

TRAUMA AND REGENERATION

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LEARNING OBJECTIVES:

1. Learn the causes and outcomes of spinal cord injury (SCI) and traumatic brain injury (TBI).
2. Learn what occurs during trauma to the CNS and the pathophysiological processes that follow those events, especially the processes that lead to secondary injury.
3. Learn about degenerative changes that result from loss of trophic support to neurons.
4. Learn about the processes of regeneration that occur after traumatic injury to peripheral nerves.
5. Begin to learn about existing and potential treatments for patients affected by SCI and TBI.

REFERENCES: Parts of Chapters 22 and 24 in Purves et al. *Neuroscience*, 3rd edition.

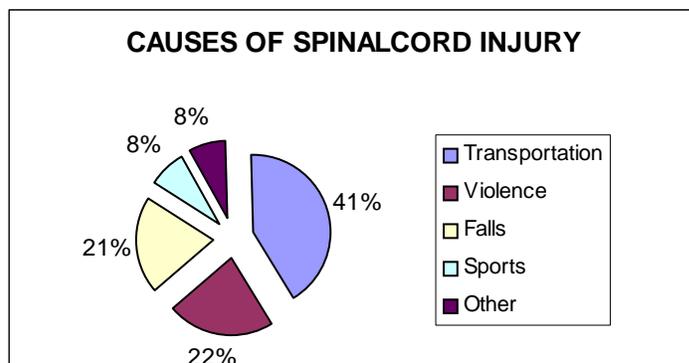
OVERVIEW: Trauma is the 3rd or 4th most common cause of death in the U.S. and the leading cause of death in the 1- to 44-year-old age group. This lecture will focus on mechanical Spinal Cord Injury (SCI), Traumatic Brain Injury (TBI), and injury to the PNS. Progress toward improved clinical treatments and better outcomes for patients are likely to depend on improvements to knowledge of the biological mechanisms that operate in traumatic injury to the CNS.

The Incidence of Spinal Cord Injury (SCI):

- In the U.S there are 8,000 to 11,000 new SCI cases each year.
- There are currently 250,000 to 400,000 Americans living with SCI or SC dysfunction.
- The risk of SCI is greatest for 16- to 30-year-olds.
- Over 80% of the injured patients are males.

Causes of Spinal Cord Injury (SCI):

- 41% of spinal cord injuries result from transportation accidents
- 22% from acts of violence
- 21% from falls
- 8% from sports
- 8% from other causes.



Clinical Outcomes of Spinal Cord Injury:

~52% **quadriplegia**

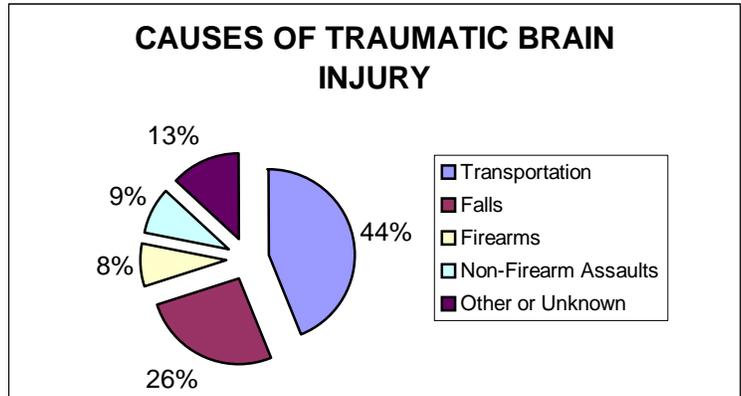
~47% **paraplegia**

The Incidence of Traumatic Brain Injury (TBI):

- Each year > 50,000 Americans die as the result of TBI.
- TBI occurs in 75% of fatal road accident victims.
- Annually, ~1,000,000 patients are treated and released after TBI.
- ~80,000 patients/yr begin to experience long-term disabilities from TBI
- The risk of TBI is highest in 15- to 24-year-olds and people over 75.

Causes of Traumatic Brain Injury:

- 44% of TBI results from transportation accidents
- 26% from falls
- 8% from firearm assaults and accidents
- 9% from non-firearm assaults
- 13% other or unknown causes.



Clinical Outcomes of Traumatic Brain Injury:

- coma, seizures, spasticity, and sensory dysfunctions
- short and long-term memory loss
- slowed processing of information, trouble concentrating, difficulty in word finding, and spatial disorientation
- headaches, fatigue, and changes in emotion.

What Happens in Spinal Cord Injury?

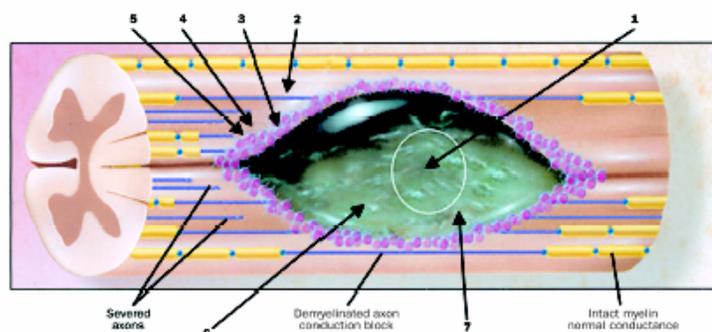
1. SCI is usually caused by violent torsion or impacts that result in:
 - Displacements and dislocations of vertebrae
 - Crushing or breaks in vertebrae.
2. The cord is usually injured through contusions (i.e., by bruising) or compressions (i.e., by crushing). Only rarely is there a partial or complete transection of the cord.
3. The transections that do occur are usually the result of gunshot wounds to the thoracic cord.
4. Most spinal cord injuries involve the cervical cord. (The neck is less stable than the trunk).
5. For more information visit: www.spinalcord.org/ or www.spinalvictory.org/

The Pathophysiology of SCI and TBI:

1. Just after the injury, the cord and brain are grossly and microscopically intact in most cases of SCI and TBI.
2. Traumatic injuries result in the immediate death of some neurons, but many portions of the damaged CNS tissue are still alive immediately after the injury. Many more neurons are destroyed over the subsequent minutes, hours, days, weeks, and months through **secondary injury** processes that kill or damage those cells.
3. Local vascular and biochemical changes within the spinal cord and brain themselves are largely independent of external factors and those local changes appear to drive secondary injury.

The processes that contribute to Secondary Injury include:

1. **Hemorrhagic necrosis.** Extravasation of blood and breaching of the normal blood-brain barrier leads to an inflammatory response and edema. Cell death may result from toxic cytokines and from the generation of free radicals in the damaged tissue.
2. **Ischemia.** Interruption of blood flow can be caused by edema and pressure in the vertebral canal, by vasospasm, and by loss of vascular autoregulation after trauma to the CNS. The CNS also can be injured by reduced blood flow due to hypotension, vasospasm, emboli and thromboses arising from traumatic injuries elsewhere in the body. Ischemia of long duration can lead to the immediate death of some neurons. Transient ischemia can result in re-perfusion injury.
3. **Re-perfusion injury.** Some neurons may survive the period of ischemia but die after perfusion is re-established. This is thought to involve the generation of oxygen free radicals and/or excitotoxic cell death as in stroke. (Please refer to Dr. Lee's lecture handout on Stroke).
4. **Excitotoxic cell death.** In TBI massive and prolonged release of excitatory amino acid neurotransmitters appears to lead to excitotoxic death of neurons. It is controversial whether excitotoxic cell death is an important component of secondary injury in the spinal cord.
5. **Progressive necrosis.** This is thought to result, at least in part, from the continued release of toxic cytokines by macrophages and their CNS counterparts, the microglia, that participate in a reactive response to injury by phagocytosing debris from dead neurons.
6. **Neurodegeneration through loss of trophic support** occurs as a result of denervation and through loss of contact with synaptic targets. (This will be covered below).
7. **Cystic cavitation.** This occurs when dead and dying nervous tissues are removed by phagocytosis. Fluid-filled cystic cavities are left in their place.



Glial scarring. Astrocytes form **glial scars** in areas of damage and they establish glial limiting membranes at wound margins. In the spinal cord, both astrocytes and connective tissue cells contribute to “glial” scar formation. Glial scars are not thought to contribute to secondary degeneration, but they may create a tissue environment that is not supportive for regenerative growth of axons.

Clinical Events in Traumatic Brain Injury:

1. Most traumatic brain injuries are contusions that occur when the brain moves result linearly or rotationally within the skull. Such movements are caused by:
 - a. Accelerations from blows to the head as in boxing.
 - b. Decelerations as in automobile accidents or falls. In car accidents, most brain damage is caused by deceleration of the brain. (*Speed doesn't kill; stopping does...*)
2. **Coup** (“coo”) injuries to CNS tissue occur on the side of the impact.
3. **Contre-coup** injuries affect tissue opposite to the side of the impact.
4. **Epidural hematoma** can accompany direct contusions.
(Why would these be dangerous? *Answer:* Because they can quickly occupy volume in the brain case.)
5. **Subdural hematomas** can arise by rupture of bridging vessels.
6. Most penetrating brain injuries are the result of gunshot wounds.

Dysregulation of Homeostatic Systems Can Be Important Causes of Secondary Injury.

1. Trauma can disrupt the physiological activity of vital regulatory centers in the brain stem, such as the Ascending Reticular Activating System (A.R.A.S.) and the ventilatory control center. Loss of consciousness is often accompanied by a disruption of respiration (**apnea**) and the duration of apnea is usually related to duration of unconsciousness.
2. TBI also may disrupt the autoregulation of cerebral blood flow resulting in hypotension and hypoperfusion.
3. Apnea, hypotension, and loss of autoregulation can all lead to hypoxemia and hypercarbia with acidosis, which can cause further tissue injury and may cause death.
4. **Fortunately, all these events are amenable to clinical treatment.**

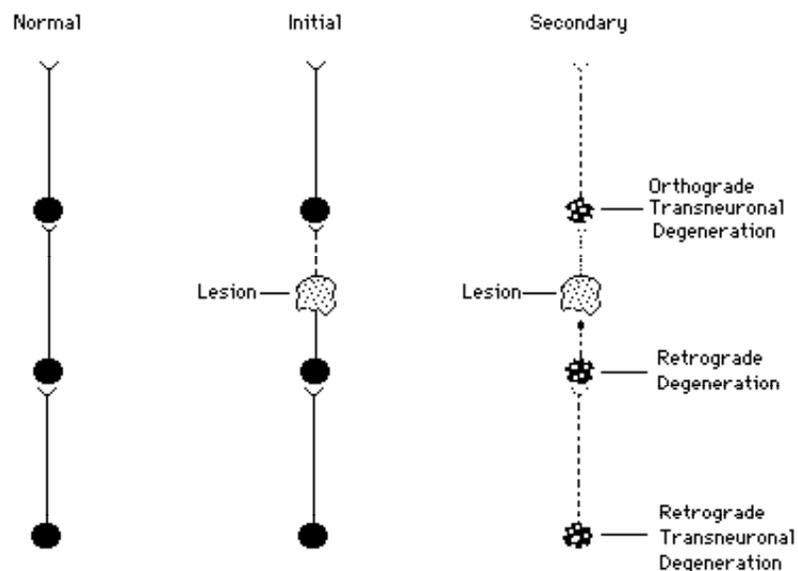
Neurodegeneration Can Occur as a Result of Denervation.

1. When axons are cut off from cell bodies those axons die by **orthograde degeneration**, because they depend on the cell body for the production of proteins.
2. If damage is restricted to the axon, the neuron either may die or survive.
3. When a neuron dies after axotomy that is termed **retrograde degeneration**.
 - Axotomy close to the cell body has a greater likelihood of leading to retrograde degeneration.
 - Axotomized neurons that retain undamaged collateral projections are less likely to undergo retrograde degeneration.

4. Axotomized neurons that survive often exhibit signs of **chromatolysis**. Chromatolysis is a histopathological state characterized by:
 - a. dispersal of Nissl substance
 - b. eccentric nucleus position in the soma
 - c. neuronal soma swells
 - d. the neuron may exhibit some axonal regeneration
5. Some of the changes that occur in chromatolysis may reflect growth processes

Secondary Neurodegeneration can result from Interruption of Trophic Interactions

1. Many types of neurons continuously depend on trophic signals received from the cells that they are connected to by synapses. Both denervation and disconnection from their targets can lead to secondary neurodegeneration because of the interruption of trophic interactions.
2. In the absence of trophic (survival-promoting) signals **apoptosis** can be activated. Unlike **necrotic cell death**, apoptosis does not evoke inflammatory responses.
3. Neuronal degeneration caused by loss of inputs is termed **orthograde transneuronal degeneration** (or **trans-synaptic degeneration**).
4. Neuronal degeneration caused by loss of the trophic support from the target is termed **retrograde degeneration**.



5. Specific types of neurons and glia depend on specific protein trophic/survival factors, such as NGF, BDNF, CNTF, NT-3, NT-4/5, and Neuregulins, which are ligands for receptor tyrosine kinases, such as: TrkA, TrkB, TrkC, ErbB2, ErbB3, and ErbB4.
6. Under experimental conditions neurons have been "saved" from retrograde degeneration by artificially delivering NGF and other trophic factors.

Treating SCI and TBI:

The sooner treatment is initiated after a traumatic injury to the CNS, the less secondary damage will develop. Physicians and E.M.T.'s can influence the pathophysiological processes that develop over minutes, hours, days and months, with profound consequences for the ultimate functional outcome for the patient.

Patients should receive:

1. **Oxygen.**
2. **Positive pressure ventilation.**
3. **Treatments to ensure that blood pressure is maintained.**

Methylprednisolone (MP) administered within 8 hours after SCI has been shown to reduce long-term deficits by ~15%.

Most potential avenues for treatment still depend exclusively on research in animal models. A few have progressed from animal research into clinical trials.

Potential therapies include:

1. Treatments to limit reperfusion injury.
2. Drugs to block glutamate receptors.
3. Agents that may modulate inflammatory responses, macrophage function, and cytokine release.
4. Caspase inhibitors and other drugs that interrupt apoptotic cell death processes.
5. Regenerative replacement of lost cells.
6. Treatments to encourage regeneration of severed axonal processes.

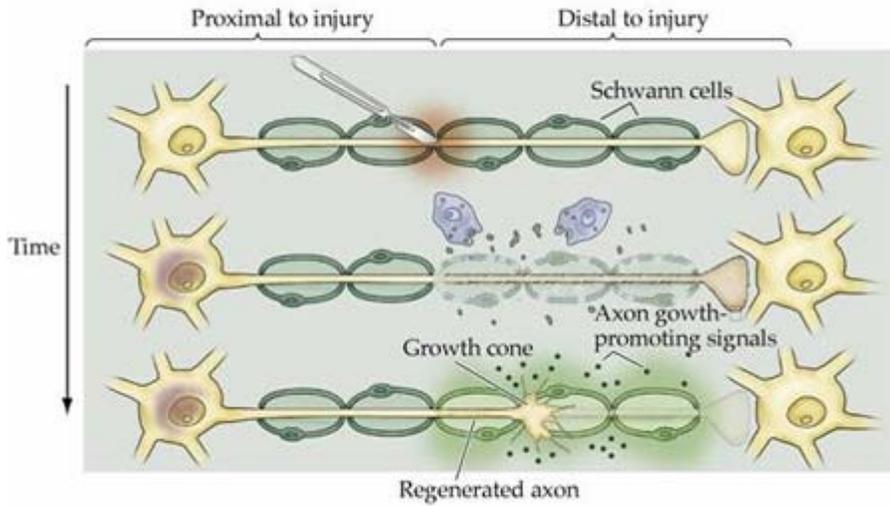
Cellular Replacement:

1. New neurons can form in the mature brain from stem cells that persist in the subventricular zones.
2. **Stem cells** are defined by having the ability to self-renew by divisions that give rise to cells like themselves and other cells that can become more specialized.
3. Animal experiments have shown that stem cells transplanted into the adult brain can develop into interneurons appropriate for the sites where they were implanted.

Axonal Regeneration in the PNS:

1. In the peripheral nervous system (PNS) severed axons can regenerate and restore function.
2. There are >50,000 peripheral nerve repair procedures/yr in the U.S.
3. Like the growth cones of developing neurons, regenerative axonal growth cones move along substrate pathways (provided by a bridge of newly replicated Schwann cells) back to their targets where synapses are re-established.
4. The rate of axonal regeneration in the PNS is **1 to 4 mm/day**.
5. The regenerative return of sensory function after PNS injury is often superior to the recovery of motor function.
6. Crush injuries and partial transactions are followed by more successful regeneration than complete transactions.

(A) Peripheral nervous system

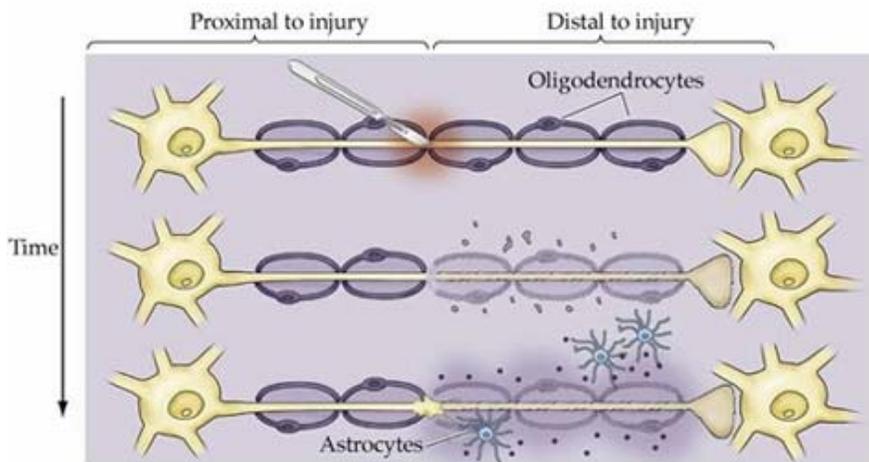


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Regeneration of Neural Processes and Connections in the CNS:

Axonal regeneration is severely limited in the CNS of mammals, but that type of regeneration can lead to dramatic recovery of function after SCI in non-mammals.

(B) Central nervous system



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Promising research:

1. In a surgical experiment, when axons in the CNS were cut and then allowed to grow into a cut segment of peripheral nerve tissue those CNS axons regenerated and extended for millimeters inside the ectopically inserted peripheral nerve environmental “bridge.” And they formed new synapses with their target cells.
2. **This showed that the limit to axonal regeneration is not so much within the neurons of the mammalian CNS themselves, instead it is a property of the environment where their axons have the opportunity to grow.**
3. Cells in the mature mammalian CNS express molecules that can inhibit the growth of axons and cause growth cones to collapse. Martin Schwartz and colleagues in Zurich, Switzerland identified such a protein and named it IN-1. They then generated an antibody to IN-1 that has the ability to neutralize its action.
4. In rodents the anti-IN-1 antibody enhances regeneration of some CNS axons across a site of spinal injury. Blockers of the growth-inhibitory molecules like IN-1 are one potential avenue for future SCI treatment.
5. Another approach has involved twice weekly immunizing injections of a homogenate from mouse spinal cord to try to induce the development of antibodies in recipient mice that would neutralize all the various growth inhibitory molecules that may act like IN-1. (In effect immunizing before SCI.)
6. After SCI those immunized mice showed considerably greater regeneration of axons than untreated controls or another group of mice that were immunized with a homogenate from mouse liver (which would not be expected to contain the IN-1-like inhibitors). The mice that had received the injections of homogenized spinal cord showed regeneration of axons past the SCI site and measurable recovery of hind limb function (58% showed contact placing).

How can we make a difference?

1. We can promote appropriate life choices. The immediate neuronal death that occurs following trauma can only be treated by prevention.
2. We can promote proper handling prior to the time that patients reach the hospital setting. (e.g., promote efforts to prevent hypotension and hypoxia, and support immediate drug intervention by emergency medical personnel so as to positively influence outcomes).
3. We can try to discover or adopt new therapies that may limit secondary damage in SCI & TBI.
4. We can try to promote public understanding of medical research. Unfortunately progress in this area of medicine is likely to continue to depend on use of animal research models.
5. Without giving false hope, we can take care to preserve the hope that patients may feel. (Breakthroughs in treatments and research can support reasonable hopefulness and patients sometimes experience remarkable recovery of function after experiencing injuries that would not have been expected to heal.)