanted into the spinal cord of patients within 2 weeks after injury. According to Michael Schwartz who discovered the beneficial effects of implanting activated macrophages to the spinal cord, the macrophages must be activated by exposure to peripheral nerve or myelin. Exactly how and why the macrophages are activated with myelin or peripheral nerve is not clear. Two possible mechanisms of action has been invoked. One is that appropriately activated macrophages release factors such as neurotrophins that may stimulate growth and repair in the spinal cord. The other is that macrophages are removing myelin debris which inhibit axonal growth.

The initial injury causes loss of axons cut off from their cell bodies and die back of injured axons still connected to their cell bodies. The contusion site is frequently invaded by blood vessels and glial cells. A loose matrix of cells form within cystic cavities that develop at the site. The identity and source of many of the cells in the contusion site are not known but they may have been generated by stem cells in the cord. The matrix of cells is often missed in histological examinations of the spinal cord because it falls out of frozen sections of the cord.

In the surrounding cord, the spinal tracts containing axons that have been cut off from the cell body by the injury start to degenerate. Many macrophages cluster in the tracts. Apoptotic oligodendroglial cells are abundant in these tracts. Many of the macrophages can be seen to be actively ingesting myelin fragments. At the same time, many axons are sprouting. In untreated animals, axons can be clearly seen to penetrate into the contusion site and many are growing into the contusion site on the matrix of cells. Glia proliferate in in the cord adjacent to the contusion site.

**Chronic Phase**
By several weeks after injury, the contusion site usually contains a thin rim of surviving white matter close to the pial surface. In contused rat spinal cords, the injury site has a cystic cavity filled with loose cellular matrix. In severely injured spinal cords, Schwann cells can be seen at the injury site. These cells myelinate peripheral nerves and are usually not seen in the spinal cord. They probably migrated into the injury site from spinal roots. This only occurs in severe injuries that have damaged most of the astrocytes because astrocytes usually respond to Schwann cells by walling them off. However, when the Schwann cells are present at the injury site, they thickly myelinate every axon in sight. Many of the axons in the preserved white matter rim may be thinly remyelinated by oligodendroglial cells which normally myelinated spinal axons.

Macrophages can be seen around the edges of the contusion but typically cluster around degenerating or degenerated spinal tracts. Growing axons can be often seen in these degenerated tracts with growth cones, as long as 3 months or longer after injury. This suggests that there may be continued pressure for regrowth of axons in the spinal cord that continues for long periods after spinal cord injury. Little is known about the growth factor or trophic environment of the chronically injured spinal cord. Clearly, however, some inflammation may be going on in the spinal cord.

The spinal cord usually appears to be thinner, particularly at and close to the contusion site. This is not surprising due to the loss of cells. Most rats develop expansions of the central canal either proximal or distal to the contusion site, forming cysts that look very similar to syringomyelic cysts observed in humans. These cysts sometimes have ependymal cells lining the cyst walls but not always. Ependymal cells are of particular interest because they have been claimed to be the stem cells of the spinal cord.

Relatively little is known about the chronic human spinal cord. Only about a dozen studies have been published to date when a spinal-injured patient dies from unrelated causes. The best studies to date were carried out by Richard Bunge at the Miami Project where they have examined several dozen chronically injured spinal cords. Because the spinal cords from cadavers are often not very well preserved, axons may be hard to see, particularly those that have not been myelinated. In a majority of the patients, there are relatively few myelinated axons crossing the injury site.

Physical transections of the human spinal cord are very rare. In the 20 years that I have been in the field, I have not personally seen a verified case of spinal transection in humans. Although there have been occasional cases reported of knife cuts of the spinal cord and gunshot wounds causing complete destruction of a segment of the cord, the vast majority of human spinal cord injury involve contusions or compression with an intact dura and some preserved spinal cord tissue at the injury site. The few studies of chronic contused human spinal cords, however, yield a picture of the spinal cord that is very similar to the rat.

The central dogma that the spinal cord does not regenerate is based on relatively flimsy evidence. Early animal studies usually involved transections of the cord and, due to the separation of the cut ends and the presence of fibrous scar tissue, axonal regeneration is
unlikely. Recent studies of chronic contused rat spinal cords have revealed the presence of large numbers of axons growing within the cellular matrix in the contusion site. Michael Beattie and colleagues at Ohio State University had earlier reported that many axons are growing on the cellular matrix and that many of these axons come from the brain and some from the periphery. It is not clear how many of these axons actually cross the injury site and connect with neurons on the other side.

**Summary**

Trauma initiates an intense inflammatory response in the rat spinal cord that may contribute to further tissue damage during the first 8-24 hours after spinal cord injury. At 24-48 hours, a second wave of cell death occurs, involving mostly neurons in the surrounding spinal cord. Large numbers of macrophages accumulate at the injury site. As axons that have been damaged at the injury site and separated from the cell body die, a third wave of cell death, mostly involving oligodendroglia in degenerating spinal tracts, occur. Macrophages cluster around the degenerating tracts. Suppression of the initial inflammatory response may save some cells and tissue at the injury site but prolonged or delayed anti-inflammatory treatments may interfere with tissue repair and recovery. Pro-inflammatory therapies may be beneficial during the weeks that follows injury, during the subacute phase. During the chronic phase, a cyst often develops at the injury site, filled with a loose cellular matrix. Many axons can be seen growing on the cellular matrix although the source and destination of these axons are not well understood. Syringomyelic cysts sometimes develop in surrounding cord. Relatively few studies have been carried out on injured human spinal cords but most of these suggest strong similarities between injured rat and human spinal cords.

This project was supported, in part by grant number 90PR3002, from the U.S. Administration for Community Living, Department of Health and Human Services, Washington, D.C. 20201. Grantees undertaking projects under government sponsorships are encouraged to express freely their findings and conclusions. Points of view or opinions do not, therefore, necessarily represent official Administration for Community Living policy.