

Reaction to Injury & Regeneration

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Houses Stark, Lannister, Baratheon, Tyrell, Targaryen, etc.

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Possible GOT spoilers ahead if you aren't caught up with the show....

Yes I'm that person....

But also, hello, we're on the last season, plz get with the program.

INJURY AND REGENERATION

There are a lot of players, it's confusing!



PNS



Wallerian

Glia

Myelin

axon



soma

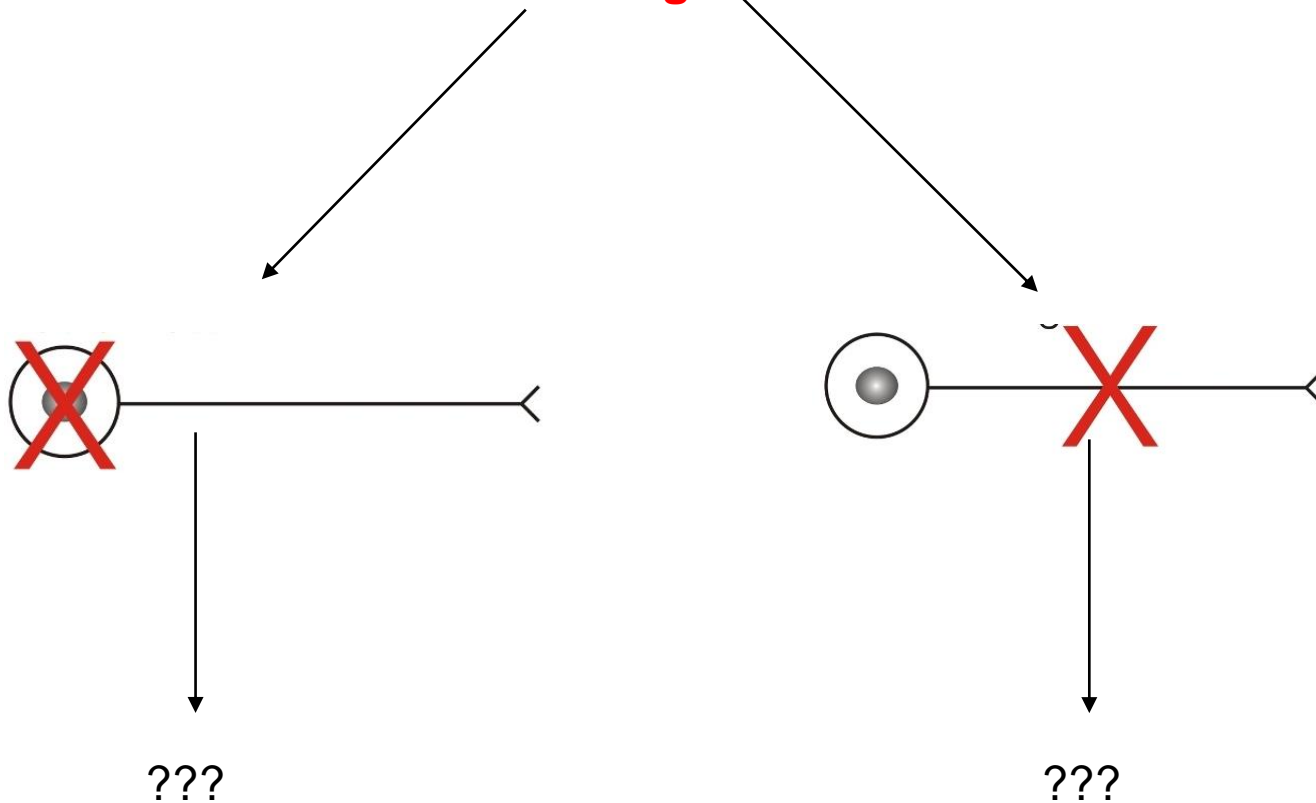


Chromatolysis

CNS

So, let's make a flow chart! With tablemates, compare what happens to the cell with loss of the soma versus axon damage.

Season 1: Is the cell damaged at the soma or the axon?



Season 1: Is the cell damaged at the soma or the axon?



Neuronal death



Well, that depends...
Let's find out!



Even though the cell dies with soma loss, at least the soma can still update its twitter account!



The image shows a Twitter profile card for a user named "Eddard Stark's Head". The profile picture is a circular image of a decapitated head with long brown hair, set against a white background. The header of the profile is a solid blue bar. To the right of the profile picture is a "Follow" button. Below the profile picture, the name "Eddard Stark's Head" is displayed in bold, followed by the handle "@HeddardStark". The bio reads: "His Lord of Winterfell's decapitated head, Eddard Stark. It's not so bad up here... Not affiliated with HBO or Game of Thrones just a head with something to say". Below the bio, there is a location tag "A pike in King's Landing" and a join date "Joined May 2012". At the bottom of the profile card, it shows "74 Following" and "45 Followers". Below the profile card, there are four tabs: "Tweets", "Tweets & replies", "Media", and "Likes". The "Tweets" tab is selected. Below the tabs, a tweet is visible, posted by "Eddard Stark's Head @HeddardStark" on "Mar 24, 2013". The tweet text is "Game of Thrones spin off idea: The Real Housewives of Westeros. Feat.: Catelyn, Lysa, Cersei and Daenerys. #GameofThrones 🏰 #GoT 🏰". Below the tweet text are icons for replies, retweets (with a count of 1), likes, and share.

Eddard Stark's Head
@HeddardStark

His Lord of Winterfell's decapitated head, Eddard Stark. It's not so bad up here... Not affiliated with HBO or Game of Thrones just a head with something to say

📍 A pike in King's Landing 📅 Joined May 2012

74 Following 45 Followers

Tweets Tweets & replies Media Likes

Eddard Stark's Head @HeddardStark · Mar 24, 2013

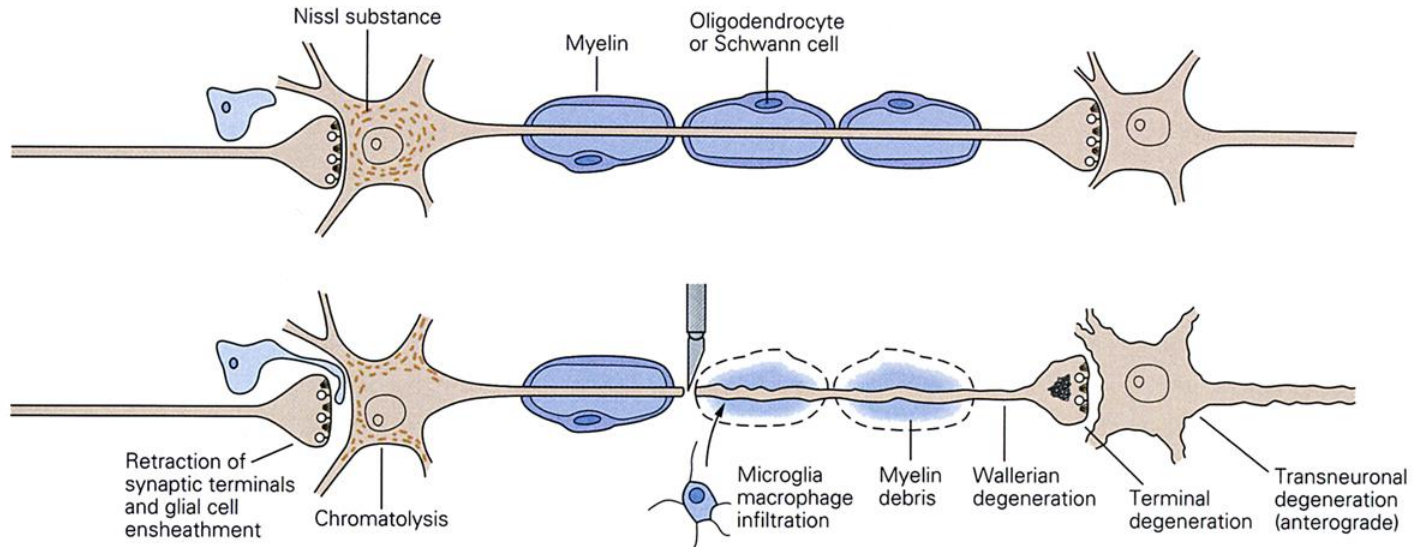
Game of Thrones spin off idea: The Real Housewives of Westeros. Feat.: Catelyn, Lysa, Cersei and Daenerys. #GameofThrones 🏰 #GoT 🏰

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- Following axotomy, what effects occur within 2 hours?

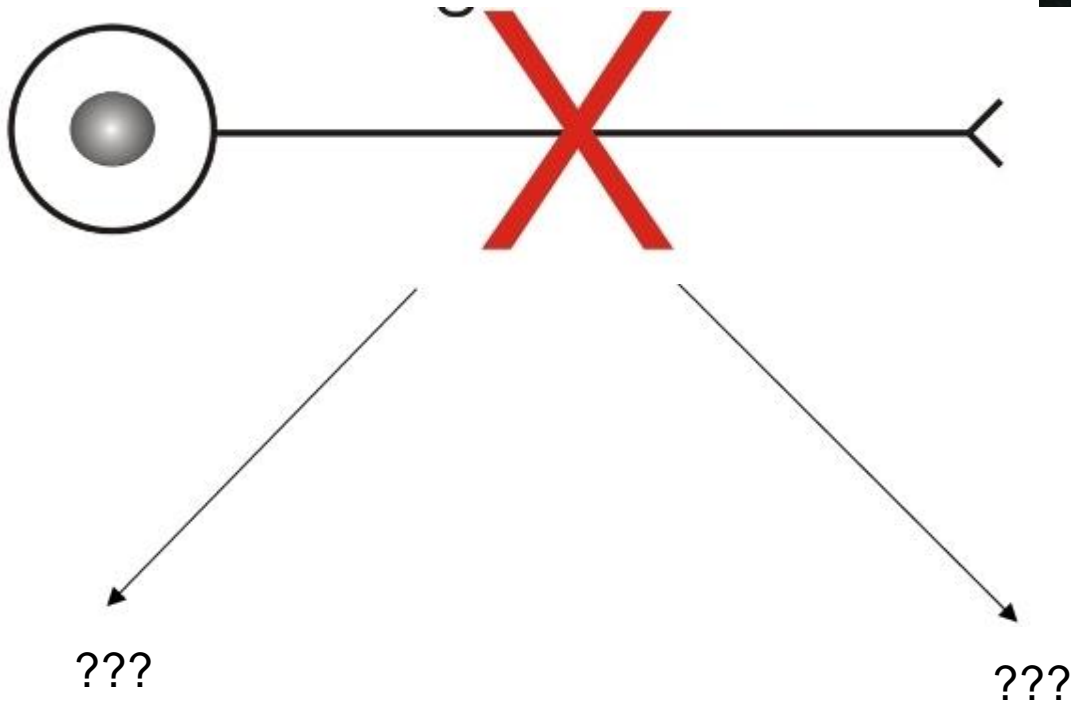
(Discuss with your tablemates.)

Reaction to Axotomy

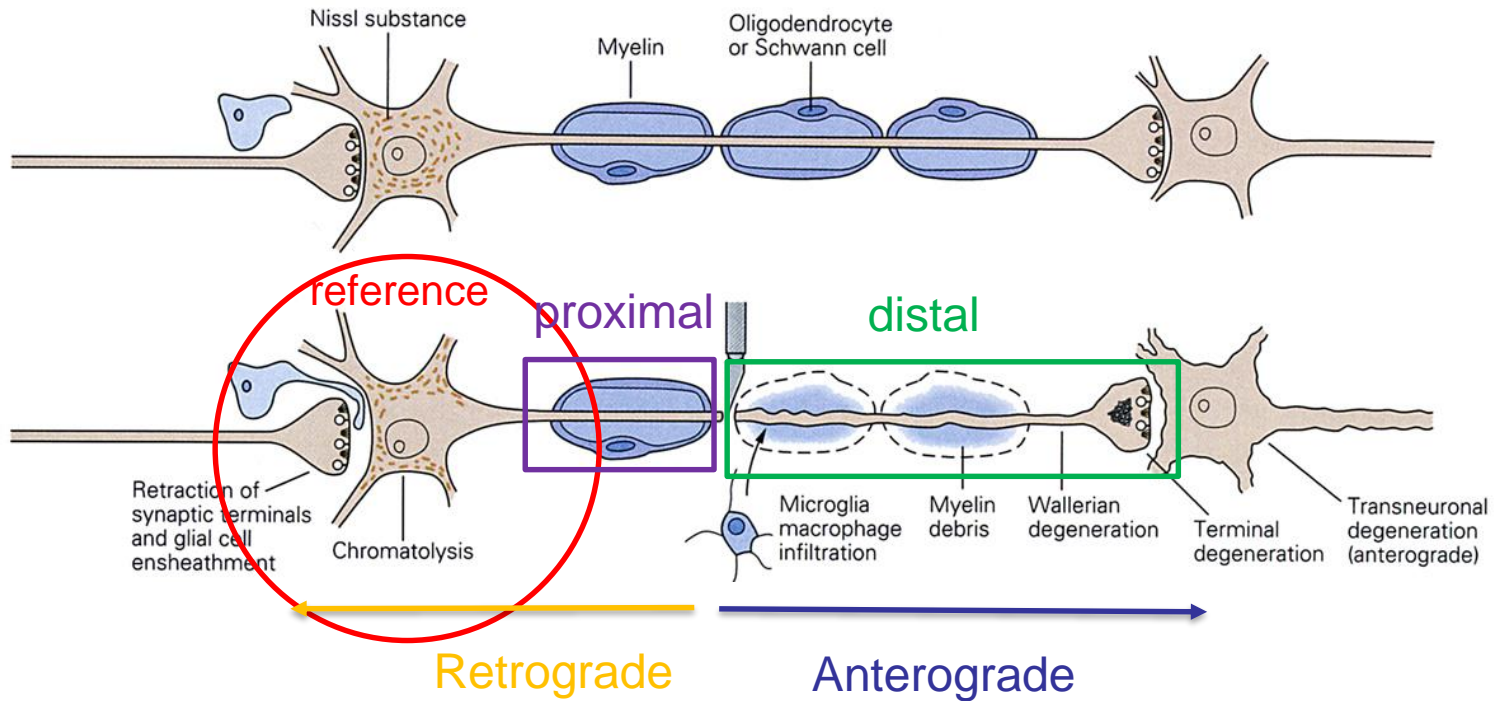


- Function distal to the axon cut is lost. (immediately)
- K^+ leaks out of the cell and Na/Ca^{++} leak into the cell. (within seconds)
- Proximal and distal segments of the axon reseal slightly away from the cut ends. (within 2 hrs)
- Subsequent anterograde & retrograde effects ...

Season 2: With tablemates, compare and contrast anterograde and retrograde effects of axotomy.

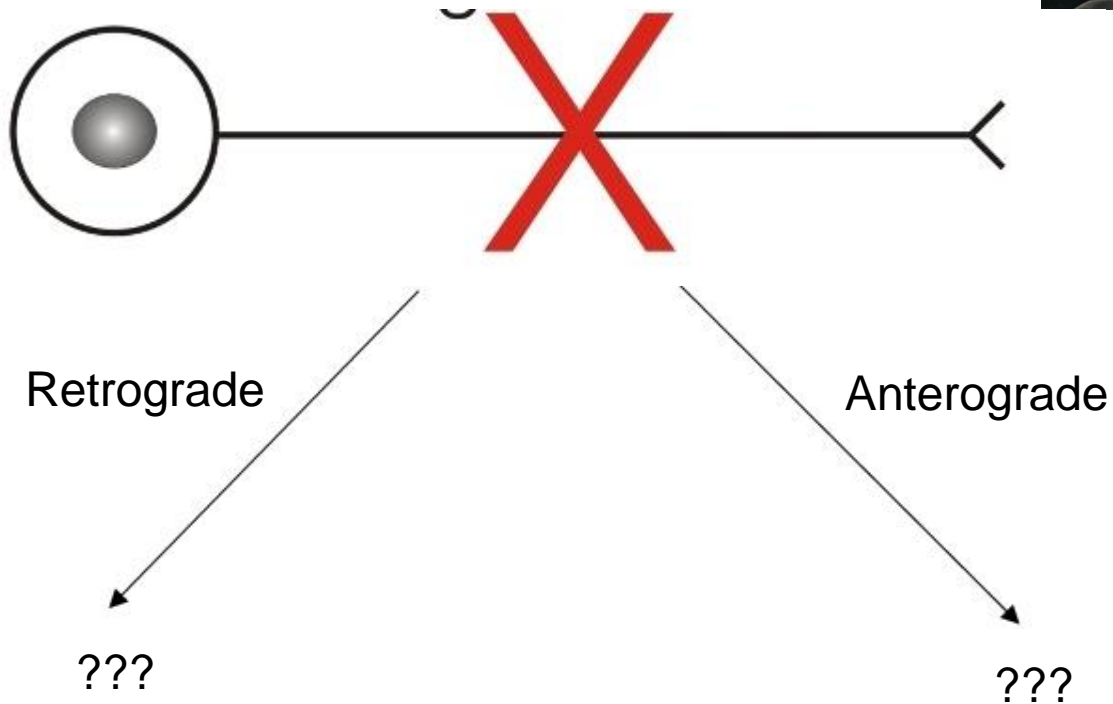


BUT FIRST--- let's review the definitions of proximal/distal, anterograde/retrograde.



- Proximal= close.
- Distal= far.
- Our reference point on the injured neuron is the cell body. The proximal half of the injured axon is the portion of the axon closest to the cell body of that neuron. The distal half of the injured axon is the portion of the neuron/axon that is farther from the cell body, or separated from the cell body.
- Anterograde= Forward.
- Retrograde= Backward.
- Our reference point is the direction of communication, which typically travels down the axon towards the axon terminal. Anterograde effects occur in the direction of the distal portion of axon, retrograde effects occur in the direction of the proximal portion of axon.

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Retrograde

Anterograde

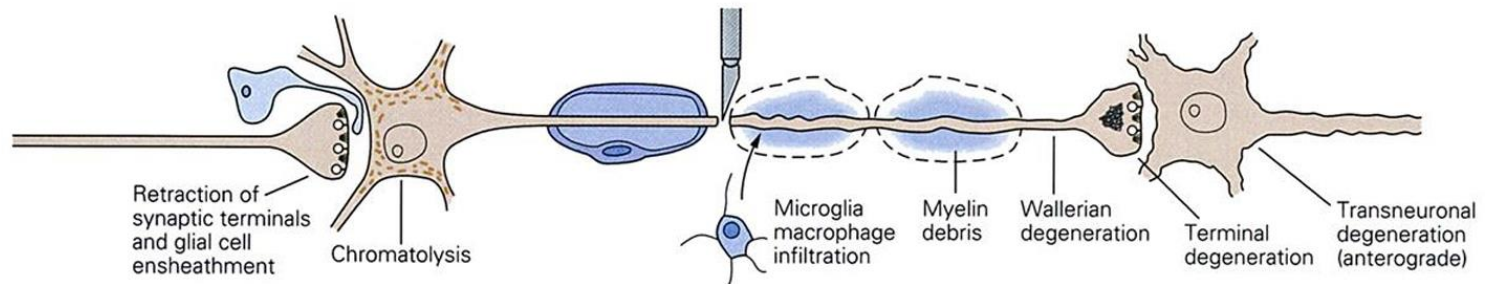
Loss of neurotrophin supply to soma, chromatolysis

Wallerian Degeneration, Denervation and atrophy of the downstream cell



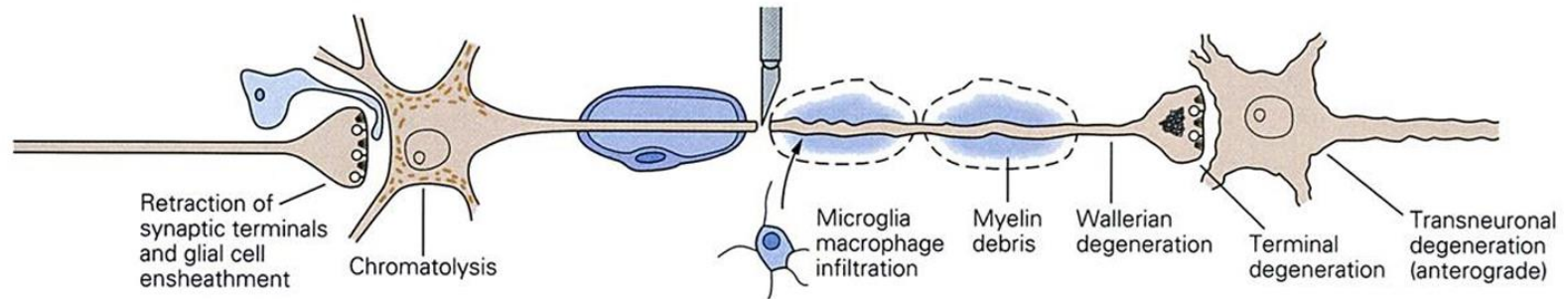
With tablemates,
describe the step by
step process of
Wallerian Degeneration

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 innervation, 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.

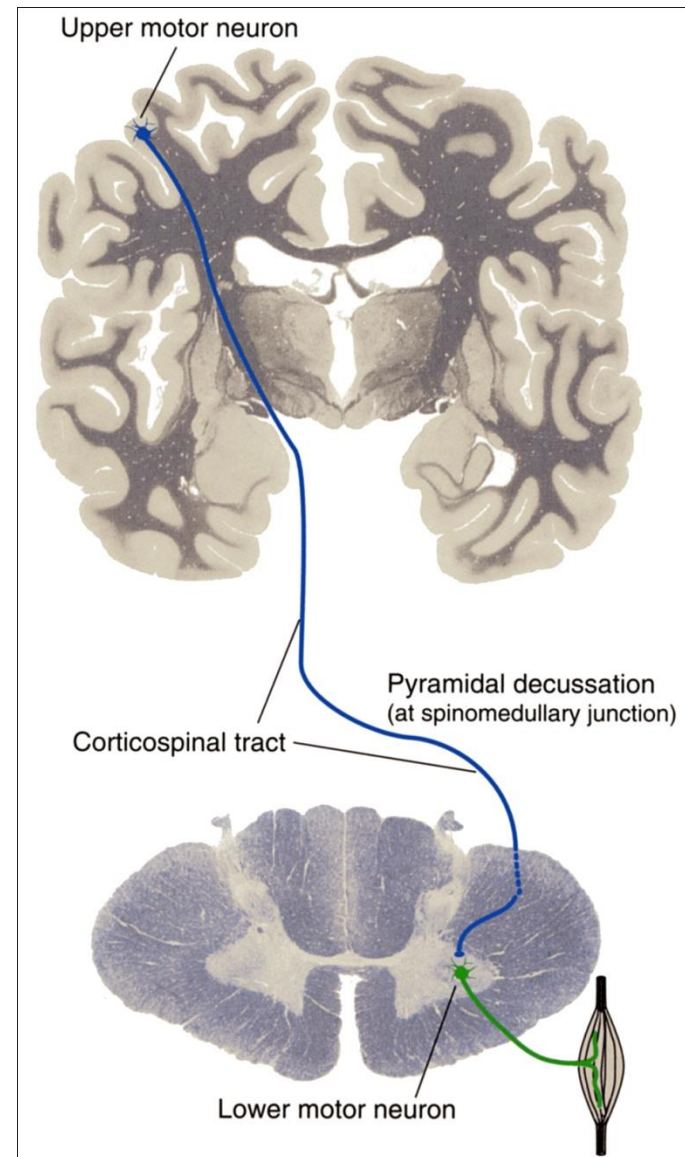
Effects of Upper vrs. Lower Motor Neuron Loss on Muscle

upper motor neuron axotomy (CNS):

- slow & mild muscle atrophy
- axon cannot regenerate

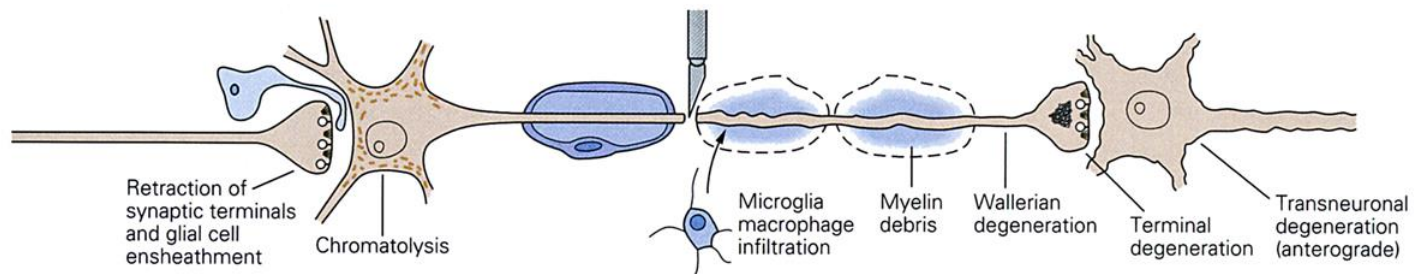
lower motor neuron axotomy (PNS):

- rapid & sever muscle atrophy
- axon can regenerate



With tablemates: with retrograde effects of axotomy, describe the effect of neurotrophin loss and the process that follows.

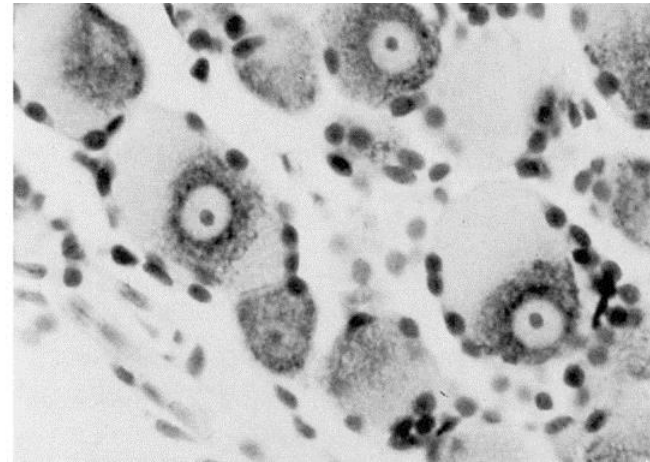
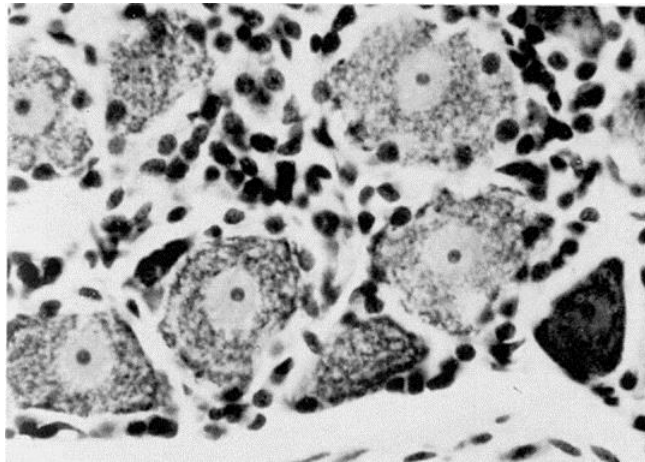
Retrograde Response to Axotomy (Axon Reaction)



- 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)

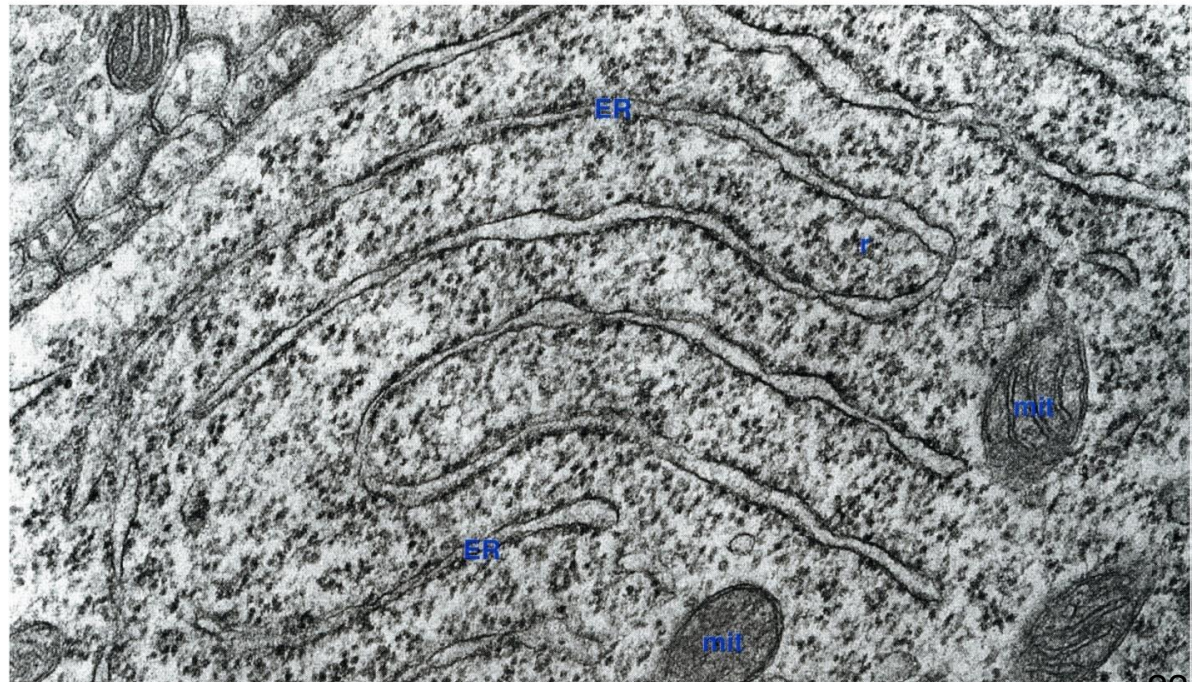
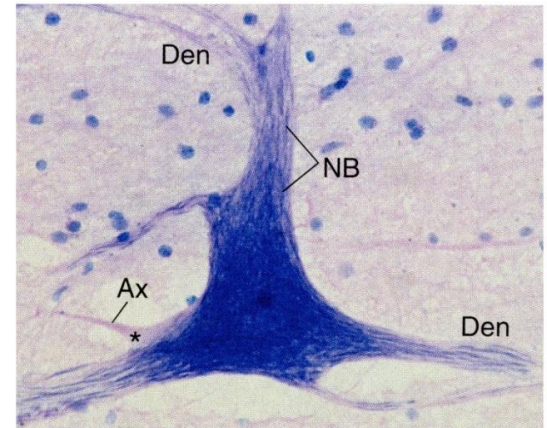


- The soma undergoes chromatolysis: loss of rER, soma swells, nucleus moves eccentric. (within 3 days)
- The cell down-regulates expression of molecules required for neuronal communication (e.g. neurotransmitters) and up-regulates synthesis of molecules needed for axon growth.
- The axon begins to regrow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

With tablemates,
describe why a Nissl
stain would be used to
assess the retrograde
response to axotomy?

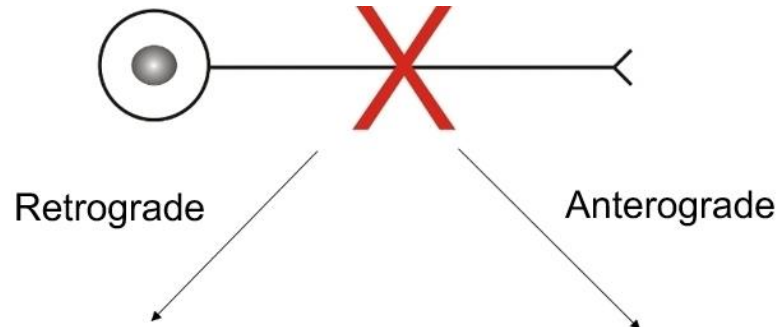
Organelles of Cells

- 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.



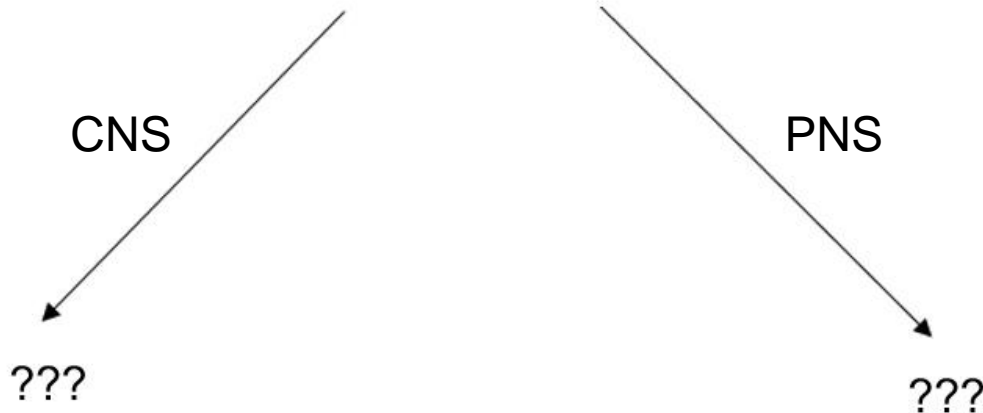


Season 3: With tablemates, compare and contrast axon regeneration in the PNS vs the CNS



Loss of neurotrophin supply to soma, chromatolysis

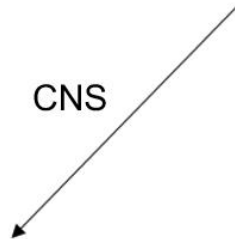
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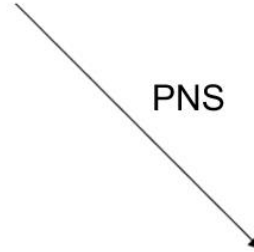
CNS



Axons begin to regrow very slowly, but stop growing after a month or so.



PNS



Axons regrow, synapses are reestablished; however, regeneration is imperfect.



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.



We have hope
for Theon!

- What is the difference between spinal cord injury and sciatic nerve injury on leg muscles?

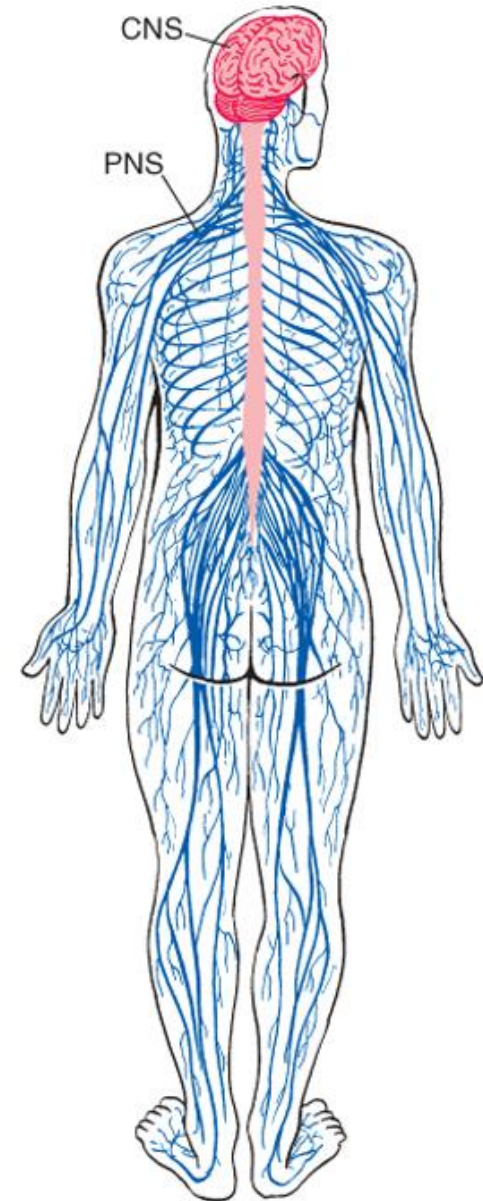
(Discuss with your tablemates.)

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.





Season 4: With tablemates, discuss why CNS axons fail to regenerate.

Loss of neurotrophin supply to soma, chromatolysis

CNS

PNS

Axons begin to regrow very slowly, but stop growing after a month or so.

Axons regrow, synapses are reestablished; however, regeneration is imperfect.

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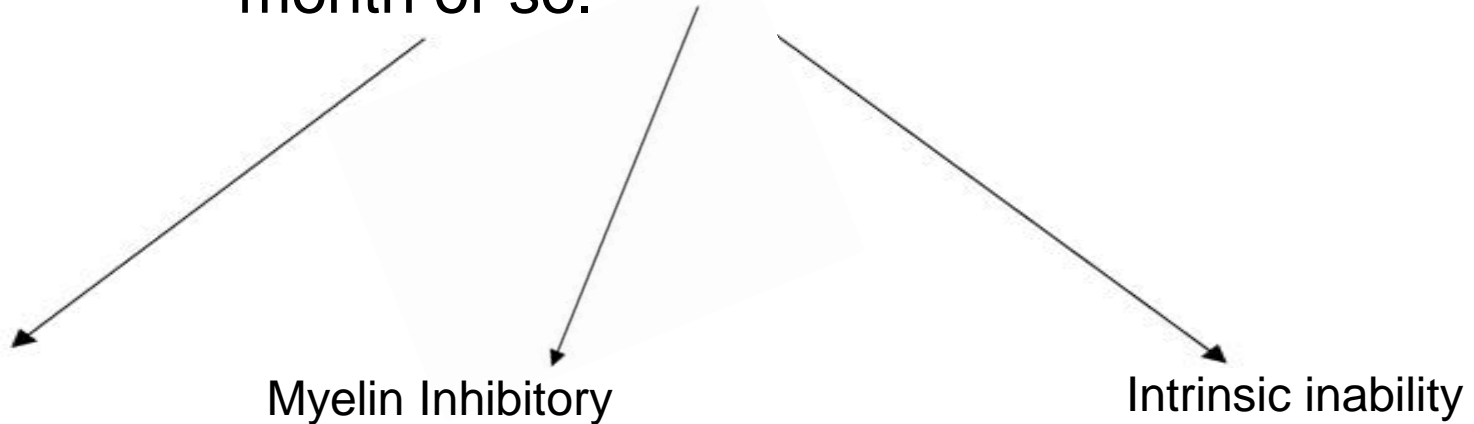
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Season 4: With tablemates, discuss why CNS axons fail to regenerate.

Axons begin to regrow very slowly, but stop growing after a month or so.



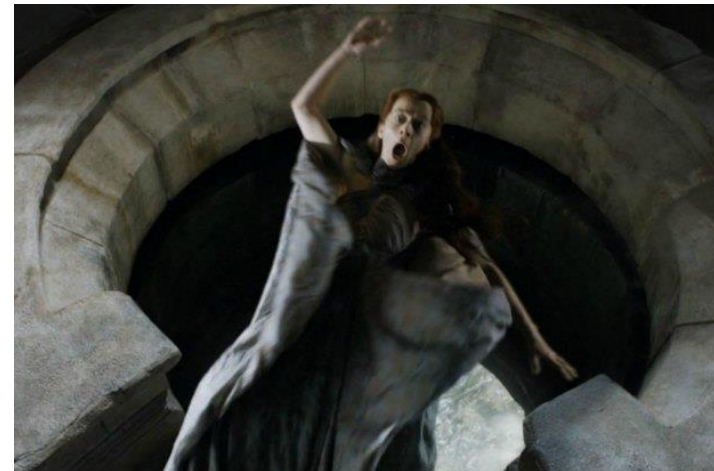
Glial Scar



Myelin Inhibitory Molecules

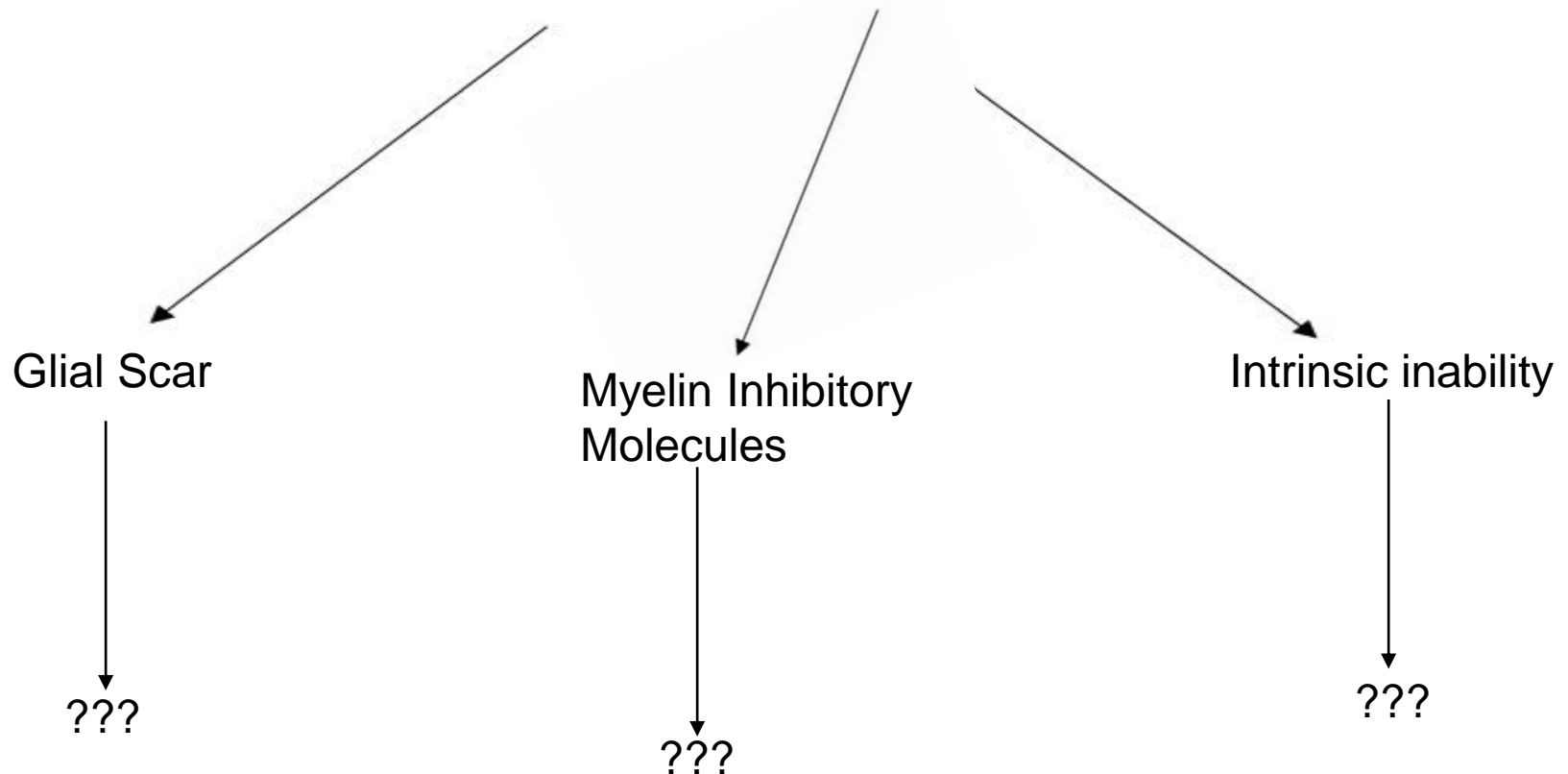


Intrinsic inability



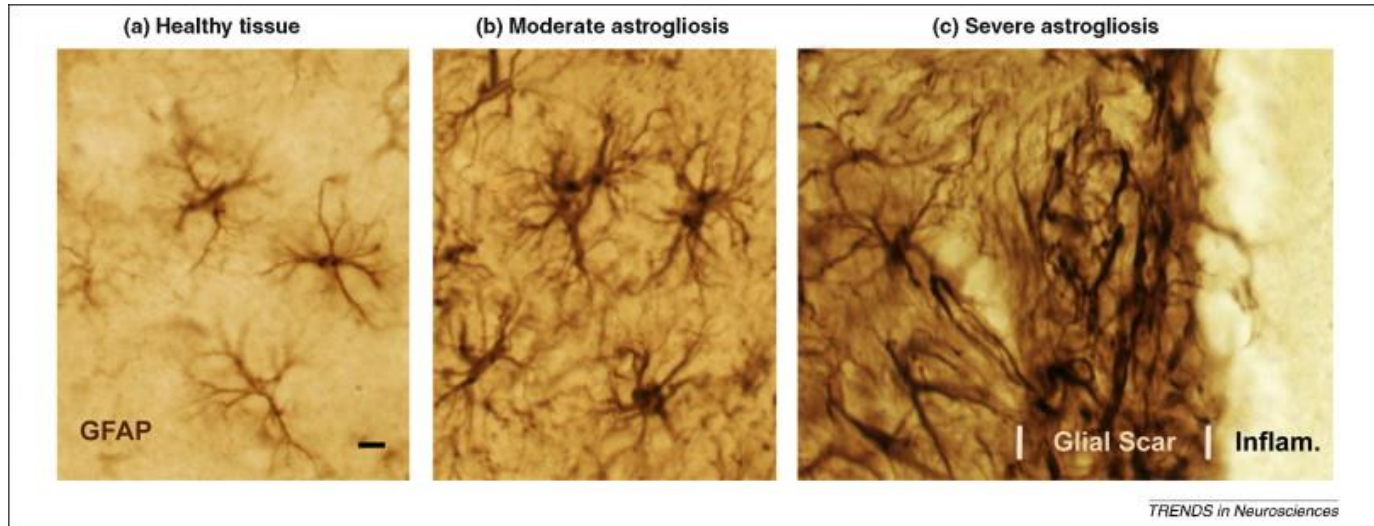
Season 5: With tablemates, further describe why CNS axons fail to regenerate.

Axons begin to regrow very slowly, but stop growing after a month or so.



Axons in the CNS fail to regenerate.

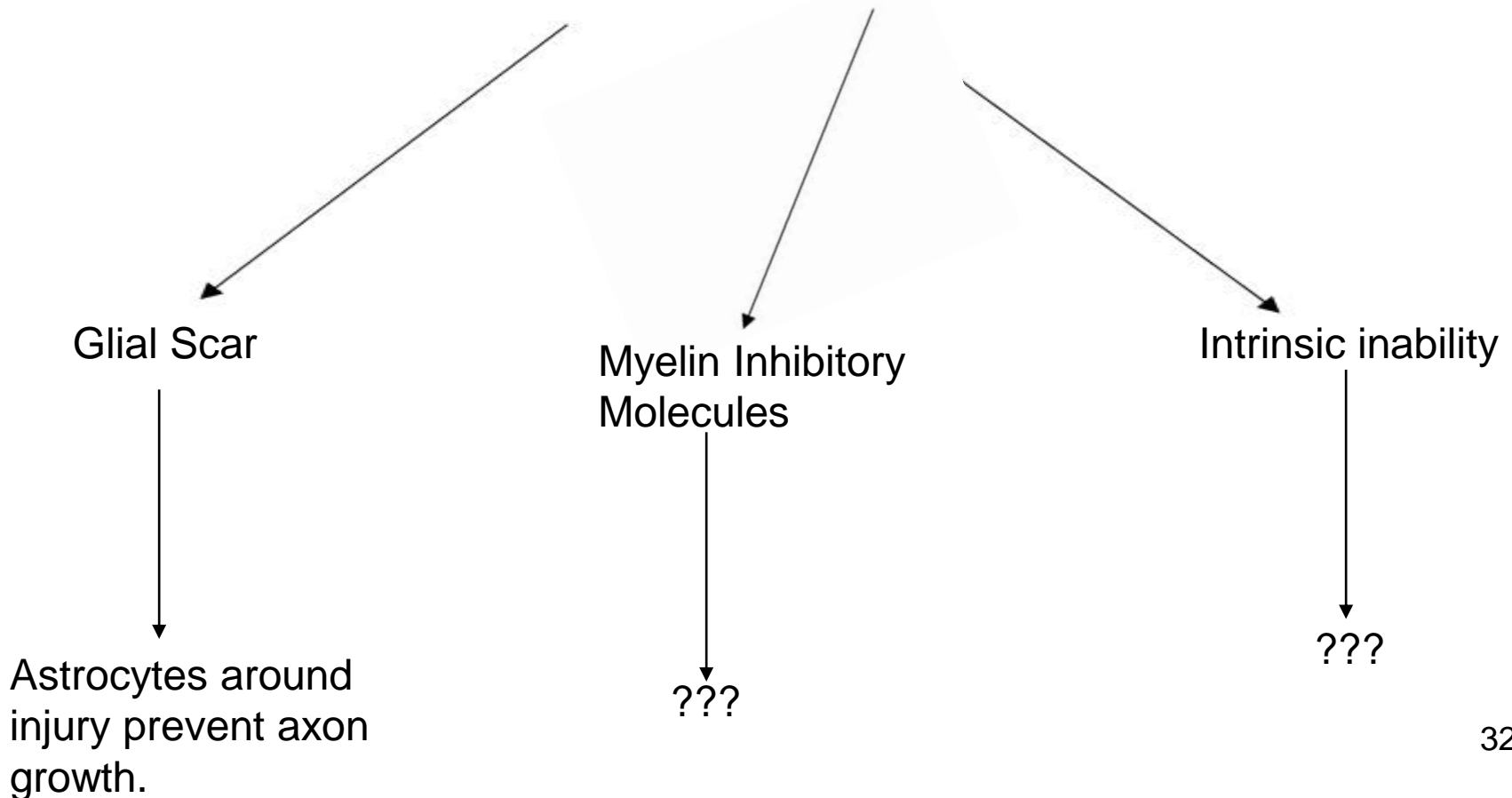
Glial Scar



- 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.

Season 5: With tablemates, further describe why CNS axons fail to regenerate.

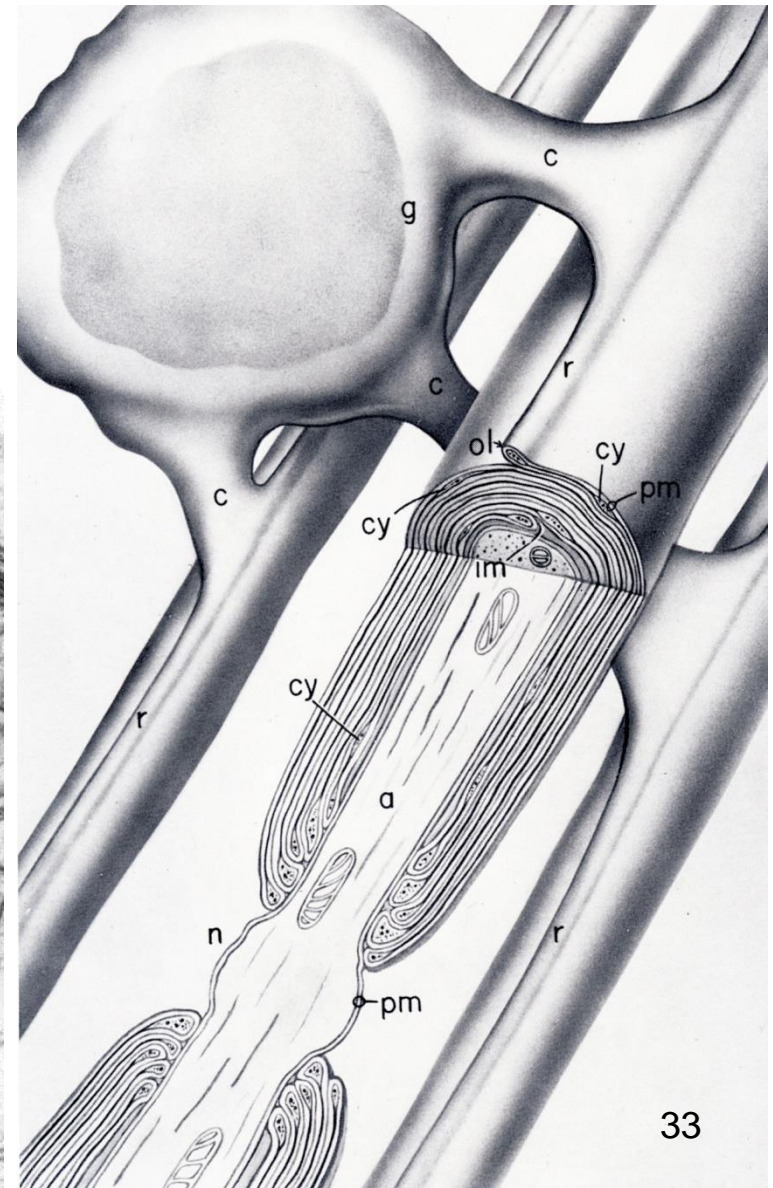
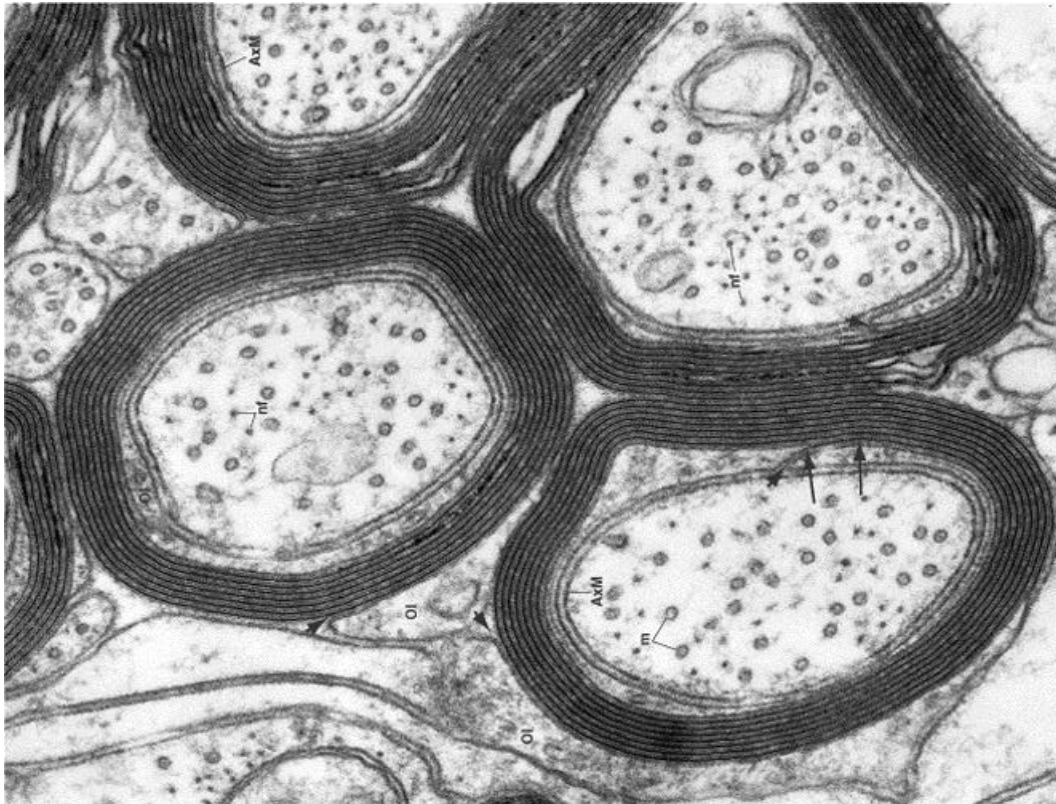
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Myelin

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

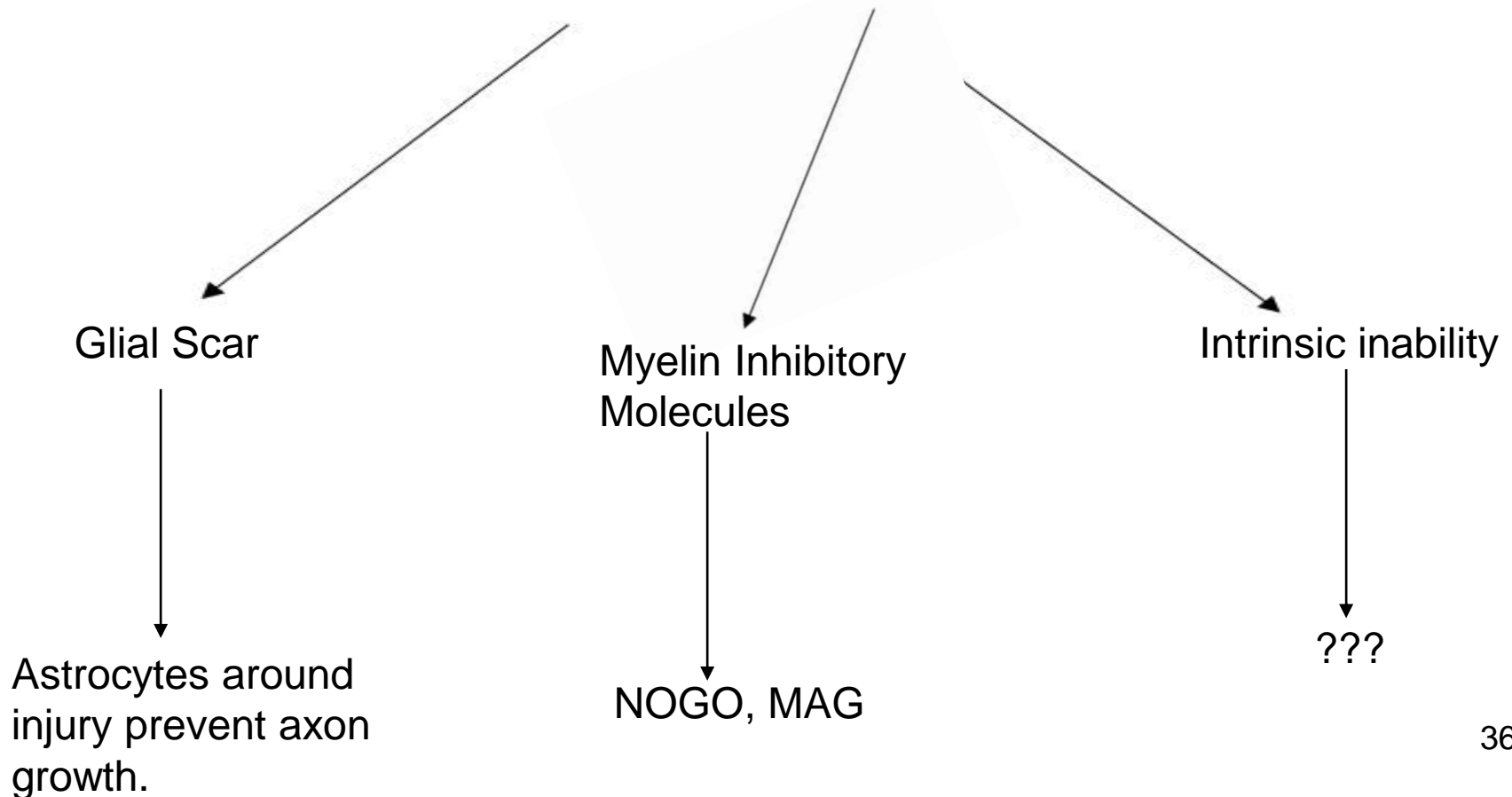
- Adult CNS myelin has molecules that inhibits axon growth:
 - CNS axons can regenerate through a peripheral nerve.
 - PNS or CNS axons cannot regenerate through an optic nerve.

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).

Season 5: With tablemates, further describe why CNS axons fail to regenerate.

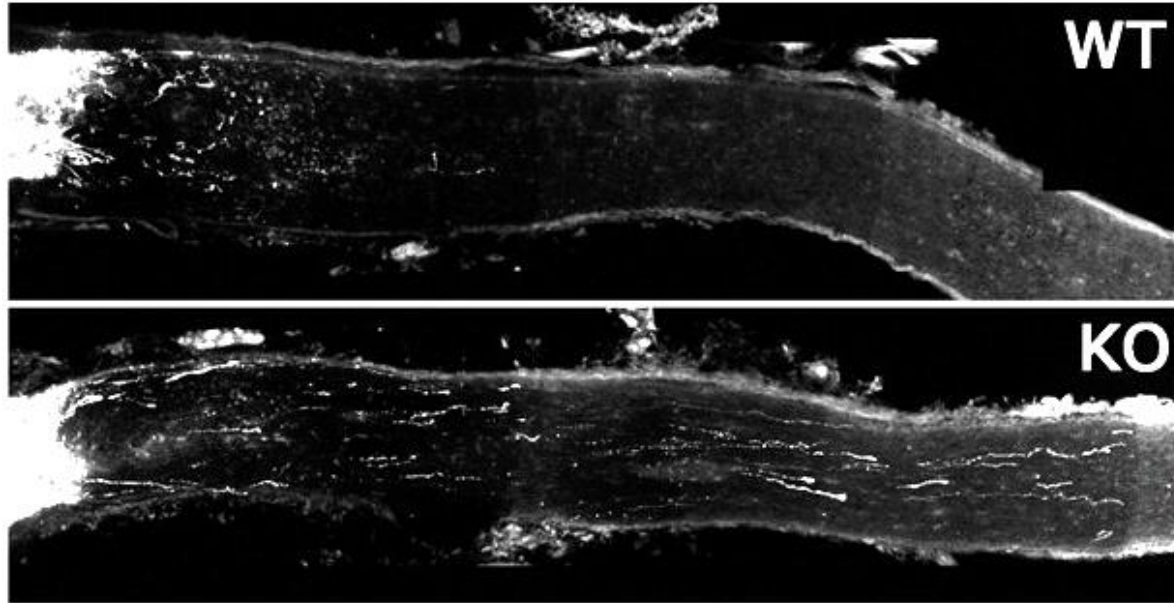
Axons begin to regrow very slowly, but stop growing after a month or so.



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 a transcription factor that blocks the ability of the cell to express molecules needed for axon growth.

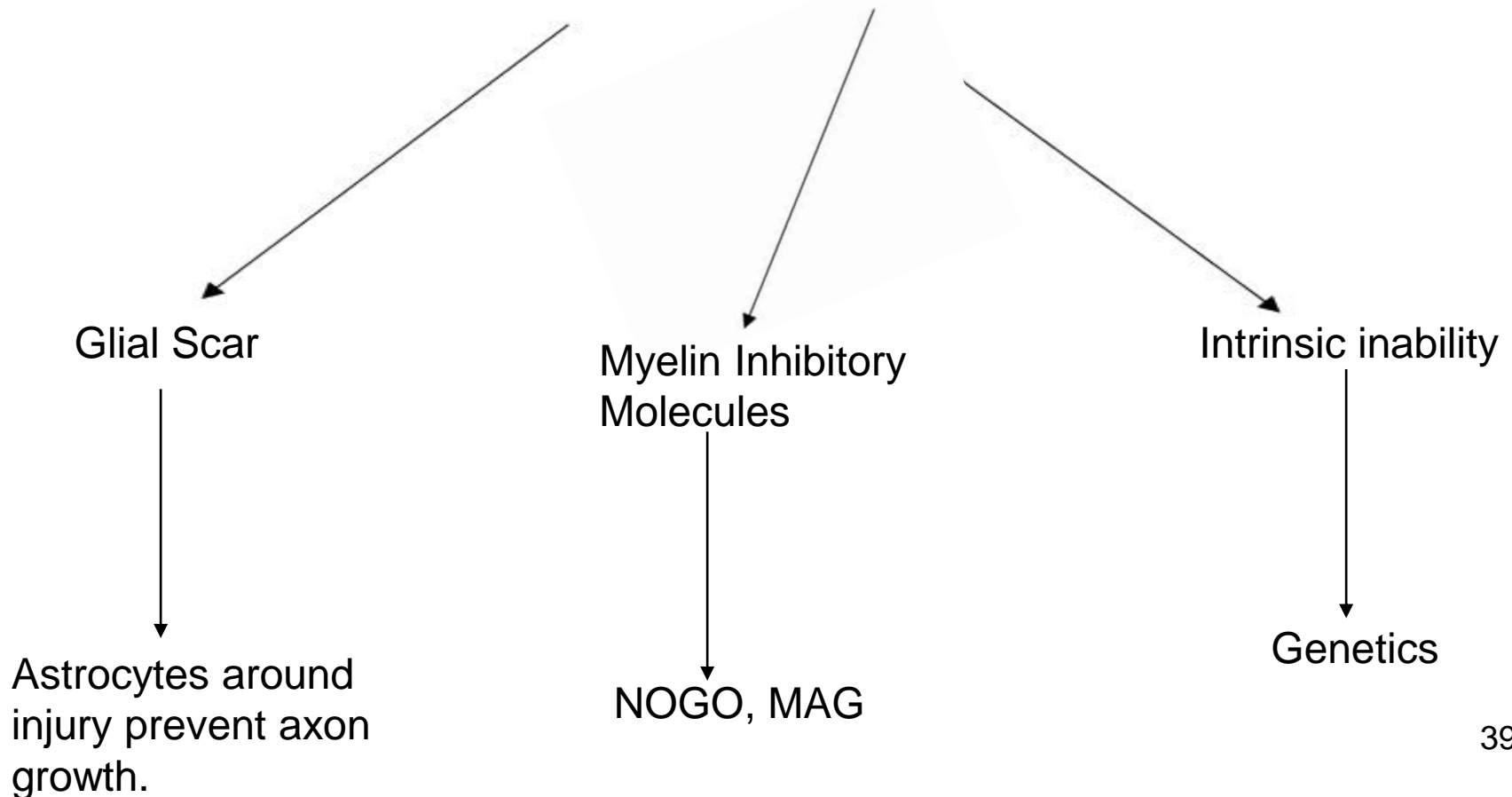
Axons in the CNS fail to regenerate. *Intrinsic Limitation*



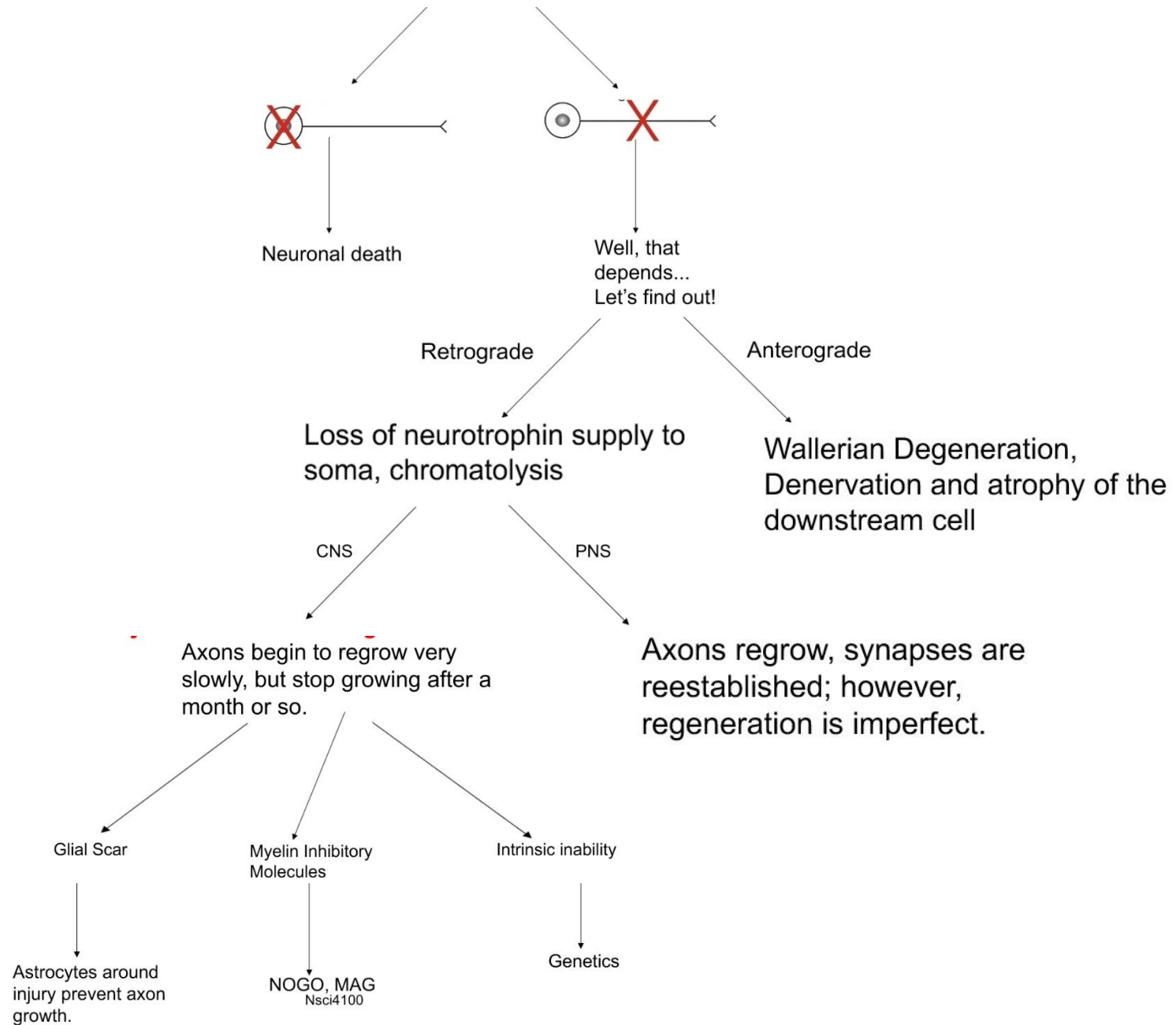
- Adult retinal ganglion cells in which this transcription factor gene was eliminated were able to regenerate axons in the optic nerve past the injury site (in laboratory mice).

Season 5: With tablemates, further describe why CNS axons fail to regenerate.

Axons begin to regrow very slowly, but stop growing after a month or so.



Is the cell damaged at the soma or the axon?



Questions???



IT'S ONLY
A FLESH WOUND