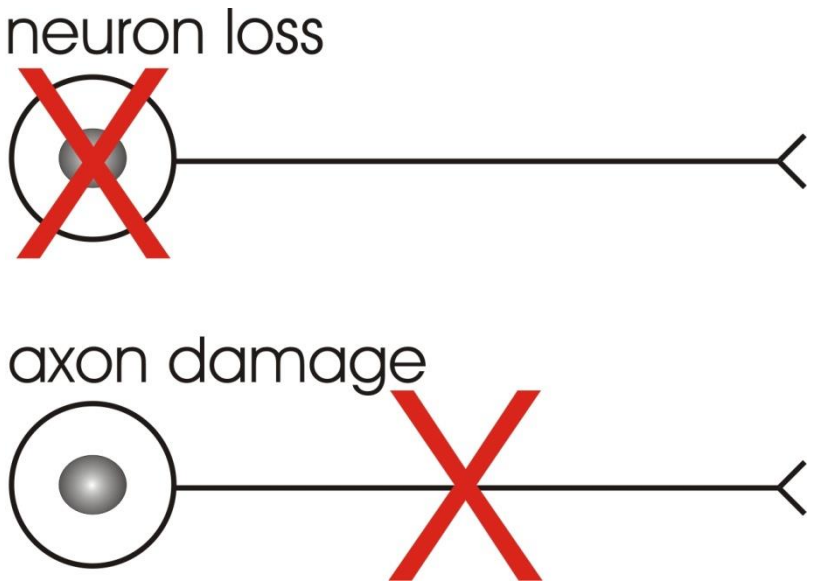
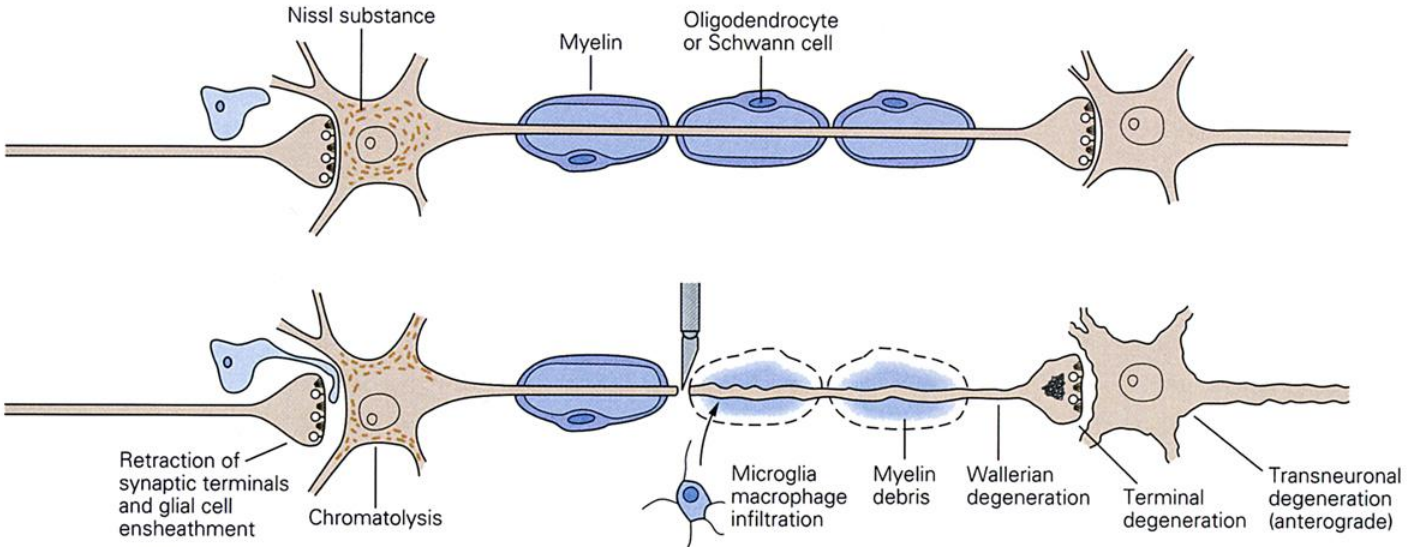
Reaction to Injury & Regeneration

Steven McLoon
Department of Neuroscience
University of Minnesota

The adult central nervous system has the lowest regenerative capacity of all organ systems.


neuron loss
axon damage

Reaction to Axotomy



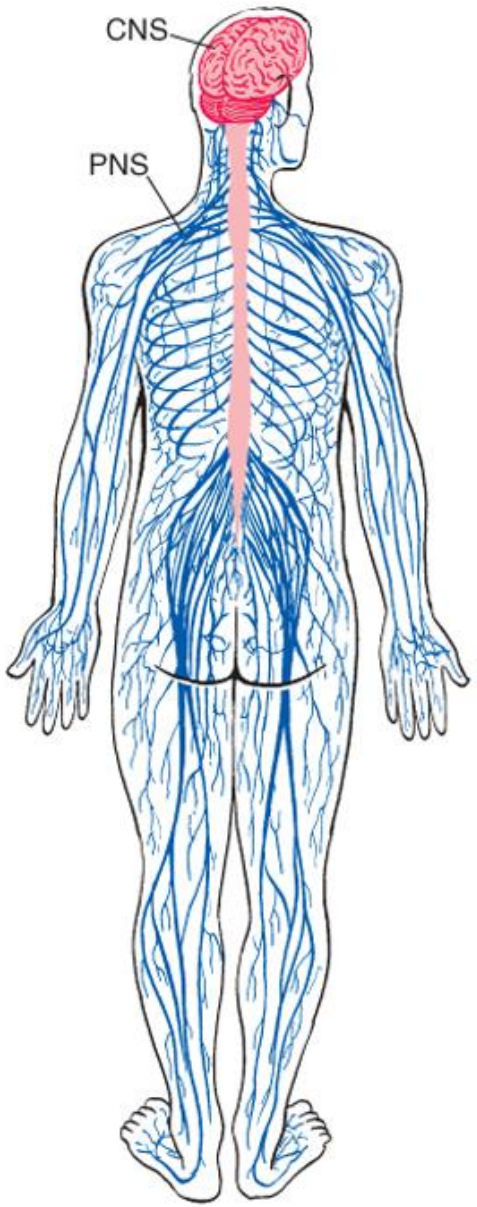
- Function distal to the axon cut is lost. (immediately)

Loss of Function Following Axotomy

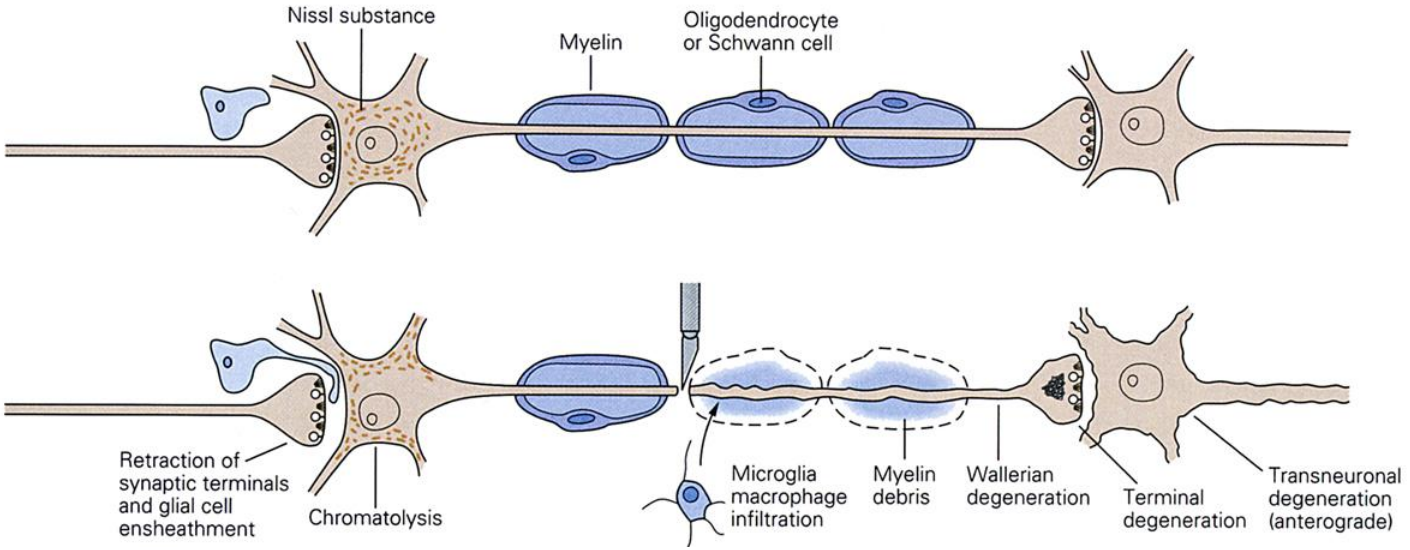
- Spinal cord injury results in a loss of sensation and muscle paralysis below the level of the injury.

  Spinal cord injury can be partial or complete, and the sensory/motor loss is proportional.

- Peripheral nerve injury results in a loss of sensation and muscle paralysis in the areas served by the injured nerve.

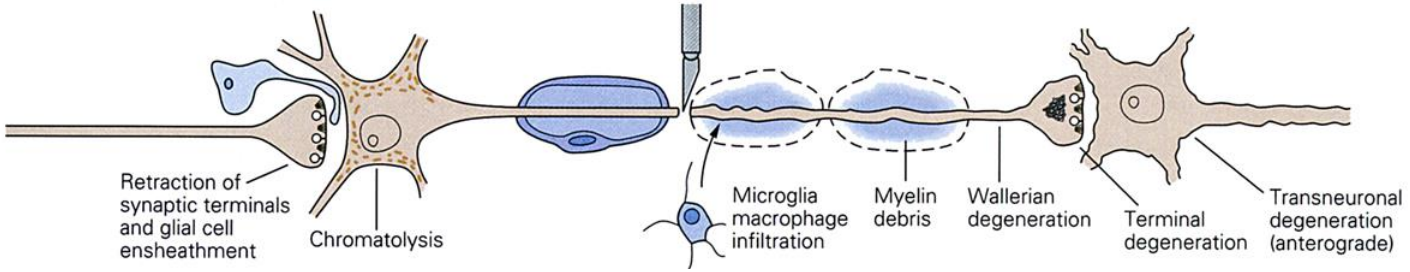


Reaction to Axotomy



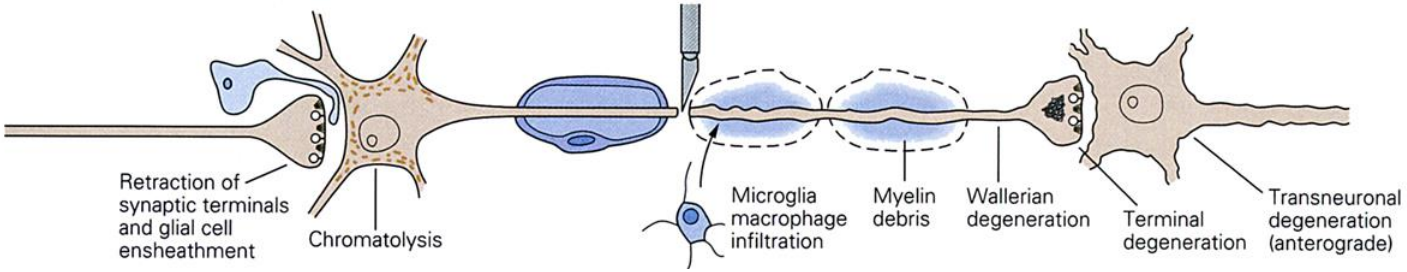
- K^+ leaks out of the cell and Na/Ca^{++} leak into the cell. (within seconds)
- Proximal and distal segments of the axon reseal slightly away from the cut ends. (within 2 hrs)
- Subsequent anterograde & retrograde effects …

Anterograde Effects (Wallerian Degeneration)



- The axon swells. (within 12 hrs)
- The cell membrane begins to fragment. (within 3 days)
- Myelin not associated with a viable axon begins to fragment. (within 1 wk)
- Astrocytes or Schwann cells proliferate (within 1 wk), which can continue for over a month.
- Glia and microglia phagocytize debris. (1 month in PNS; >3 months in CNS)

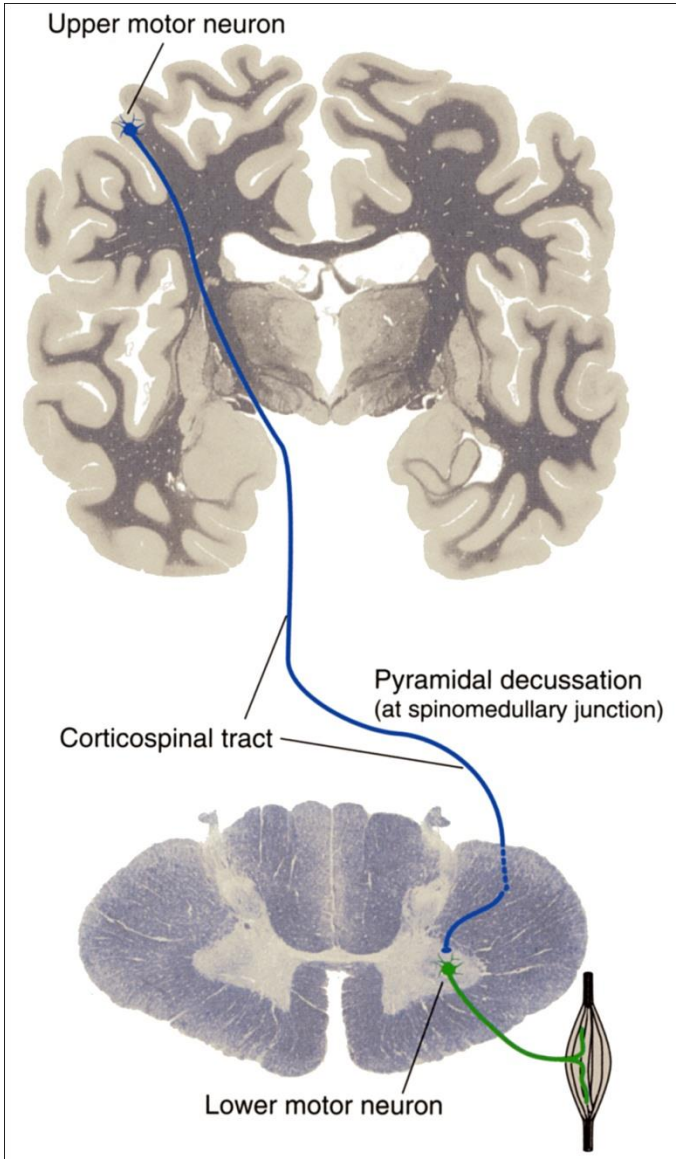
Transneuronal Effects



- In the absence of presynaptic innervataion, some neurons die; effect varies depending on the presence of other connections and age.
- Muscle atrophies with the loss of neuronal innervations:
  - As injured motor axons degenerate, action potentials are spontaneously initiated causing contractions of the muscle.
  - Once the axon has degenerated, muscle undergoes denervation atrophy.

Effects of Upper vrs. Lower Motor Neuron Loss on Muscle

Denervation atrophy is more rapid and more pronounced than the atrophy associated with disuse or with loss of innervation to the spinal motor neuron from upper motor neurons.



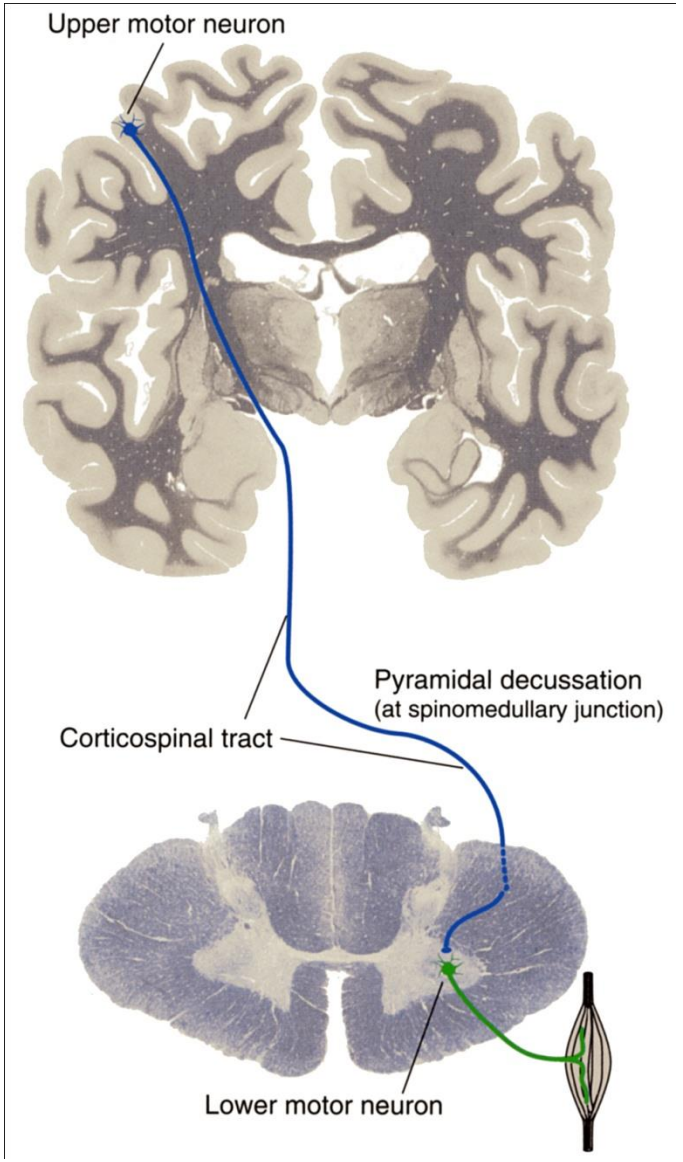
Effects of Upper vrs. Lower Motor Neuron Loss on Muscle

upper motor neuron loss (CNS):

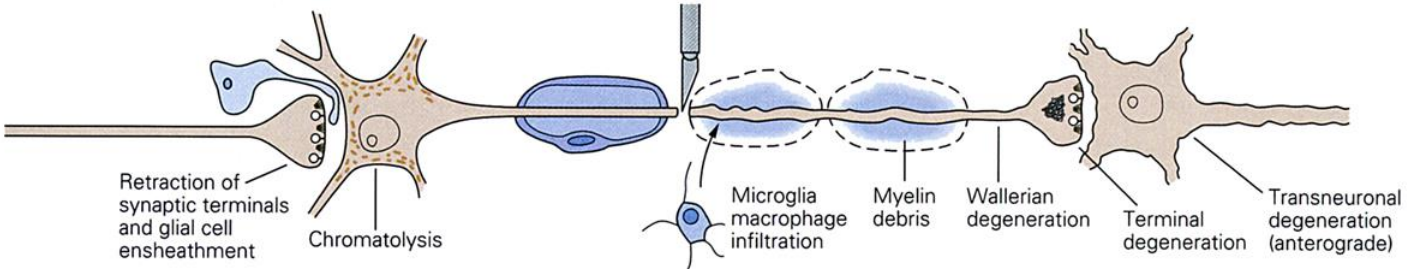
- slow & mild atrophy

lower motor neuron loss (PNS):

- rapid & sever atrophy



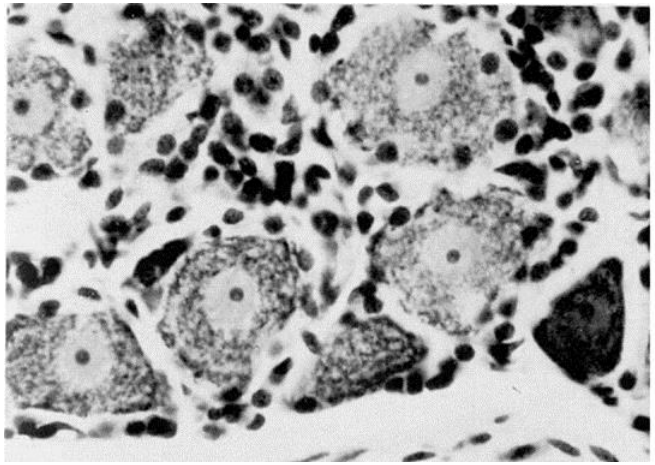
Retrograde Response to Axotomy (Axon Reaction)

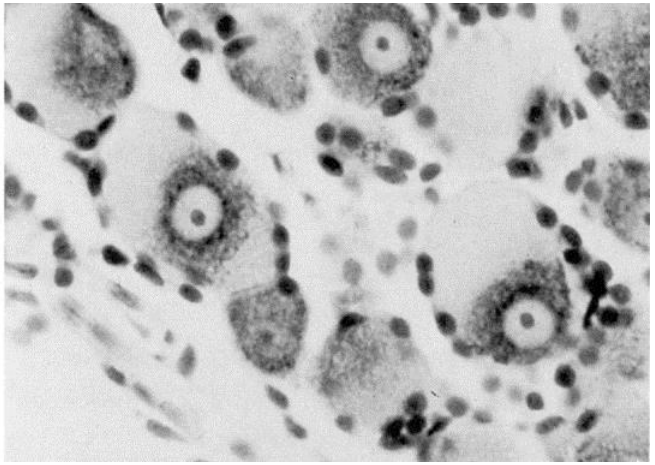


- Loss of neurotrophin supply from the target cells initiates changes in the soma. (within 2-3 days depending on the distance between the injury and the soma)

  Brain Derived Neurotrophic Factor (BDNF) is the main neurotrophin in the CNS.

Retrograde Response to Axotomy (Axon Reaction)

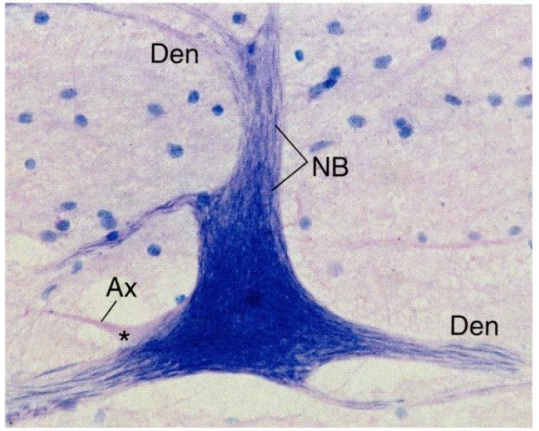




- The soma undergoes chromatolysis: loss of rER, soma swells, nucleus moves eccentric. (within 3 days)
- The cell down-regulates expression of molecules required for neuronal communication (e.g. neuro-transmitters) and up-regulates synthesis of molecules needed for axon growth.
- The axon begins to regrow (regenerate) from its cut end. (1-2 wks)

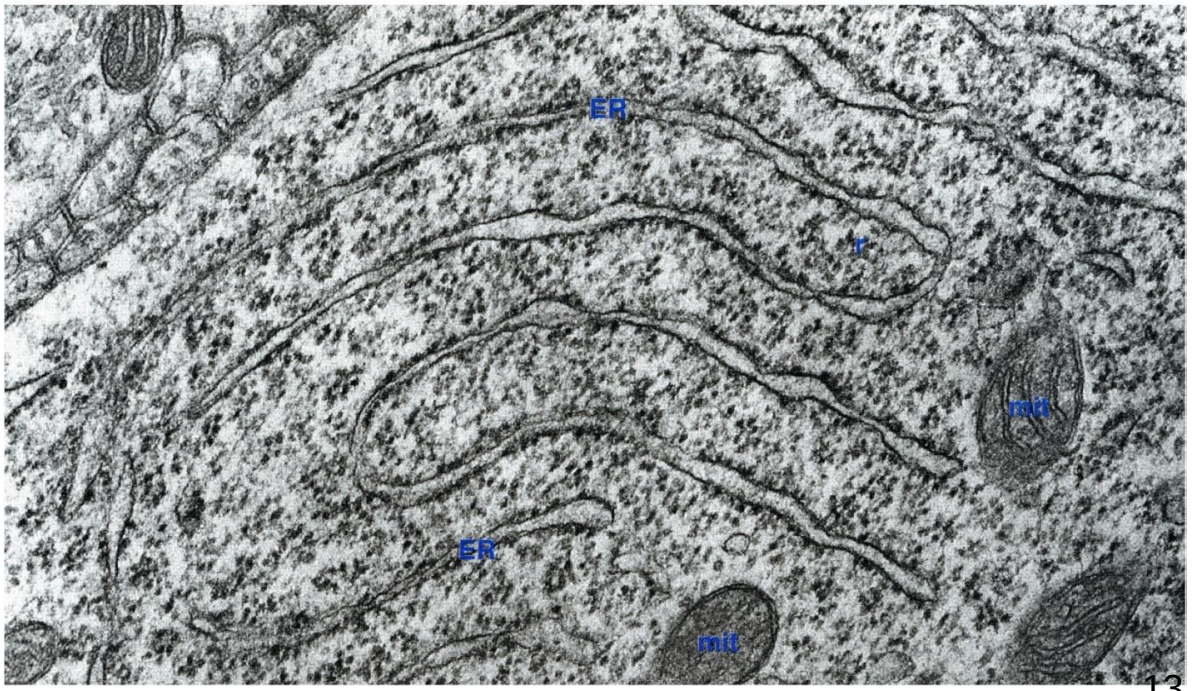
Organelles of Cells

- Neurons have large amounts of rough endoplasmic reticulum in their somas, which we call Nissl substance.



- Nissl substance is readily seen by microscopy.

- Most proteins and other molecules needed by neurons are synthesized in the soma.



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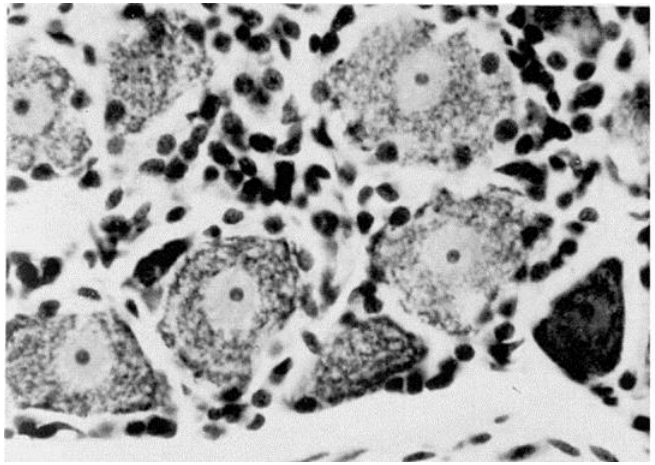

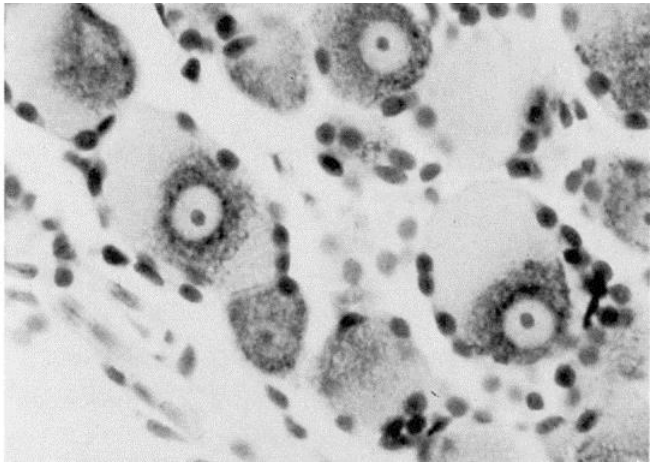

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Axons in the PNS regenerate.

- Axons grow 2-4 mm/day; 1.5 mm/day used clinically to estimate time to recovery of function.
- Axons grow within the connective tissue sheath along channels formed by Schwann cells.
- Optimal regeneration requires the nerve sheath to be intact; ends of a cut nerve can be connected surgically with sutures in the connective tissue sheath.
- Axons that grow outside of the sheath can form painful neuromas.

Axons in the PNS regenerate.

- Regenerating axons form synapses at original synaptic sites.
- Sensory axons will reinnervate their original territory and may displace axons that had invaded its territory.
- Once synapses are reestablished, gene expression in the neuron switches to a mode needed for neurochemical communication.
- The myelin sheath is eventually reestablished.

Axons in the PNS regenerate.

- Regeneration is never perfect:
  - strength & dexterity is reduced
  - sensory discrimination is poor
  - motor units are larger than normal
  - conduction velocity is 80% of normal

- Regeneration is probably most important for continually making repairs due to minor traumas.

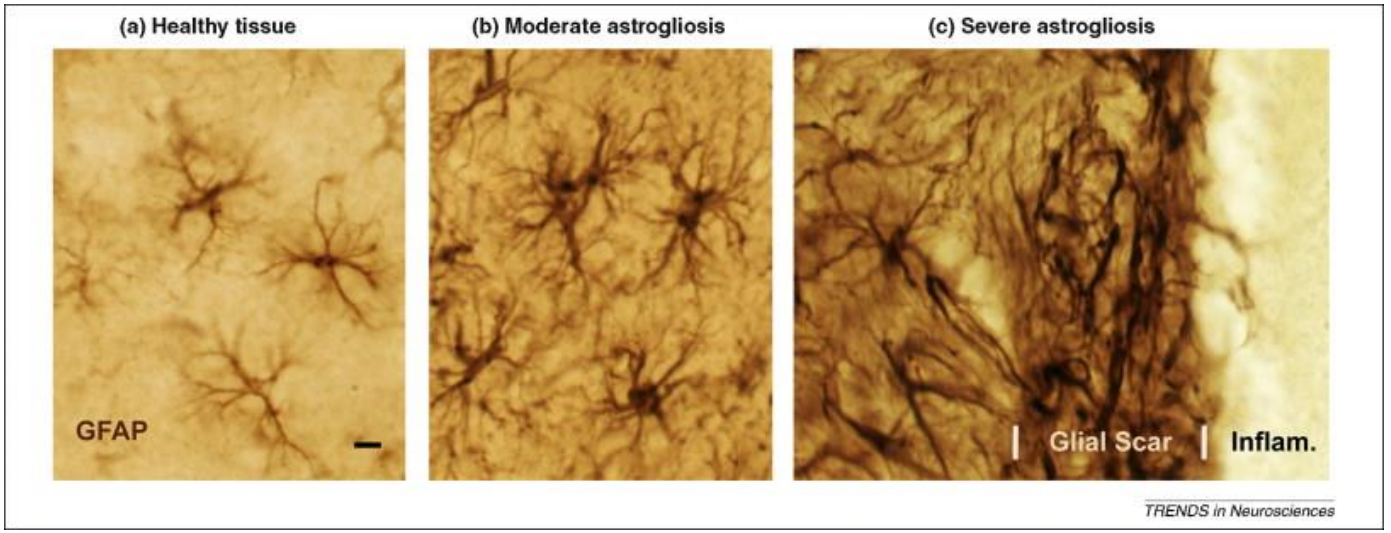
Axons in the CNS fail to regenerate.

- Axons begin to regenerate in the injured CNS, but make little progress and abort further growth after a month or more.

Axons in the CNS fail to regenerate.

- Research on the failure of axons to regenerate in the adult CNS has focused on three main issues:
  - Glial scar
  - Myelin inhibitory molecules
  - Intrinsic inability of mature CNS neurons to grow axons

Axons in the CNS fail to regenerate.
Glial Scar



- Astrocytes around an injury site in the CNS form a 'glial scar':
  - A glial scar includes a thick layer of parallel processes of the astrocytes and deposits of certain molecules that inhibit axon growth.

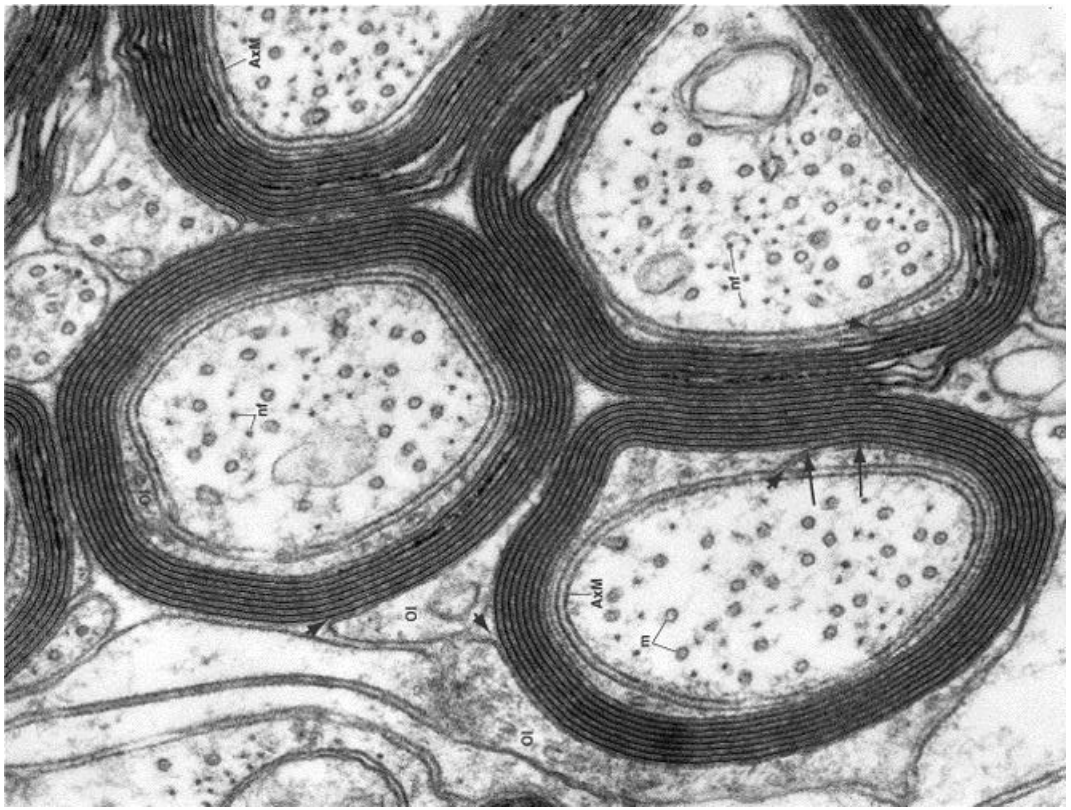
Axons in the CNS fail to regenerate.
Myelin Inhibitory Molecules

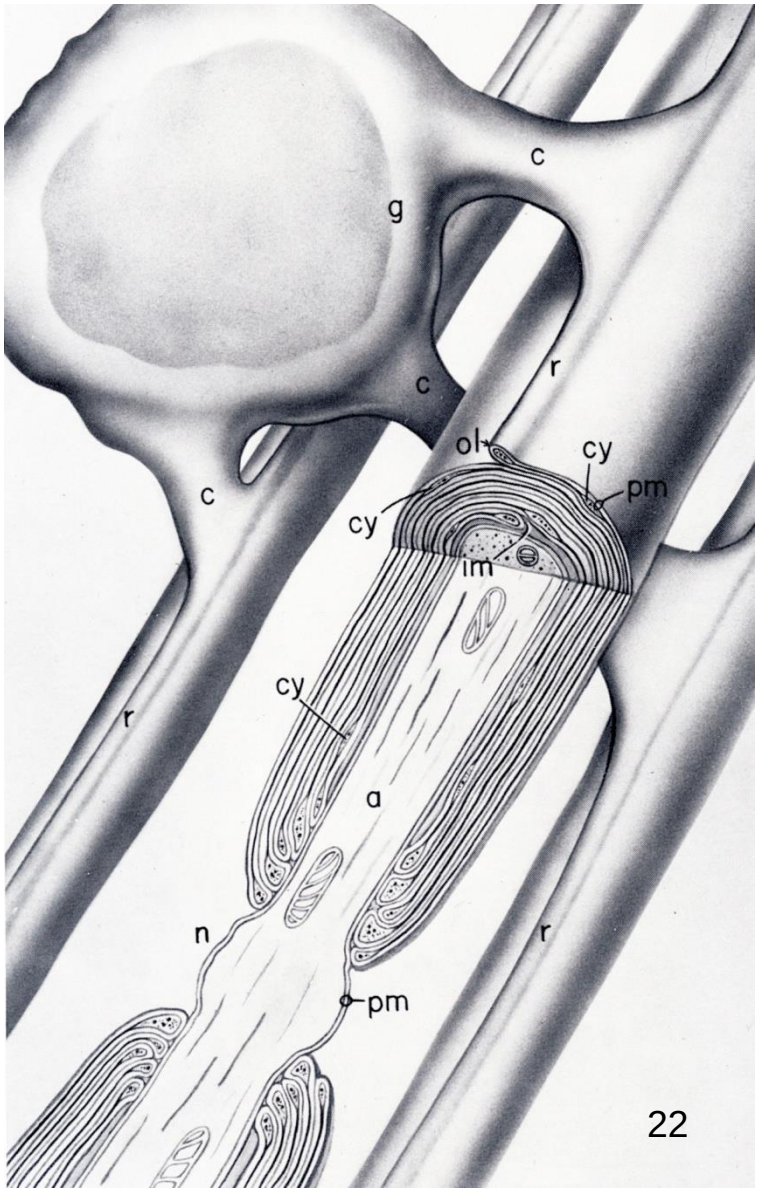
- Adult CNS myelin has molecules that inhibits axon growth:
  - CNS axons can regenerate through a peripheral nerve.
  - PNS or CNS axons cannot regenerate through an optic nerve.

Myelin

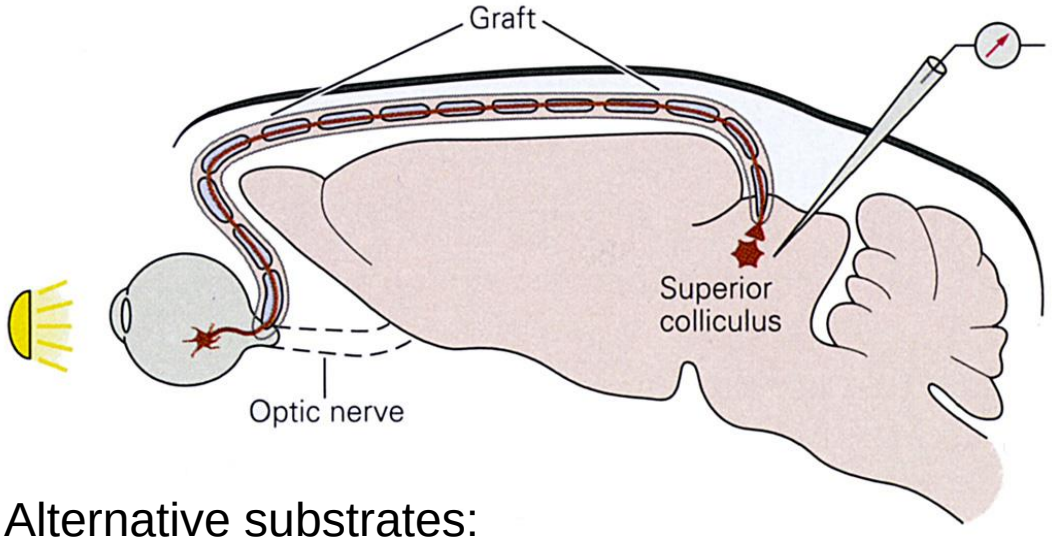
Myelin is formed by glial cells wrapping their membranes around an axon:

- Schwann cells in the PNS.
- Oligodendrocytes in the CNS.





Axons in the CNS fail to regenerate.
Myelin Inhibitory Molecules

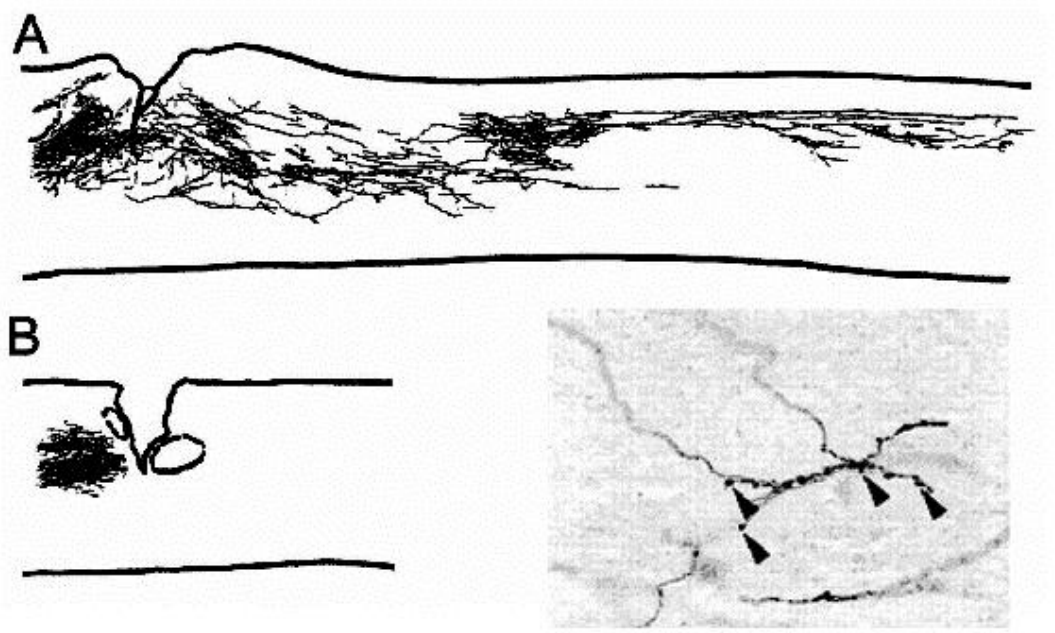


- Alternative substrates:
  - A peripheral nerve bridge can serve as a substrate for axon regeneration. However, axons stop growing once they reenter the CNS.
  - Transplanting Schwann cells into the spinal cord can promote axon regeneration following injury.
  - In the best cases, only 10% of the axons regenerate.

Axons in the CNS fail to regenerate.
Myelin Inhibitory Molecules

- CNS myelin includes several molecules that are known to inhibit axon growth including Nogo and Myelin-associated glycoprotein (MAG).

Axons in the CNS fail to regenerate.
Myelin Inhibitory Molecules



- Infusion of function blocking antibodies to Nogo into damaged rat spinal cord allowed regeneration of some corticospinal axons over 9mm beyond the site of injury.
- 9mm is not very far, and very few axons regenerated.

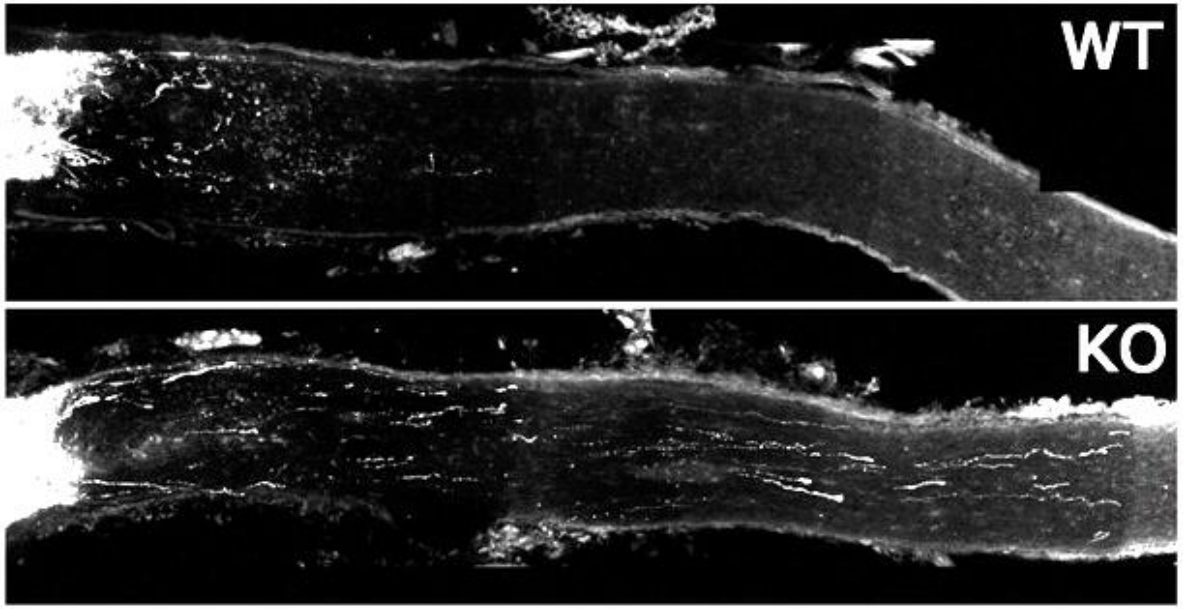
Axons in the CNS fail to regenerate.
Myelin Inhibitory Molecules

- Clinical trials are underway testing antibodies to Nogo for treatment of spinal cord injury in humans.

Axons in the CNS fail to regenerate.
Intrinsic Limitation

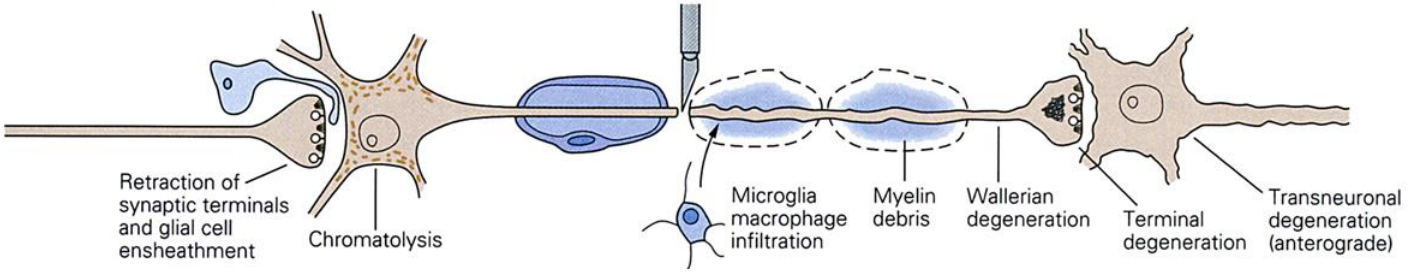
- The intrinsic nature of mature CNS neurons limits their ability to regenerate an axon:
  - PNS axons regenerate better than CNS axons through a peripheral nerve.
  - Developing CNS neurons lose the ability to regenerate an axon in tissue culture as they mature.
  - Mature CNS neurons express, Klf4, a transcription factor that blocks the ability of the cell to express molecules needed for axon growth.

Axons in the CNS fail to regenerate.
Intrinsic Limitation



- Adult retinal ganglion cells in which the Klf4 gene was eliminated were able to regenerate axons in the optic nerve past the injury site (in laboratory mice).

Axotomy Induced Cell Death



- Axotomy near the soma is likely to result in cell death.
- Young neurons are more likely to undergo cell death in response to axotomy regardless of the position of the axotomy.
- In the adult, neurons may die but are more likely to atrophy if regeneration fails.