Nervous system

Degenerative changes of the nerve cell body

- **Nuclear margination** – ***margination plus loss of staining affinity = nonspecific degeneration***

- Eccentric nucleus can be normal in mesencephalic nucleus of the trigeminal nerve and the olives (also tend to have a ‘chromatolytic‘ appearance)

Chromatolysis – change in appearance of the soma (*dispersal of the rough endoplasmic reticulum (Nissl granules)*

- Subclassified as *central or peripheral according to its locus* within the cell body.

- There are no artifactual changes that mimic chromatolysis (if accurately identified = lesion).

- Special stains (cresyl violet) will demonstrate it better.

- **Central chromatolysis** – best appreciated in large neurons of some of the brain stem nuclei, in the spinal motor neurons, and peripheral ganglia.

¬ Chromatolytic cells are swollen and rounded (normal angulated)and the nucleus is eccentric.

¬ Nissl granules clear from the central region of the cell body, leaving this zone with a smooth ground-glass appearance

- **Peripheral chromatolysis – clearing of the periphery** of the soma, with Nissl granules persisting around the nucleus.

¬ is generally associated with slight cellular shrinkage rather than swelling.

¬ It is a nonspecific lesion and can often be regarded as an early stage to necrosis.

¬ In both forms, microglia and astrocytes may proliferate and cover large expanses of the cell surface, thereby separating terminal boutons from the neuronal surface.

- **Necrosis with neuronophagia** – in many viral infections, the death of neurons provokes the gathering of phagocytes around the cell body and removal by them of the debris, forming **neuronophagic nodules**

¬ Response of the microglia, although satellite perineuronal oligodendrocytes may also proliferate in response to neuronal injury (satellitosis).

¬ Neuronophagia may also be seen in metabolic or toxigenic neuronal degenerations, but is generally not as extensive as in viral infection.

Ischemic neuronal necrosis

Microscopic lesions

- the cytoplasm of the neuronal cell body is shrunken, deeply eosinophilic, and frequently sharply angular to triangular in shape .
- The nucleus is reduced in size, is often triangular, and is pyknotic.
- The nucleolus and Nissl substance are usually not detectable.

- Ischemic neurons die and are removed either by a process called neuronophagia, which is phagocytosis by microglial cells and macrophages or by lysis.

- Following neuronal necrosis, there is swelling of perineuronal and perivascular astrocytic processes

CHRONIC NEURONAL NECROSIS (BRAIN ATROPHY)

- slowly progressive neurologic diseases, aging, primary and multisystem and cerebellar neuronal degeneration.
- Gross lesions - atrophy of cerebral gyri, which results in widening of the sulci

- Microscopic lesions - diminished numbers of neurons and astrogliosis.
- Loss of neurons over time results in progressively worsening neurologic dysfunction.

- **Wallerian degeneration** – denotes the changes that follow acute focal injury to **a myelinated axon**
- The sequence of Wallerian degeneration :

1. Degeneration and fragmentation of axon and myelin within several days. Proximal segment degenerates back to the next node of Ranvier, but all the distal segment dies.
2. Removal of axonal and myelin debris by phagocytosis. Some phagocytes are from the blood and some phagocytosis is by Schwarm cells.

- All of the debris is cleared out of the endoneural tube within a few weeks.
- When the **soma** is uninjured, there is potential for regeneration and, in peripheral nerves, this may be complete.

3. Regeneration of axon if the endoneurium is intact to allow the axon of the proximal segment to enter and slide down the tube.
- Remyelinization by Schwann cells.

- These conditions do not apply in the CNS, where the oligodendrocyte/axon relationship is far more complex

- The oligodendrocyte is a relatively poorly regenerative cell type, there is no basal lamina scaffold, and the debris from central myelin is thought **to** inhibit axonal sprouting

- Axonal sprouting and some remyelination can occur. However, the poverty of the regenerative response results mostly in the *permanent disappearance of the axons, myelin, and oligodendrocyte cell bodies.*

- Some of the myelin debris may be phagocytosed by reactive astrocytes, and their processes extend to fill the vacancy, creating a ramifying network of astroglial scar tissue.

- Wallerian degeneration in the CNS is most commonly seen in the spinal cord, the optic tract, and the brain stem.

- Probably the best–known association is with the focal compressive myelopathies in the horse and dog (the wobbler syndromes).

Microscopic lesions

- Axons are initially swollen and are eventually removed by phagocytosis to leave clear spaces, which were once the sites of nerve fibers.
- central chromatolysis, characterized by swelling of the neuronal cell body, dispersion of cenrrally located Nissl substance, and peripheral displacement of the nucleus

RESPONSES OF MACROGLIA TO INJURY

- **ASTROCYTES**
- Common astrocytic reactions in CNS injury are swelling, hypertrophy, division, and the laying down of intermediate fllaments in cell processes.
- Swollen astrocytes have clear-staining or vacuolated cytoplasm

- If injury is severe, astrocytic processes fragment and appear followed by lysis of the cell body.
- Hypertrophied astrocytes often referred to as "reactive," represent a response to a **milder** and **more protracted** injury to the CNS.

- In protracted degenerative conditions, astrocytes termed gemistocytes can be observed.

- Swelling and eosinophilia of the cytoplasm, with some cells acquiring two or more nuclei.

- These cells have eccentric nuclei and abundant pink homogeneous cytoplasm, in contrast to the lack of visible cytoplasm in

- Reactive astrogliosis is expected in Wallerian degeneration, following neuronal loss, and in sustained cerebral or spinal edema, and is a feature of many viral encephalitides in which viral infection of astrocytes is probably a prime stimulus.

- This is certainly the case in canine distemper, in which inclusion bodies are common in reactive astrocytes.

- Astrocytes are the cells primarily responsible for repair and scar formation in the brain.

OLIGODENDROCYTES

- There are two types of oligodendroglia:
  - (1) interfascicular
  - (2) satellite oligodendrocytes
- Oligodendroglia react to injury by cell swelling, hypertrophy, and degeneration.
- Microscopically, these cells swell and hypertrophy around injured neurons, and this response to injury has been called satellitosis

- **Microgtia**
- Microglia are derived from the mononuclear phagocyte lineage, and function as the fixed macrophage system of the CNS.
- In the normal brain and cord, they appear by routine microscopy as inconspicuous, small hyperchromatic nuclei, often wedge–shaped, and with no visible cytoplasm.

- However, special staining techniques reveal extensive thin cytoplasmic processes

- They are most numerous adjacent to blood vessels.

- **RESPONSES Of *MICROGLIA TO INJURY***
- Activated microglia at the site of injury express increased levels of major histocompatibility antigens and, like other macrophages, microglia release inflammatory cytokines that
- amplify the inflammatory response by recruiting other cells to the site of injury.

- The simplest microglial response to tissue injury is a *hTpertrophic reaction in which the nucleus becomes rounded and the cytoplasm* visible as a narrow, often

- The responses of microglia to injury include hypertrophy, hyperplasia, phagocytosis of cellular and myelin debris, and neuronophagia, the removal of dead neuron cell bodies.

- These reactive cells readily proliferate, either focally, forming glial nodules, or more diffusely, depending on the nature of the injury.

- Focal proliferation gives rise to nodules of 30–40 or more cells, while diffuse proliferation creates an overall impression of increased cellularity in the microscopic field

- Microglial nodules are very common feature of viral encephalitis
- Reactive microglia may develop greatly elongated and sometimes tortuous nuclei, in which case they are called *rod cells. These again are often seen in viral diseases.*

- Activated microglia release cytokines and chemokines that aid in defense against CNS

- The most vigorous response of the microglia is their transformation to macrophages, when they assume the morphology typical of cells engaged in phagocytosis.

- When ingesting **myelin debris**, their cytoplasm becomes foamy as they load themselves with lipid vacuoles. Often the nucleus becomes pyknotic, and they are referred to as **gitter cells**, **compound granular corpuscles**, **or fat–granule cells**

- In severe lesions, many of the gitter cells will have arisen from blood monocytes as well as from microglia.

- Microglial phagocytes are usually responsible for **neuronophagia,** in which ***phagocytic cells gather around fragmenting degenerate neuronal cell bodies*** .

- This response is a feature of many viral infections in which neurons die, but *is uncommon* in ischemic or other forms of neuronal necrosis.

EPENDYMAL CELLS

- Ependymal and choroid plexus epithelial cell responses to injury include atrophy, degeneration, and necrosis.
- Atrophy usually occurs in response to enlargement of the ventricles as occurs with hydrocephalus.
- The cilia and microvilli of affected cells are reduced in number,

- An additional lesion that accompanies ventricular enlargement is stretching and tearing of the ependymal lining.
- astrogliosis, whichvaries greatly in degree and uniformity, occurs in the exposed areas.
- Astrogliosis can extend into the ventricular space or be minimal in extent and confined to the periventricular area.
- Periventricular interstitial edema, myelin loss, and axon loss can ensue.

- **Microcircutation & perivasculitis**
- There are some structural peculiarities of blood vessels in the CNS that have a bearing on the development of pathologic processes.
- The capillaries differ from those in other tissues by being surrounded by an investment of astrocytic end-feet. Also, the endothelial cells are sealed together by tight junctions, and the basement membrane divides to incorporate pericytes into the capillary wall.
- This arrangement in its totality creates the **blood–brain barrier**

- Both arterioles and venules of the CNS are thin walled, with very little elastica and no muscle.

- They are thus susceptible to injury and prone to hemorrhage.

- The veins are valveless and, backflow of blood after death is usual, so cerebral venous congestion can be difficult to assess.

- Both arteries and veins have an outer adventitial

- In diffuse inflammatory or neoplastic diseases, this space, more potential than real under normal conditions, becomes patent and accumulates reactive and invading cells.

- The tendency for these cells to be confined to the space gives rise to the neuropathologic term **perivascular cuffing**

- The size of cuffs is usually related to the size of the space, and they may vary from one cell thick abouthe smallest venules to 10–12 or more cells

Perivascular cuffing

- is classically seen in inflammatory conditions, and all classes of reactive leukocyte may be seen depending on the cause.
- Lymphoid perivascular cuffing is a feature of many viral encephalitides.
- Both arteries and veins have an outer adventitial layer of variable thickness, and a **perivascular Virchow–Robin space**

- In diffuse inflammatory or neoplastic diseases, this space, becomes patent and accumulates reactive and invading cells.

- The tendency for these cells to be confined to the space gives rise to the neuropathologic term **perivascular cuffing** in **Virchow–Robin space**

- The size of cuffs is usually related to the size of the space (1 cell thick about the smallest venules to 10–12 or more cells thick around the larger vessels).

- *Perivascular cuffing is classically seen in inflammatory conditions,* and all classes of reactive leukocyte may be seen depending on the cause

RABIES

- Gross lesions of the infected central nervous tissue are often absent.
- Microscopic lesions of the CNS are typically lymphomonocytic (nonsuppurative) and include variable leptomeningitis and perivascular cuffrng with lymphocytes, macrophages, and plasma cells
- Microgliosis which sometimes is prominent; variable, but often not severe, neuronal

- Occasional leptomeninges, ependyma, oligodendroglia, and astrocytes involved.
- Emphasis should be given to the fact that infected neurons often are minimally altered morphologically.
- Neurons can also contain **intracytoplasmic acidophilic** (pale red to red) inclusions called **Negri bodies**