CELLULAR INJURY IN THE NERVOUS SYSTEM

Objectives

The student should:

- Understand the role of the different constituents of Central nervous system (CNS) cells in the disease status.
- Understand the "injury" concept.
- Explain the basic pathological descriptive terms used in CNS cellular injury.
- Correlate the different patterns of cellular injury with some important clinical examples.
- Understand the concept of reaction of neurons, astrocytes and other glial cells to injury.
- Recognize the axonal injury in both CNS and Peripheral nervous system as well as the consequences and the pathological findings.

Introduction

- The principal functional unit of the CNS is the neuron.
- The CNS contains other cells, such as astrocytes and oligodendrocytes, which make up the glia.
- Mature neurons are incapable of cell division, so destruction of even a small number of neurons essential for a specific function may leave the individual with a neurologic deficit.
- Acute injuries typically result in breakdown of the blood-brain barrier and variable degrees of cerebral edema.

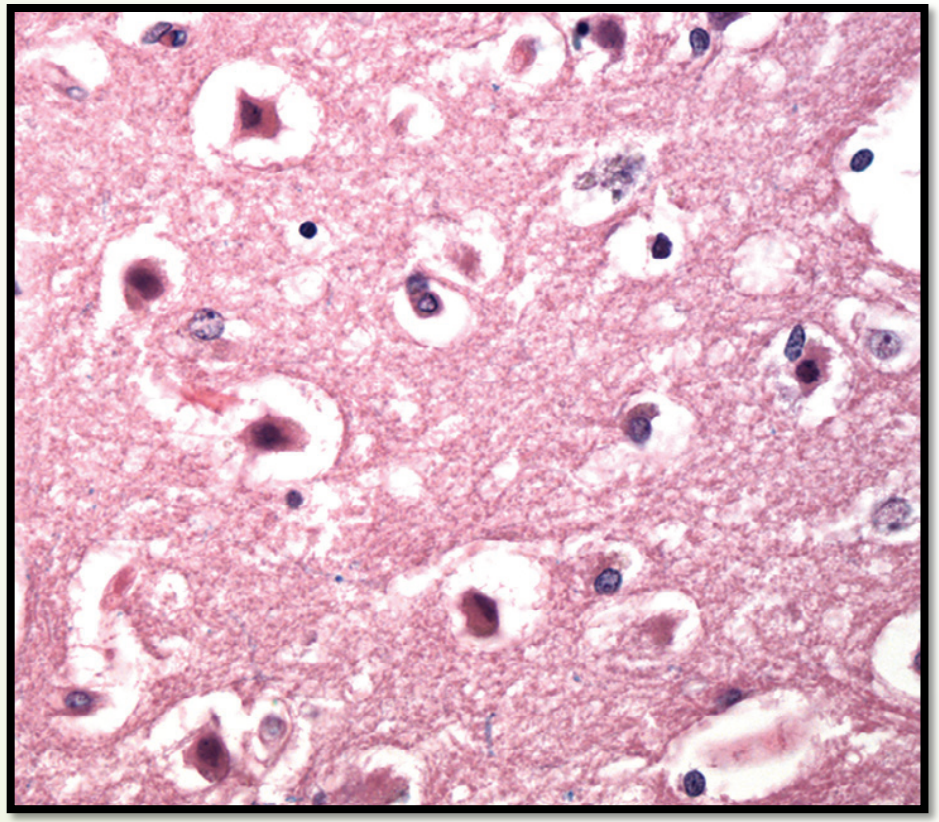
Patterns of Injury

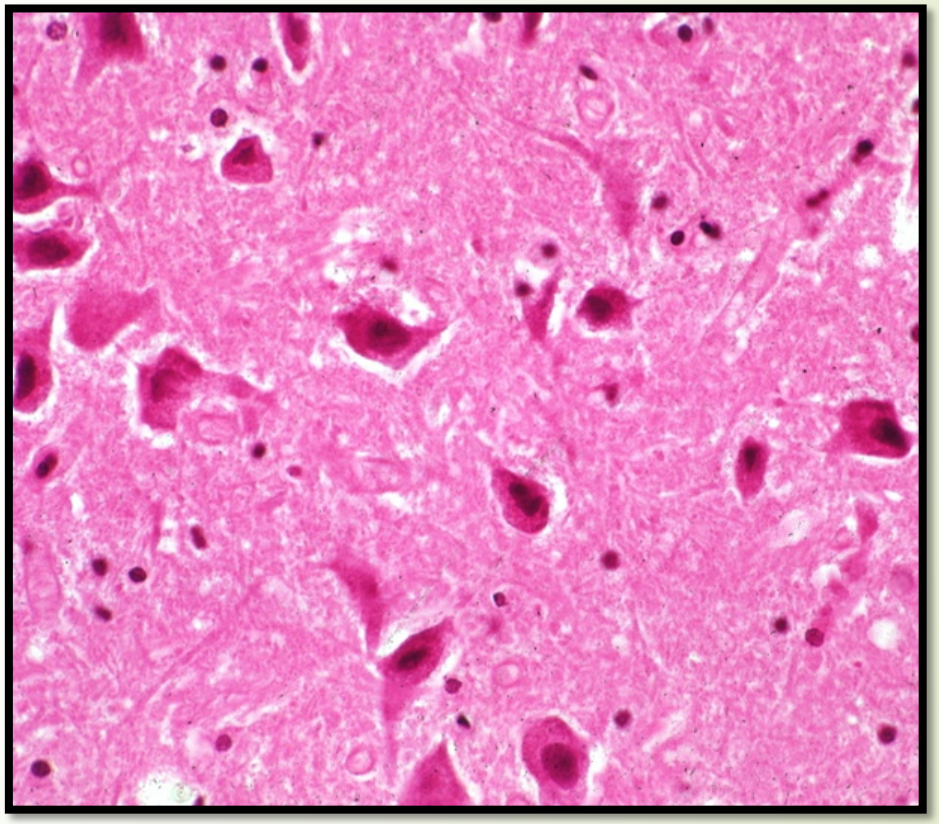
- In response to injury, a number of changes occur in neurons and their processes (axons and dendrites), examples include:
  - Red neurons
  - Intracellular inclusions
  - Dystrophic neurites
  - Spheroids
  - Chromatolysis

Neuronal Injury

- **Red neurons:**
  - Within 12 hours of an irreversible hypoxic-ischemic insult, neuronal injury becomes evident on routine H&E:
  - Shrinkage of the cell body
  - Pyknosis of the nucleus
  - Disappearance of the nucleolus
  - Loss of Nissl substance
  - Intense eosinophilia of the cytoplasm ("***red neurons***")

Red Neurons



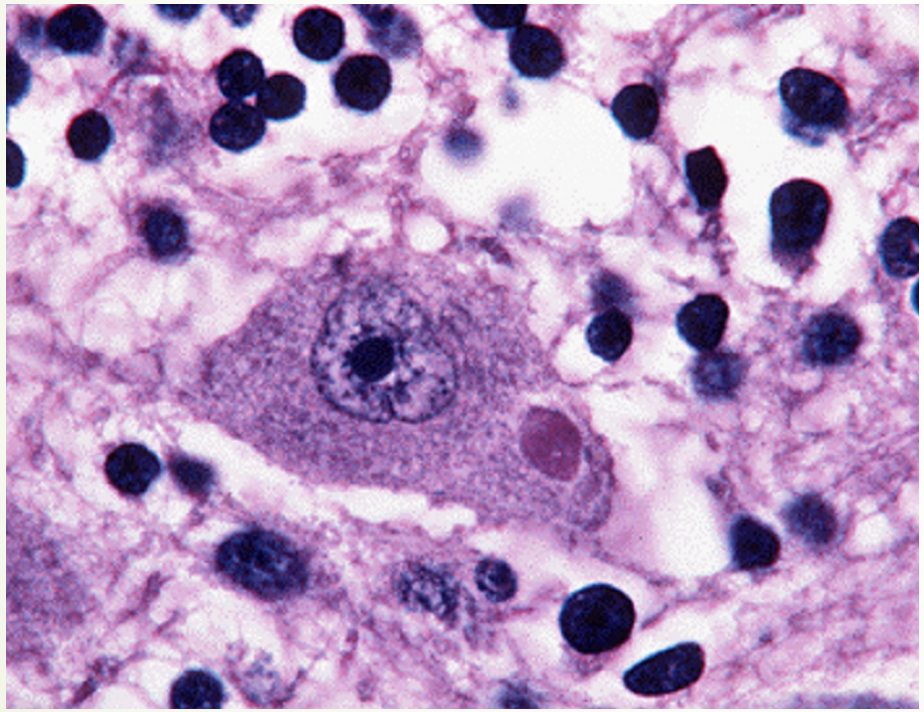


Neuronal Injury

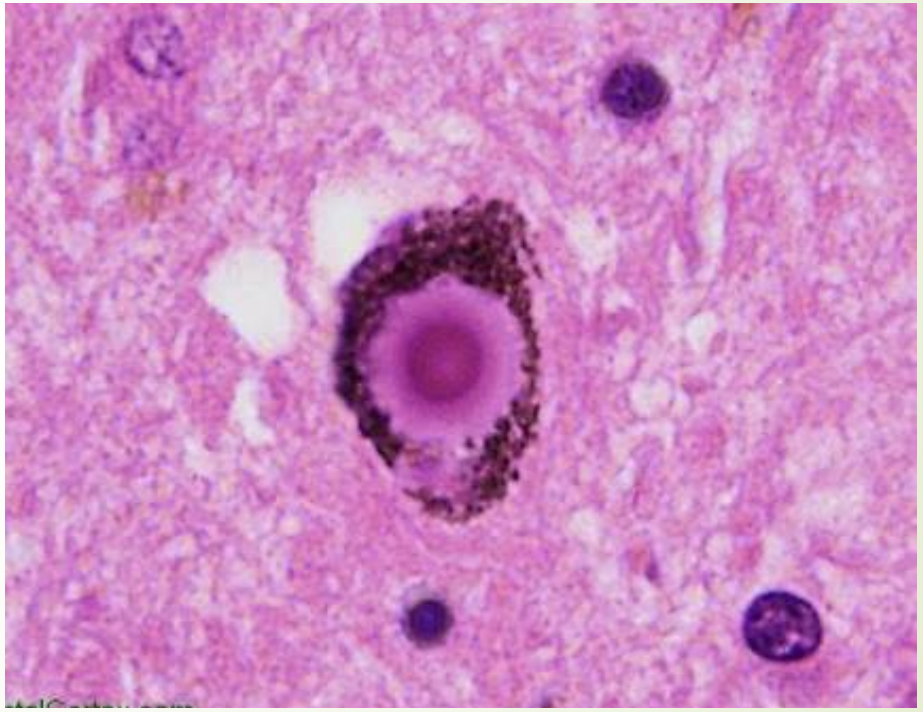
- **Intracellular inclusions:**
  - Many neurodegenerative diseases are associated with specific ***intracellular inclusions*.**
  - These are nuclear or cytoplasmic aggregates of stainable substances, usually proteins.
  - Examples include:
    - Negri bodies in rabies
    - Lewy bodies in Parkinson disease
    - Tangles in Alzheimer disease

Intracellular Inclusions

Negri body



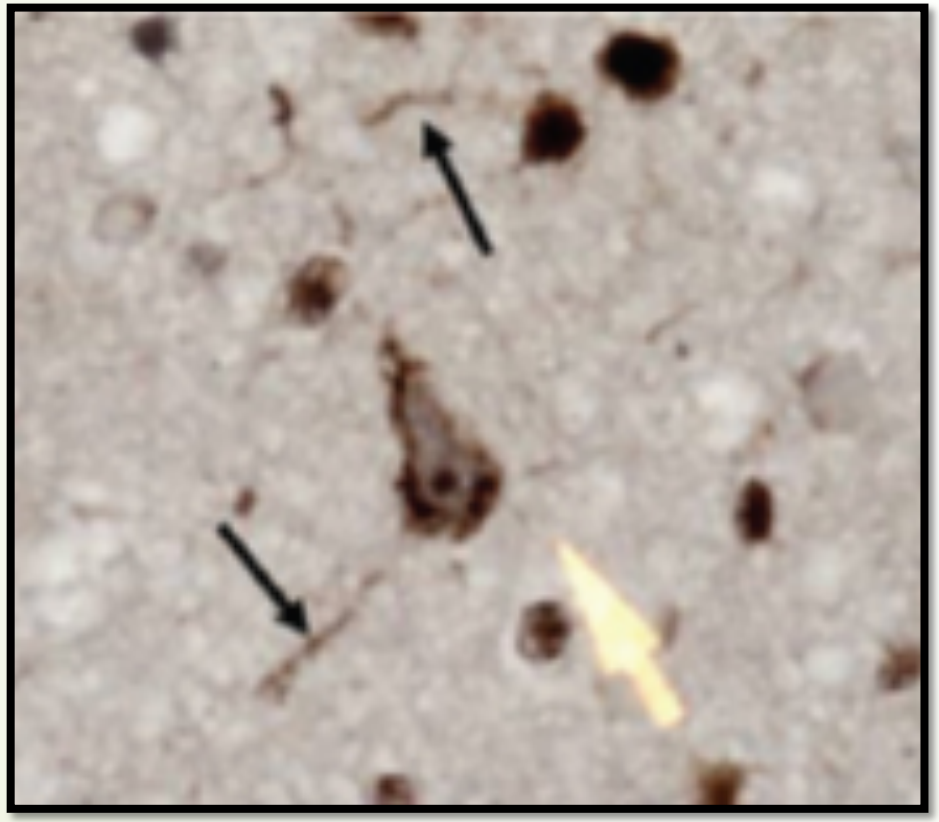
Lewy body

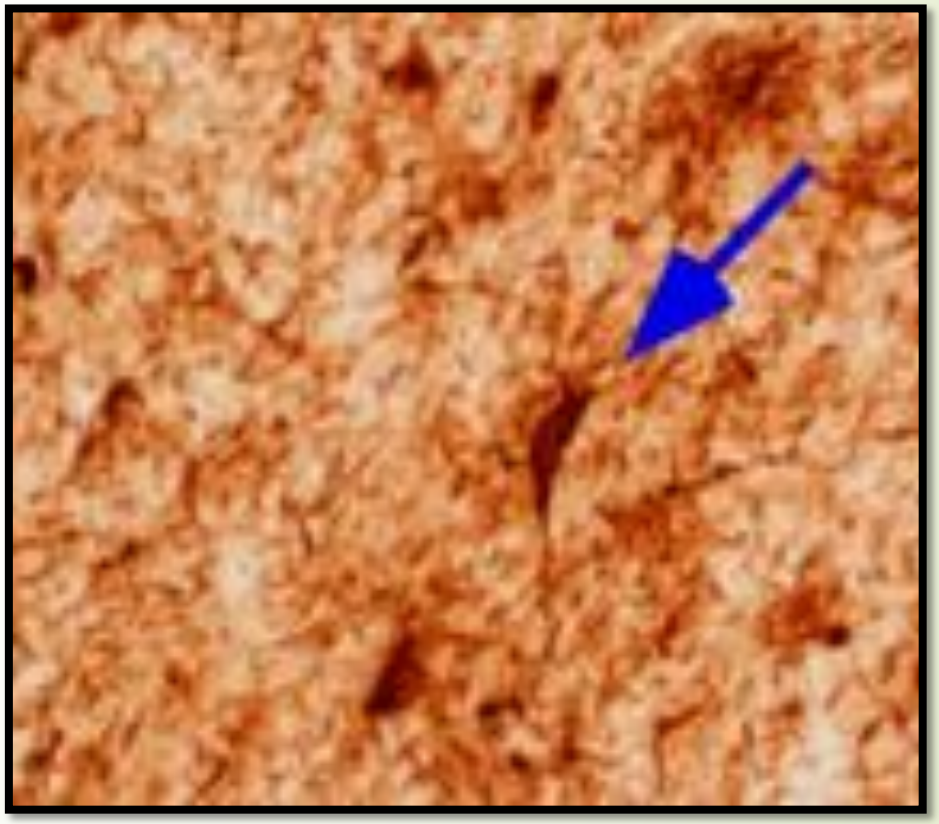


Neuronal Injury

- **Dystrophic neurites:**
  - A neurite refers to any projection from the cell body of a neuron.
  - In some neurodegenerative diseases, neuronal processes become thickened and tortuous; these are termed ***dystrophic neurites***.

Dystrophic Neurites





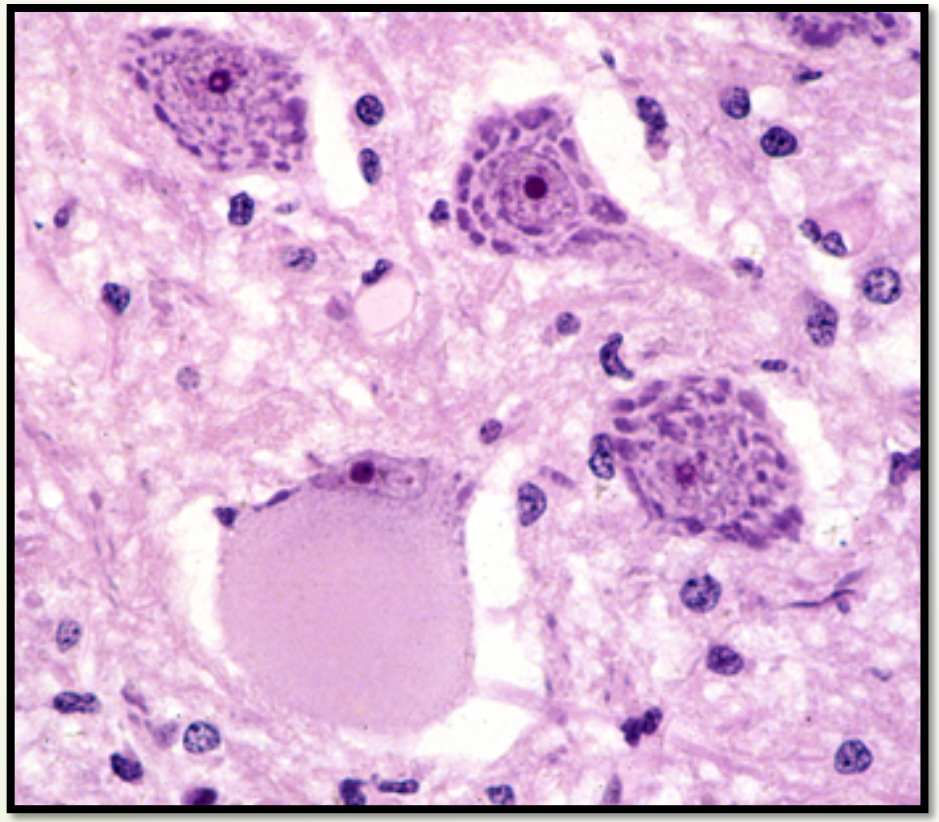
Axonal Injury

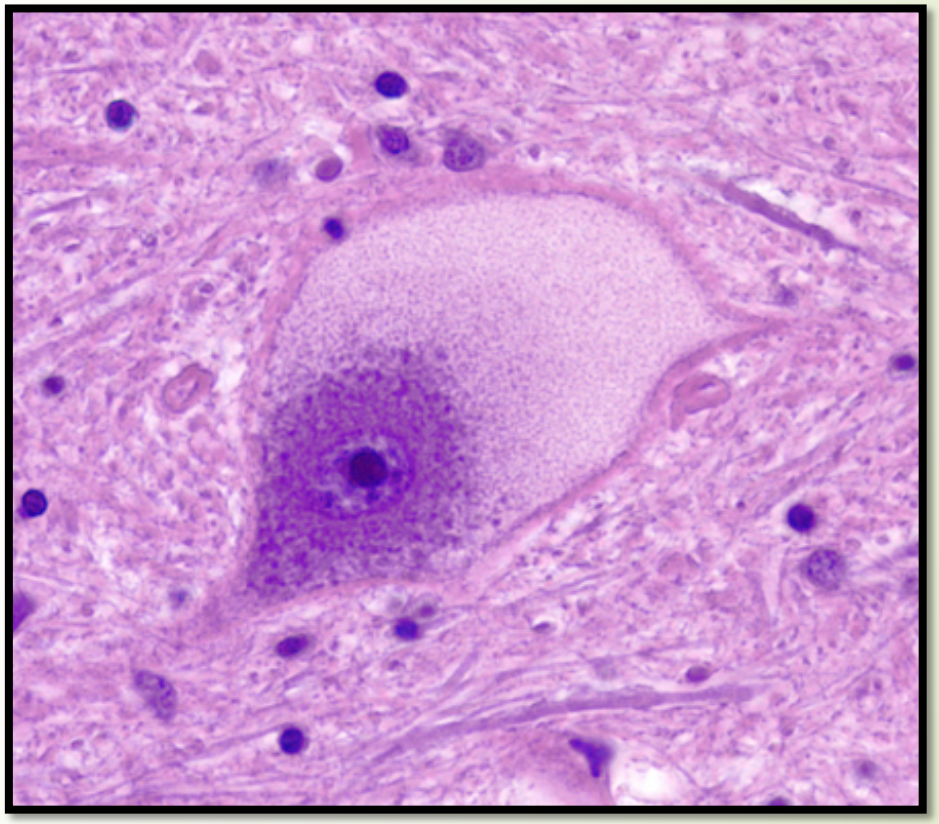
- Injured axons undergo swelling (called ***spheroids***) and show disruption of axonal transport.

- Axonal injury also leads to the following features:

  - Cellular body enlargement and rounding
  - Peripheral displacement of the nucleus
  - Enlargement of the nucleolus
  - Peripheral dispersion of Nissl substance (***central chromatolysis***).

Central chromatolysis



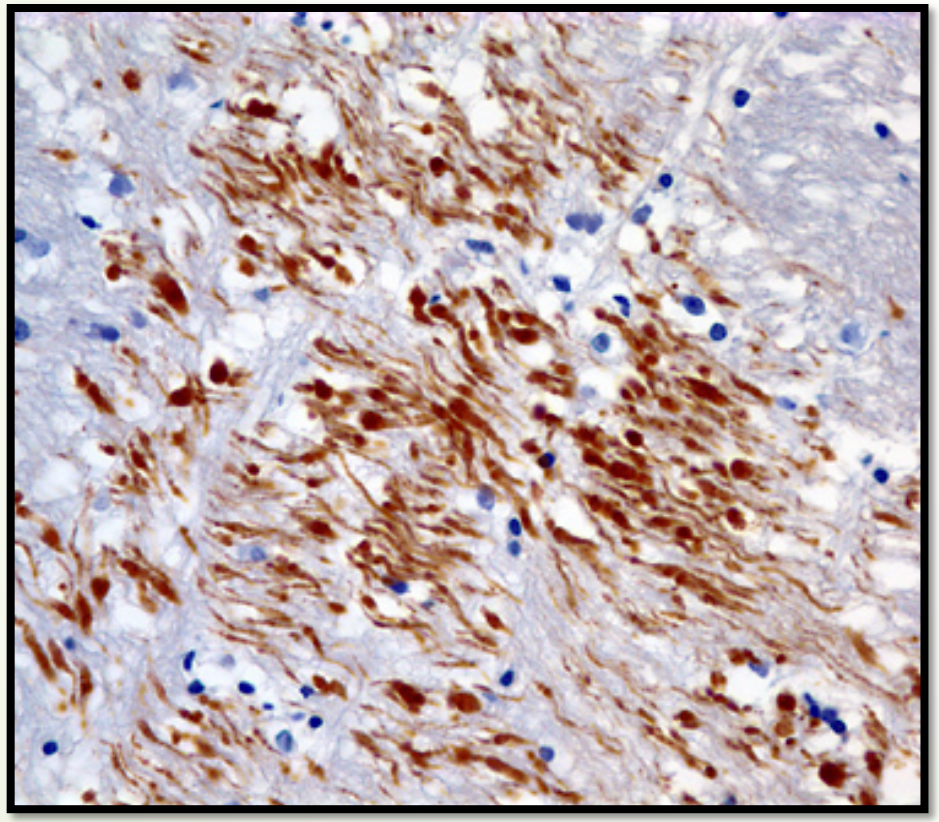


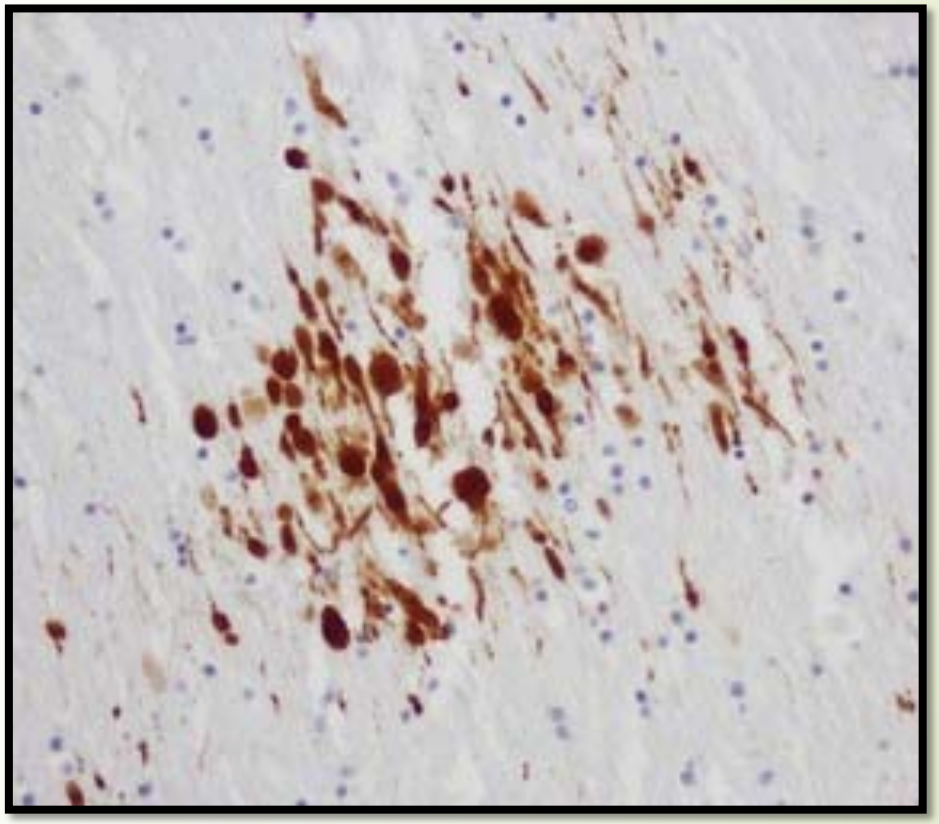
Axonal Injury

- Evidence of injury can be highlighted by silver staining or immunohistochemistry for axonally transported proteins such as amyloid precursor protein.

- Immunostains with antibodies to Beta Amyloid Precursor Protein (BAPP) can detect the axonal lesions in 2-3 hours after the injury (diffuse axonal injury).

Beta Amyloid Precursor Protein





Diffuse Axonal Injury

- As many as 50% of patients who develop coma shortly after a trauma, even without cerebral contusions, are believed to have white matter damage and diffuse axonal injury.
- The movement of one region of the brain relative to another is thought to lead to the disruption of axonal integrity and function.
- Diffuse axonal injury is characterized by the wide but often asymmetric distribution of axonal swellings that appears within hours of the injury and may persists for much longer.
- These are best demonstrated with silver stains or by immunohistochemistry for proteins within axons.

Cerebral Edema

- Cerebral edema is the accumulation of excess fluid within the brain parenchyma.
- There are two types, which often occur together, particularly after generalized injury:
  - Vasogenic edema
  - Cytotoxic edema

Vasogenic Edema

- It occurs when the integrity of the normal blood-brain barrier is disrupted, allowing fluid to shift from the vascular compartment into the extracellular spaces of the brain.

- Vasogenic edema can be localized (e.g., the result of increased vascular permeability due to inflammation or in tumors) or generalized.

Cytotoxic Edema

- It is an increase in intracellular fluid secondary to neuronal and glial cell injury, as might follow generalized hypoxic or ischemic insult or exposure to certain toxins.

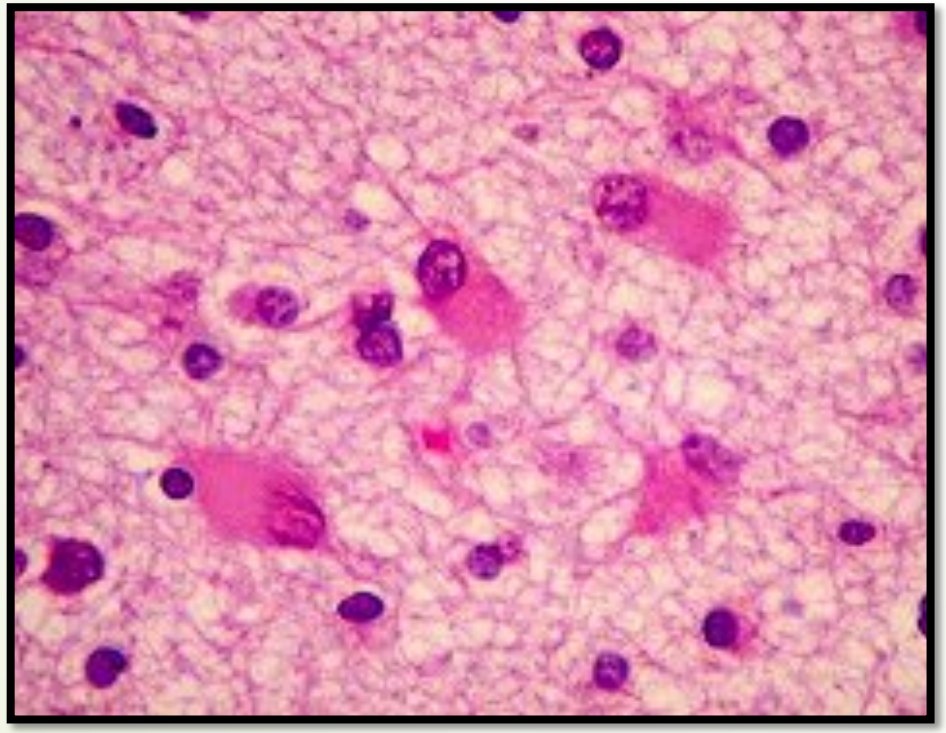
Glial Cells in Injury

- Astrocytes are the principal cells responsible for repair and scar formation in the brain, a process termed ***gliosis***.

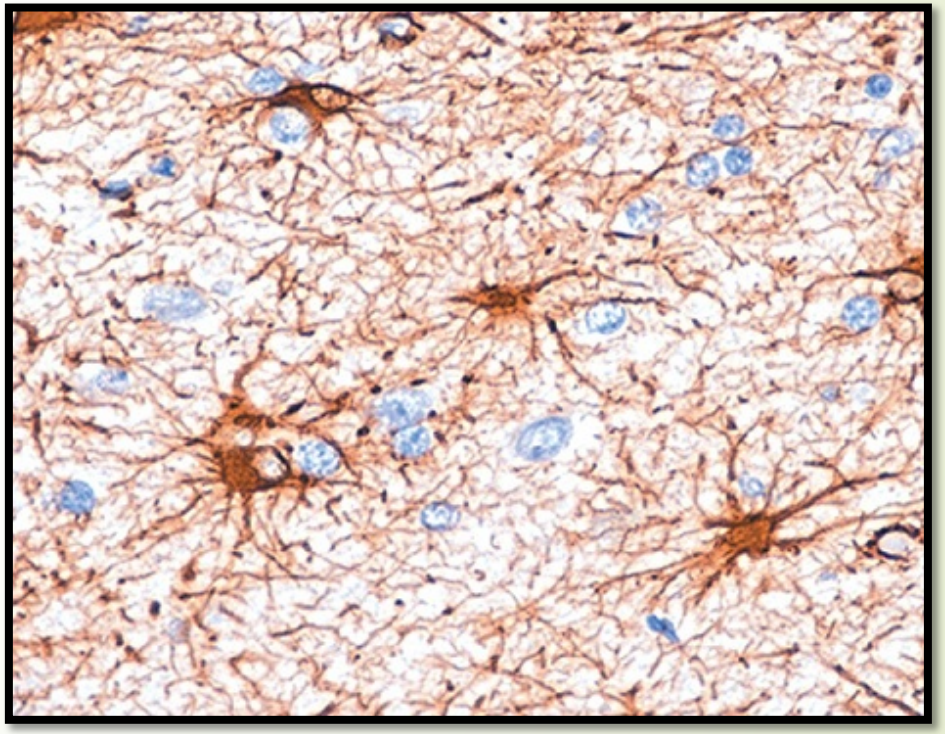
- In response to injury:
  - Astrocytes undergo both hypertrophy and hyperplasia
  - The nucleus enlarges and becomes vesicular
  - The nucleolus becomes prominent
  - The cytoplasm expands and takes on a bright pink hue, and the cell extends multiple stout, ramifying processes (called ***gemistocytic astrocytes***)
  - In long-standing gliosis, the cytoplasm of reactive astrocytes shrinks in size, and the cellular processes become more tightly interwoven (***fibrillary astrocytes***).

Glial Cells in Injury

Gemistocytic astrocytes



Fibrillary astrocytes

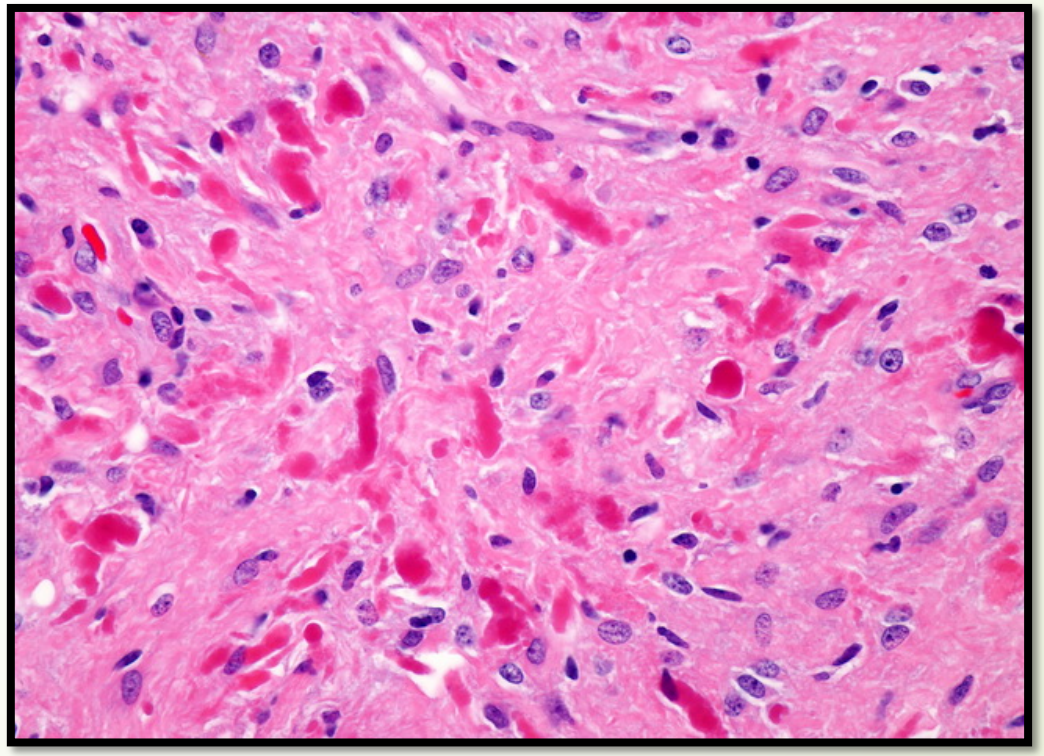


Glial Cells in Injury

- There is minimal extracellular matrix deposition in CNS injury.
- Unlike repair after injury elsewhere in the body, fibroblasts participate in healing after brain injury only to a limited extent (usually after penetrating brain trauma or around abscesses).

Glial Cells in Injury

- Rosenthal fibers are thick, elongated, brightly eosinophilic protein aggregates found in astrocytic processes in chronic gliosis and in some low-grade gliomas.

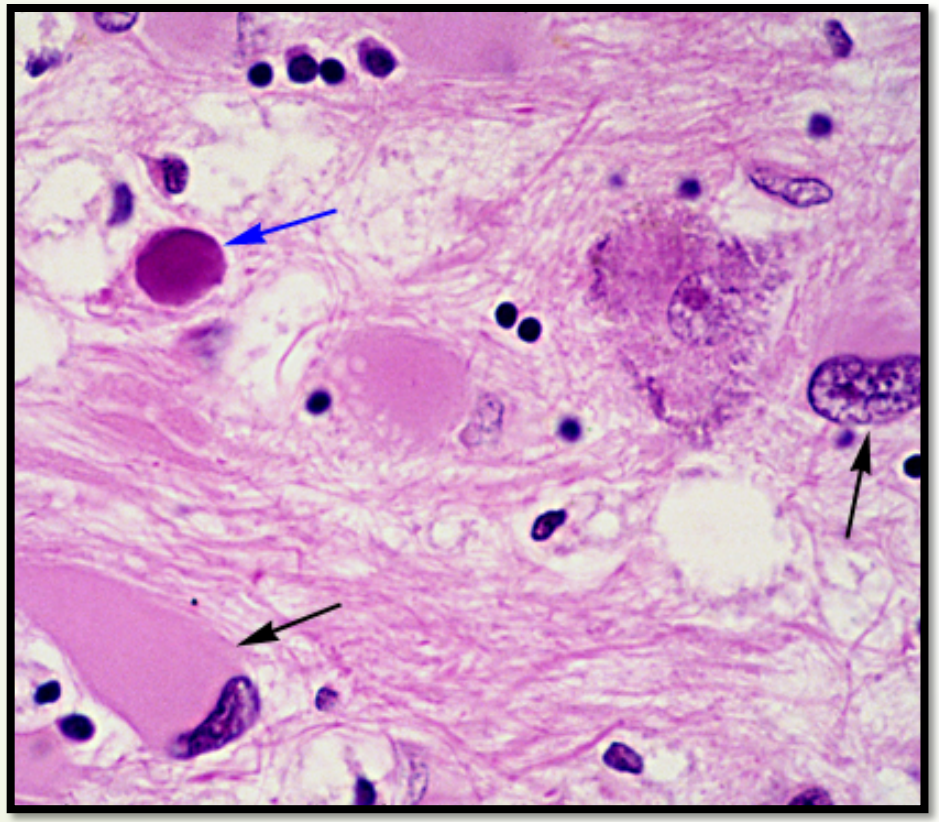


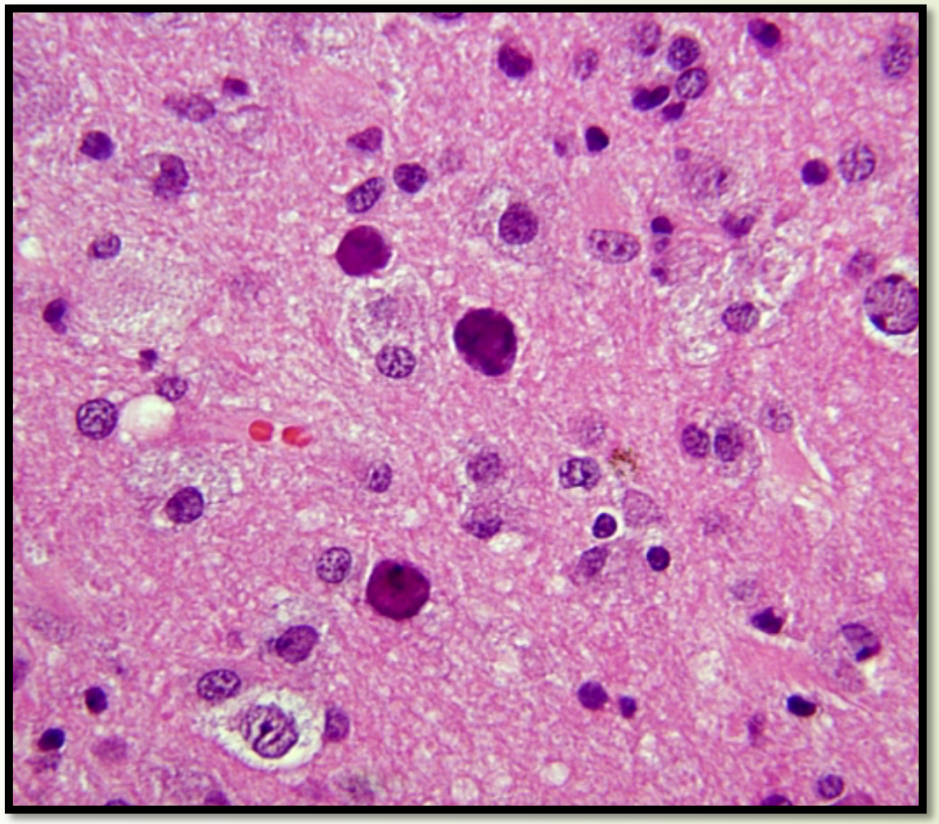
Glial Cells in Injury

- Oligodendrocytes, which produce myelin, exhibit a limited spectrum of specific morphologic changes in response to various injuries.

- In progressive multifocal leukoencephalopathy, viral inclusions can be seen in oligodendrocytes, with a smudgy, homogeneous-appearing enlarged nucleus.

Progressive Multifocal Leukoencephalopathy





Glial Cells in Injury

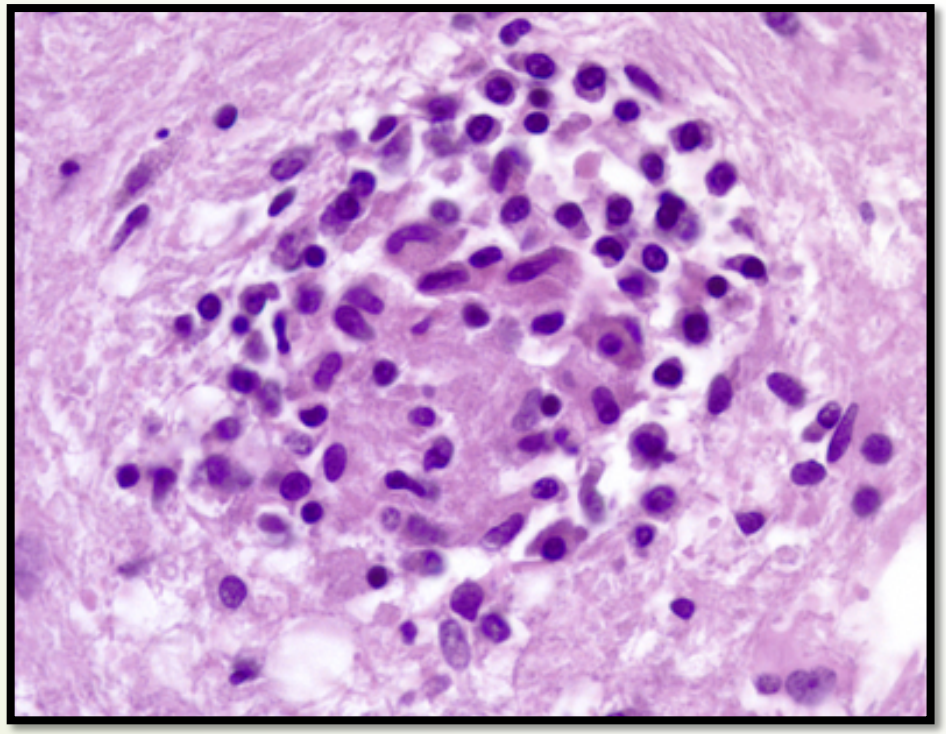
- Ependymal cells line the ventricular system and the central canal of the spinal cord.
- Certain pathogens, particularly cytomegalovirus, can produce extensive ependymal injury, with typical viral inclusions.

Glial Cells in Injury

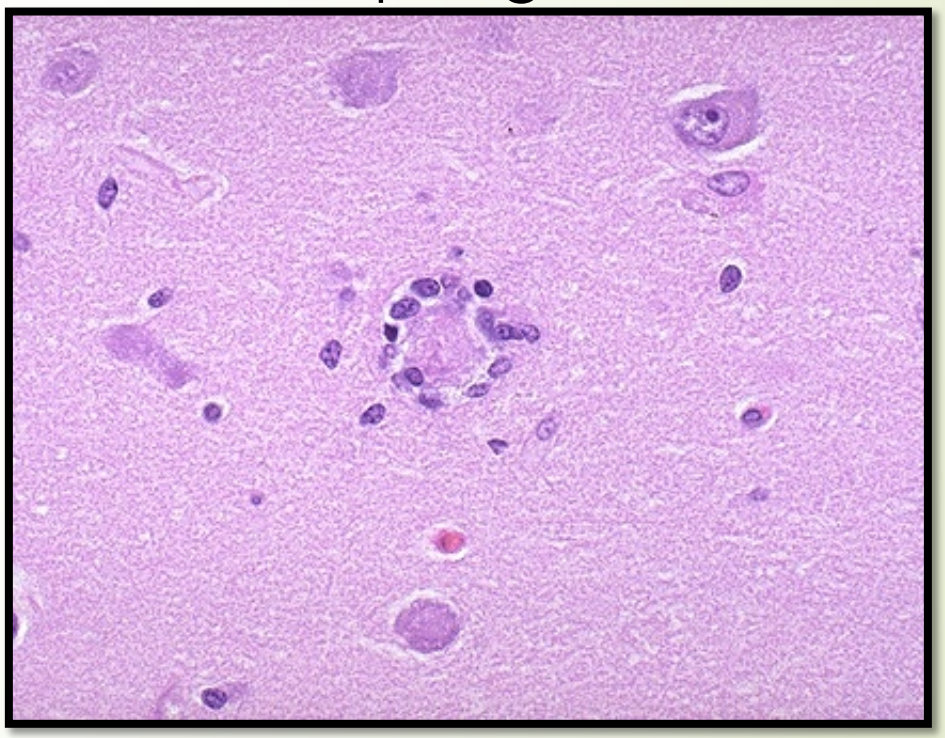
- Microglial cells are long-lived cells derived from the embryonic yolk sac that function as the resident phagocytes of the CNS.
- When activated by tissue injury, infection, or trauma, they proliferate and become more prominent histologically.
- Microglial cells take on the appearance of activated macrophages in areas of demyelination, organizing infarct, or hemorrhage; in other settings such as infections, they develop elongated nuclei (***rod cells***). Aggregates of elongated microglial cells at sites of tissue injury are termed ***microglial nodules.***
- Similar collections can be found congregating around and phagocytosing injured neurons (***neuronophagia***).

Glial Cells in Injury

Microglial nodules



Neuronophagia



Peripheral Nerve Injury

- Most peripheral neuropathies can be subclassified as either axonal or demyelinating, even though some diseases exhibit mixed features.

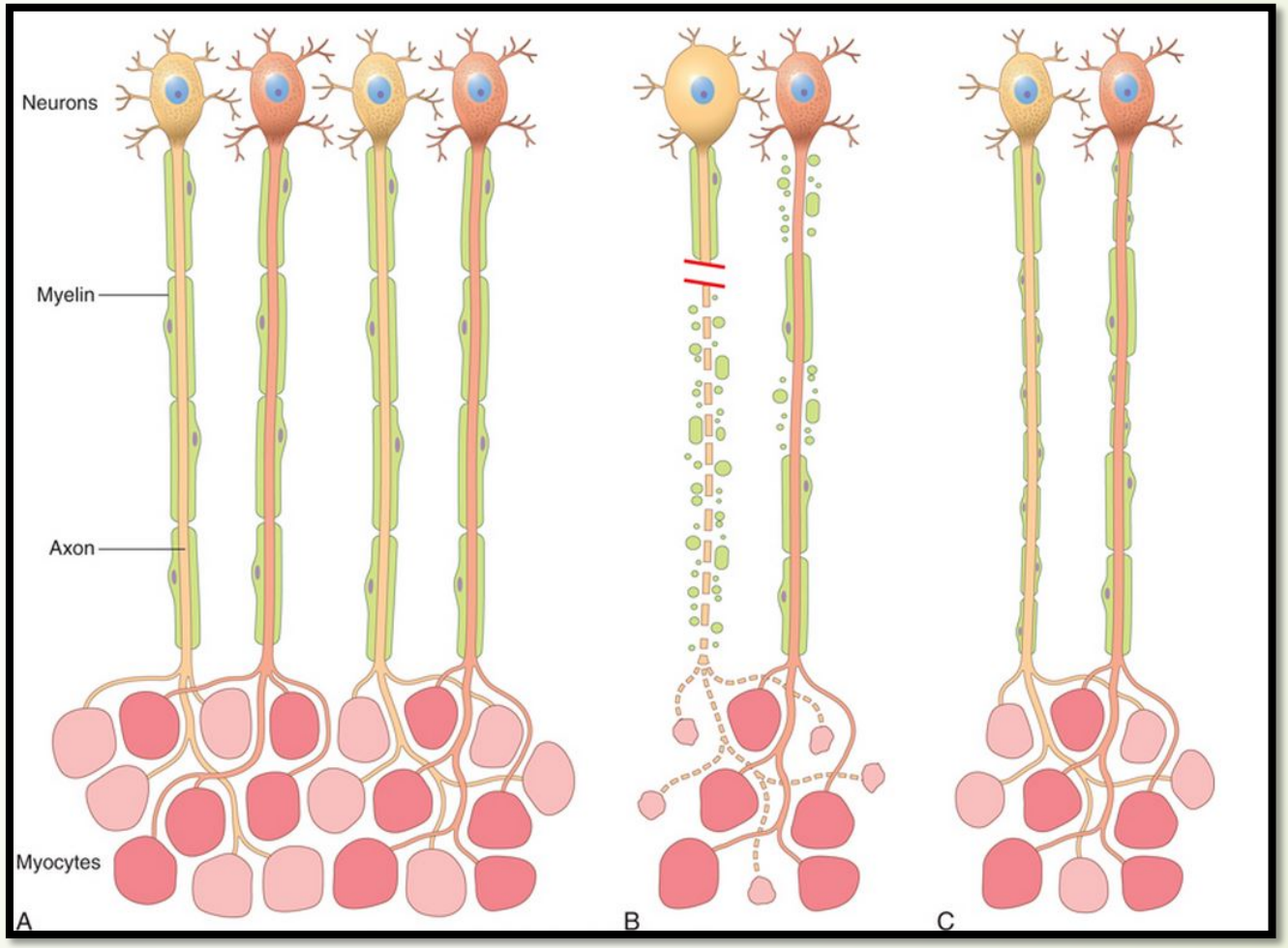
Axonal Neuropathies

- They are caused by insults that directly injure the axon.
- The entire distal portion of an affected axon degenerates.
- Axonal degeneration is associated with secondary myelin loss a process sometimes referred to as Wallerian degeneration. Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon.
- The morphologic hallmark of axonal neuropathies is a decrease in the density of axons, which in electrophysiologic studies correlates with a decrease in the strength of amplitude of nerve impulses.

Segmental Demyelination

- They are characterized by damage to Schwan cells or myelin with axonal sparing resulting in abnormally slow nerve conduction velocities.
- Demyelination typically occurs in individual myelin internodes randomly; this process is termed segmental demyelination
- Morphologically, demyelinating neuropathies show a relatively normal density of axons and features of segmental demyelination and repair >> recognized by the presence of axons with abnormally thin myelin sheaths and short internodes.

Axonal Neuropathies



Homework

- Define Corpora amylacea.
- Where and when they are deposited in the CNS?

Reference

Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10th ed. Elsevier; 2017. Philadelphia, PA.

End of Lecture

Thank You