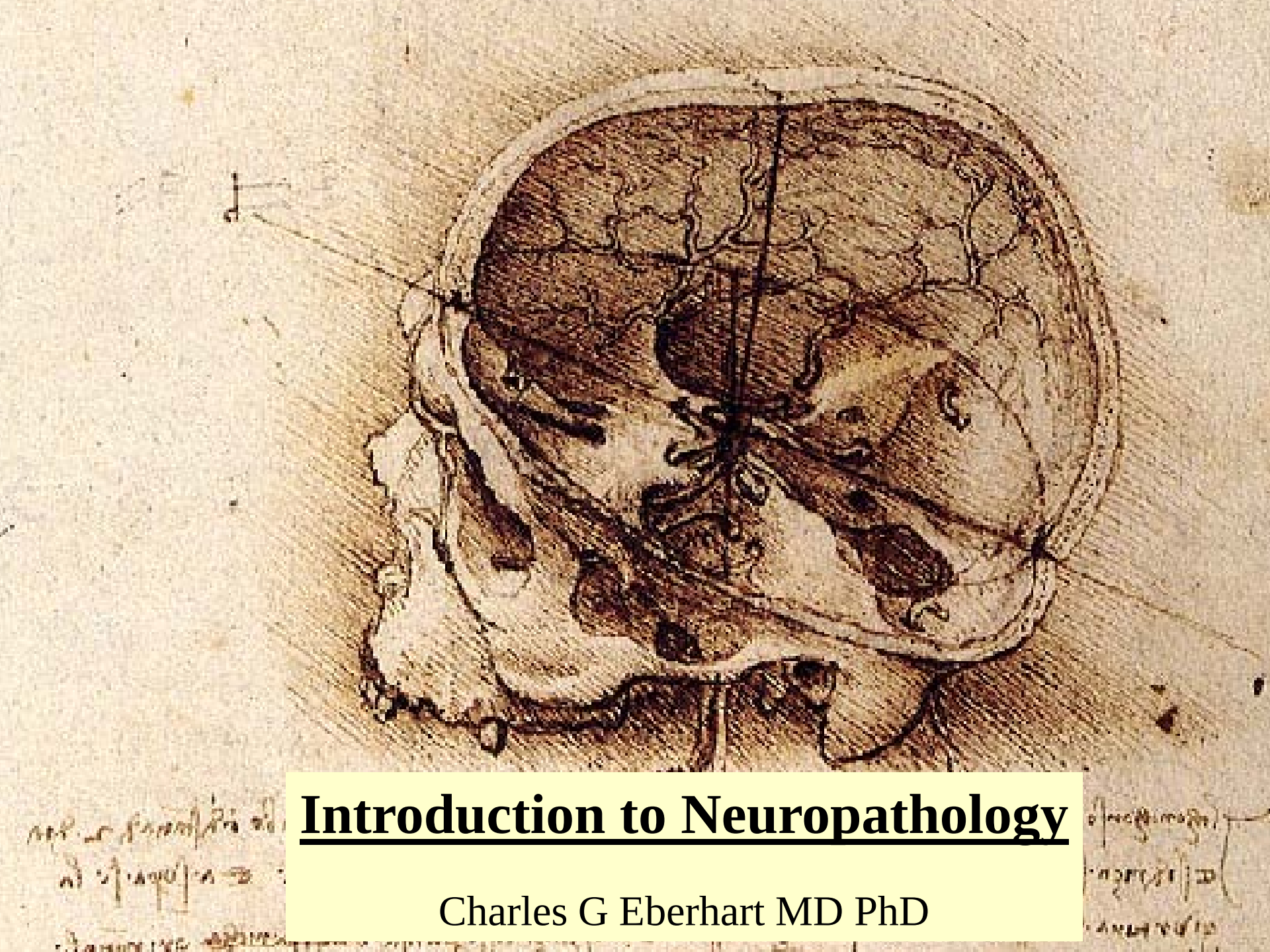


Introduction to Neuropathology

Charles G Eberhart MD PhD

OUTLINE

- Cellular components of the CNS
- Pathology of Neurons
- Pathology of Glia
- Microscopic appearance of common CNS disease processes
- Introduction to CNS development

Cellular components of the CNS

- Meninges
- Neurons
- Glia
  - Astrocytes
  - Oligodendroglia
  - Ependymal Cells
- Choroid Plexus
- Microglia

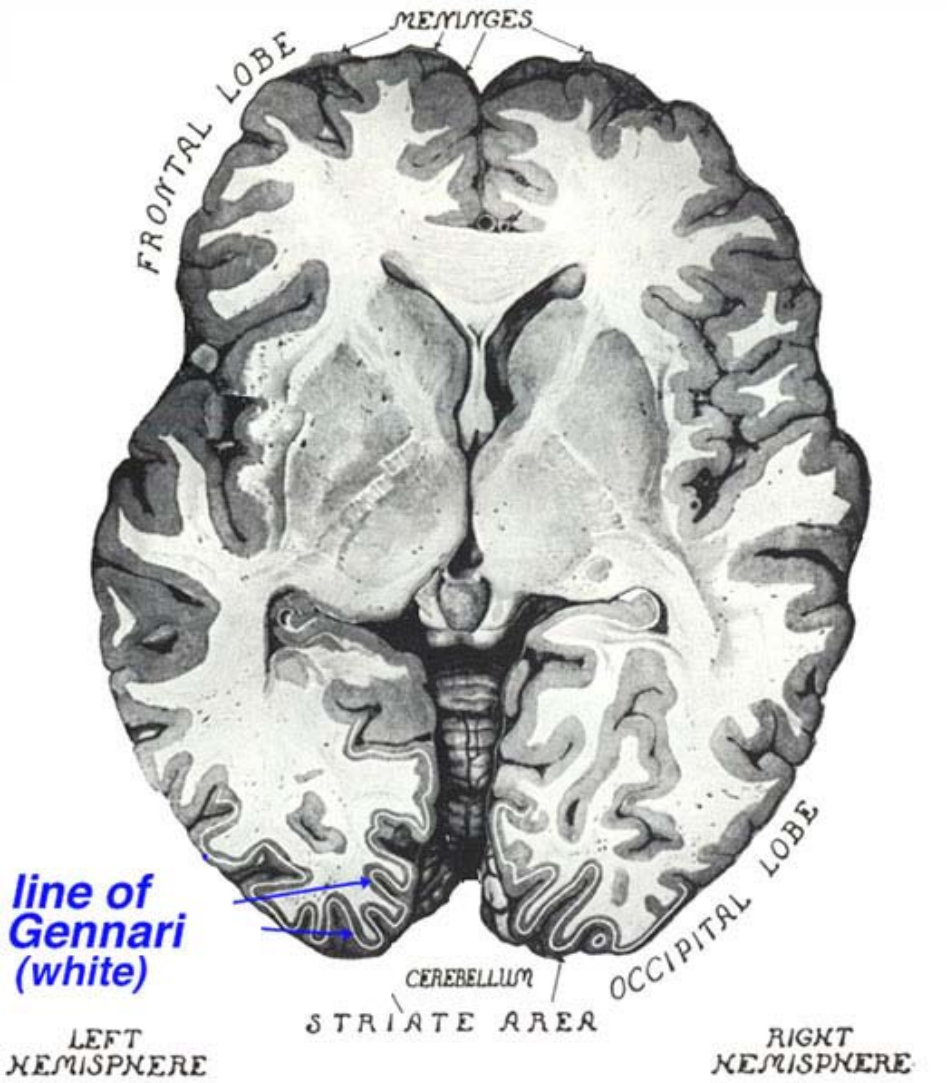
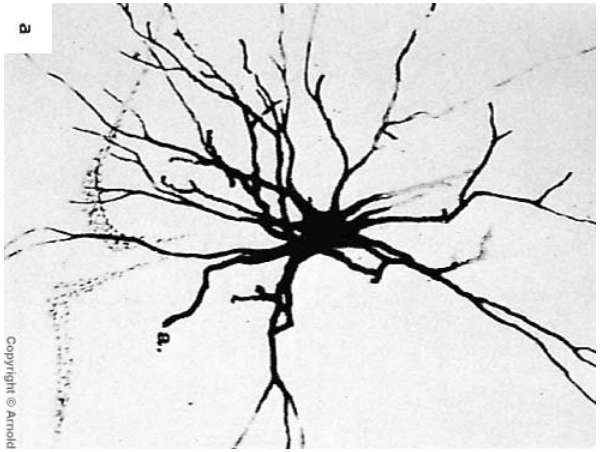


Figure 5. Horizontal section of the brain showing the line of Gennari in the striate cortex. From Polyak (1957).

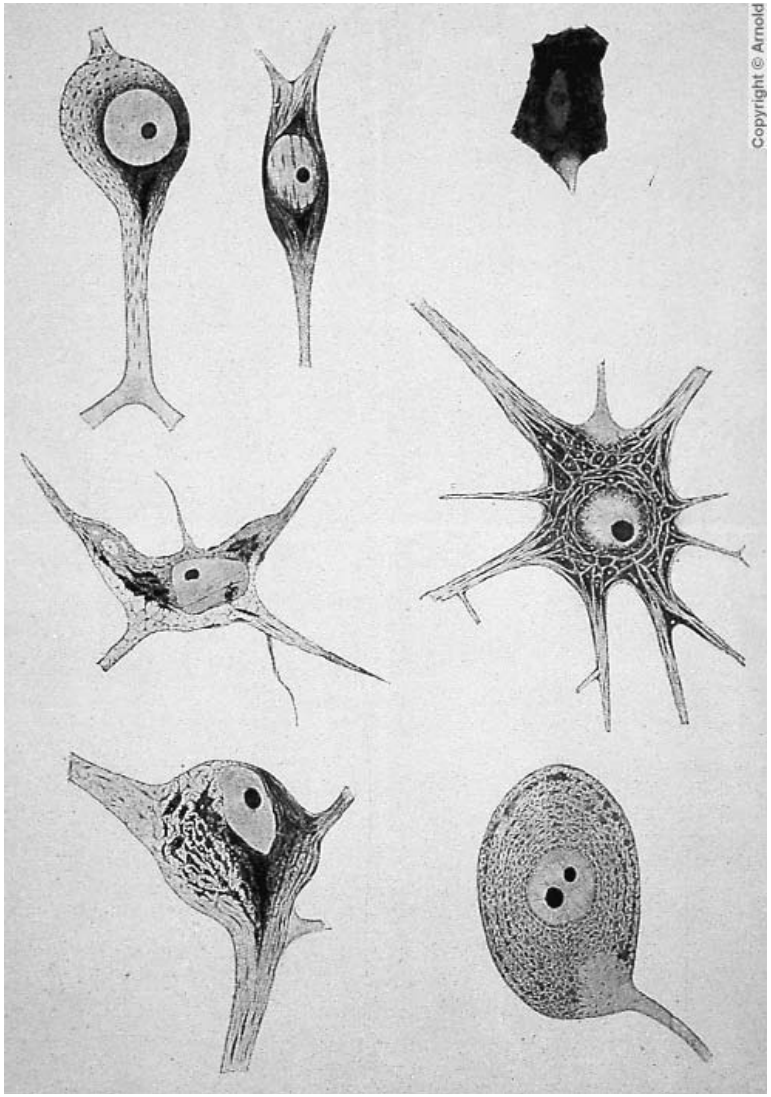
An Axial Section Of Human Cortex

Neurons

- About 10^{11} neurons in the CNS
- Great variation in size and shape
- All have dendrites, soma and axon
- Generally have abundant cytoplasm and prominent nucleolus (“fried egg”)
- Nissl substance composed of RER
- Can be organized in groups (nuclei, ganglia) or in layers
- Selective vulnerability of some types

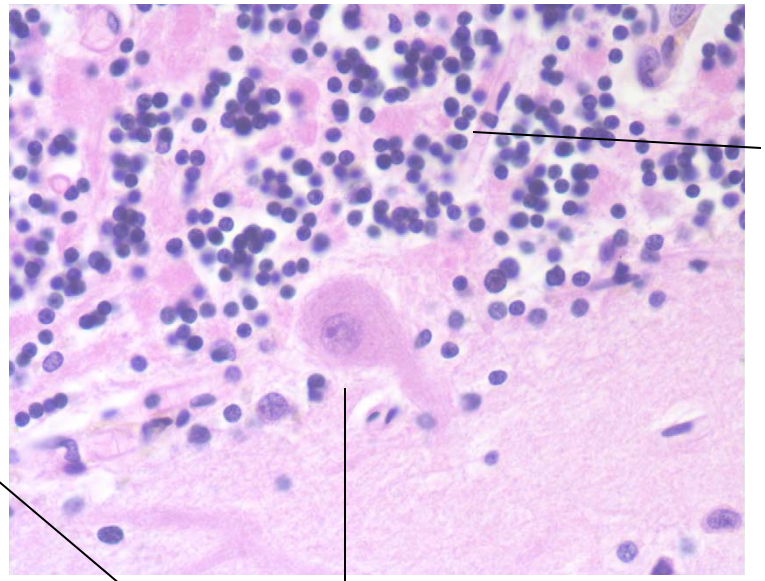


Dendritic Tree

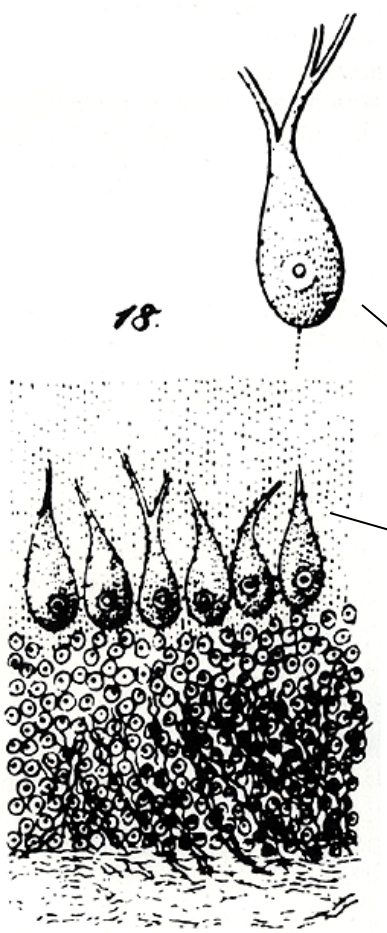


Neurons Drawn by Franz Nissl 1860-1919

Neurons

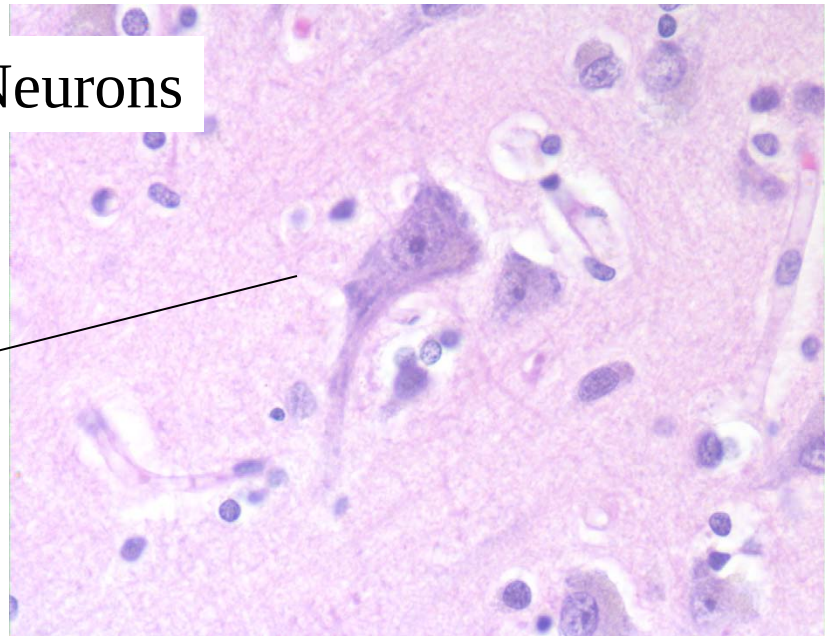


Cerebellar granule neurons



Cerebellar Purkinje Neurons

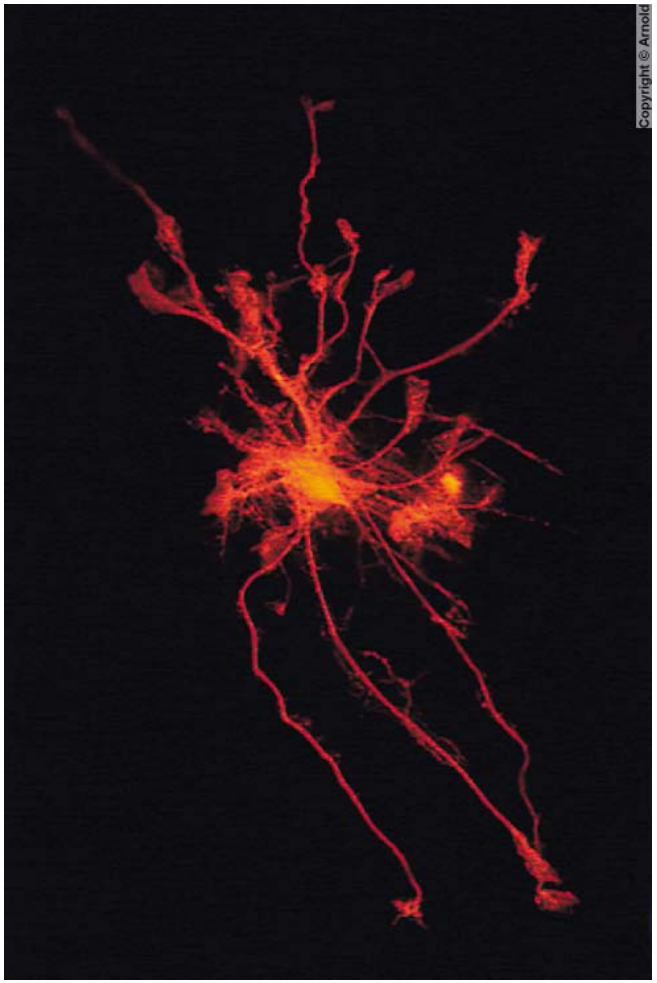
Cerebral Cortical Neuron



Glia

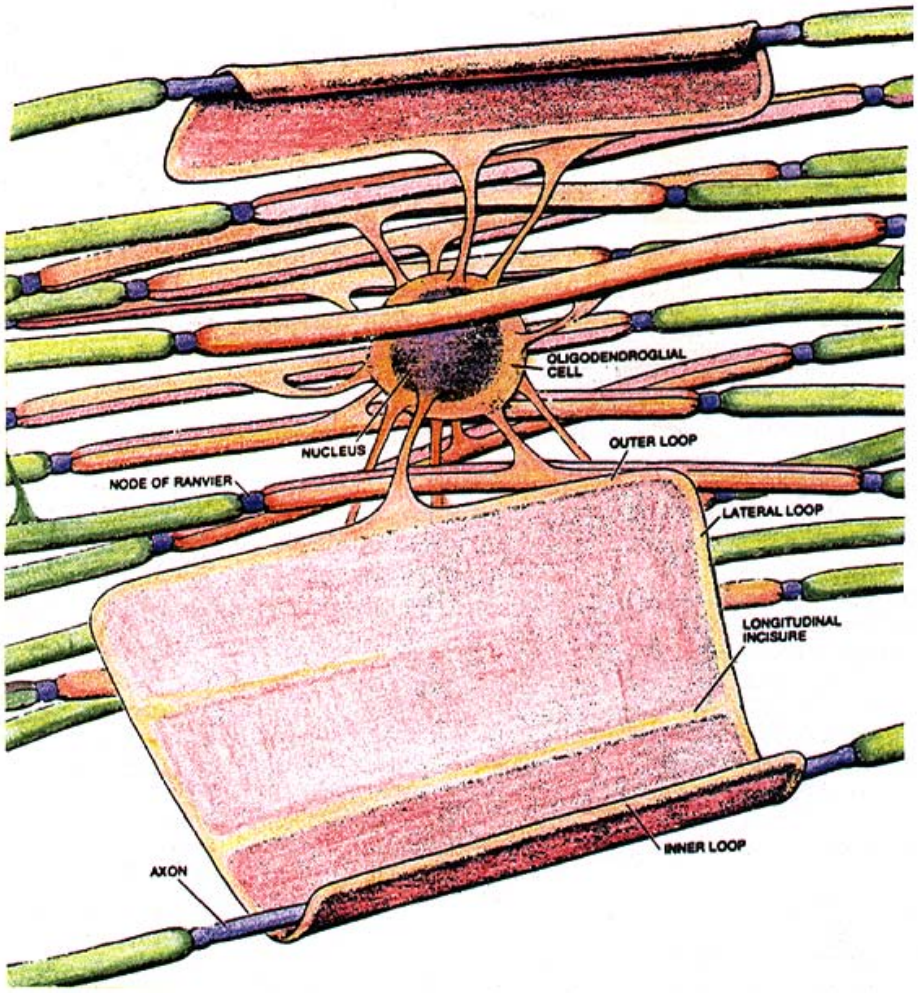
- Astrocytes
- Oligodendroglia
- Ependymal Cells

(Microglia)

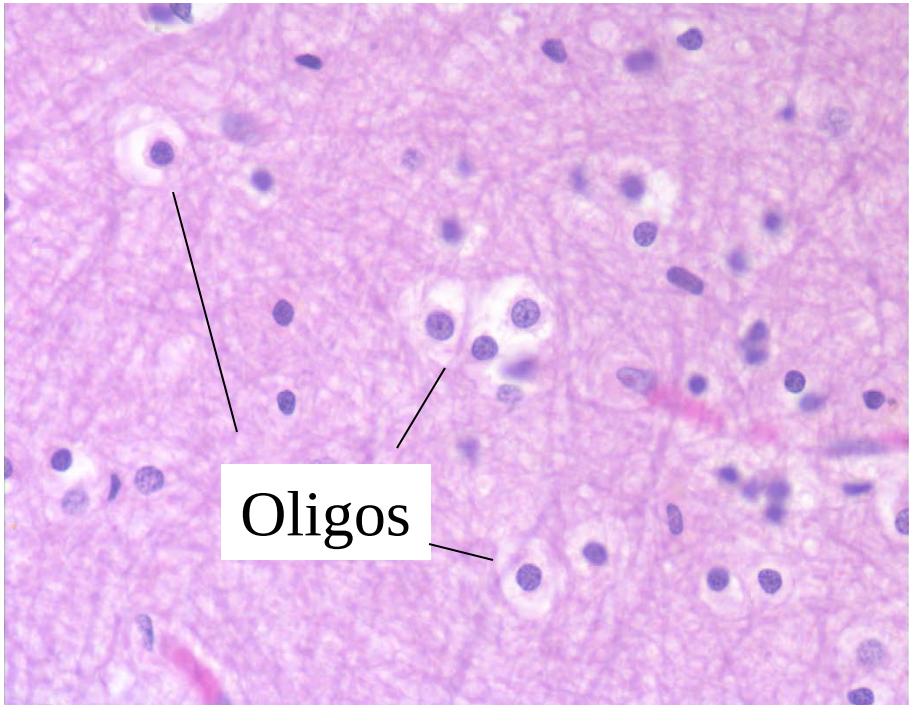


Act as neuronal support system, react to injury, regulate metabolism

Glia - Oligodendrocytes



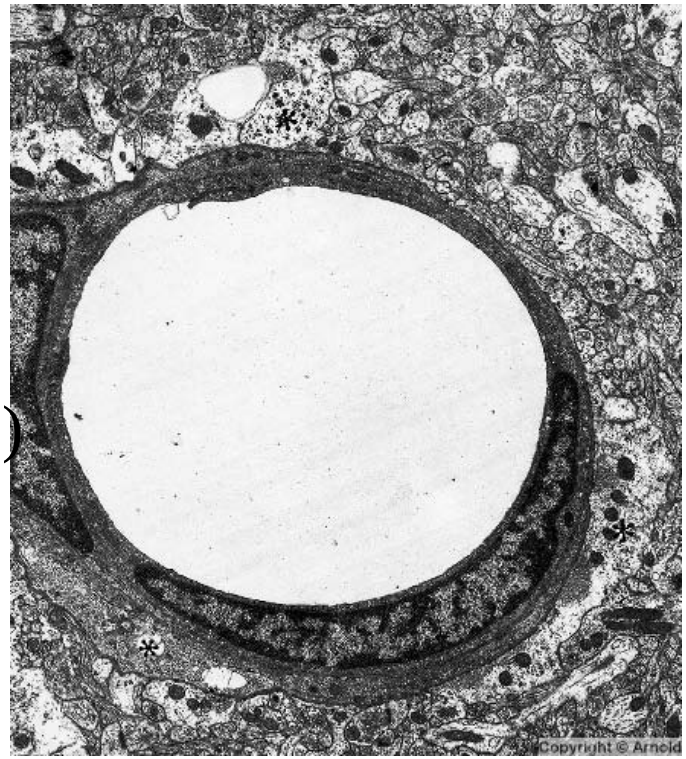
- Common in white matter
- Cytoplasmic processes of oligodendrocytes wrap around and insulate axons.
- Small, round, lymphocyte-like nuclei with dense chromatin

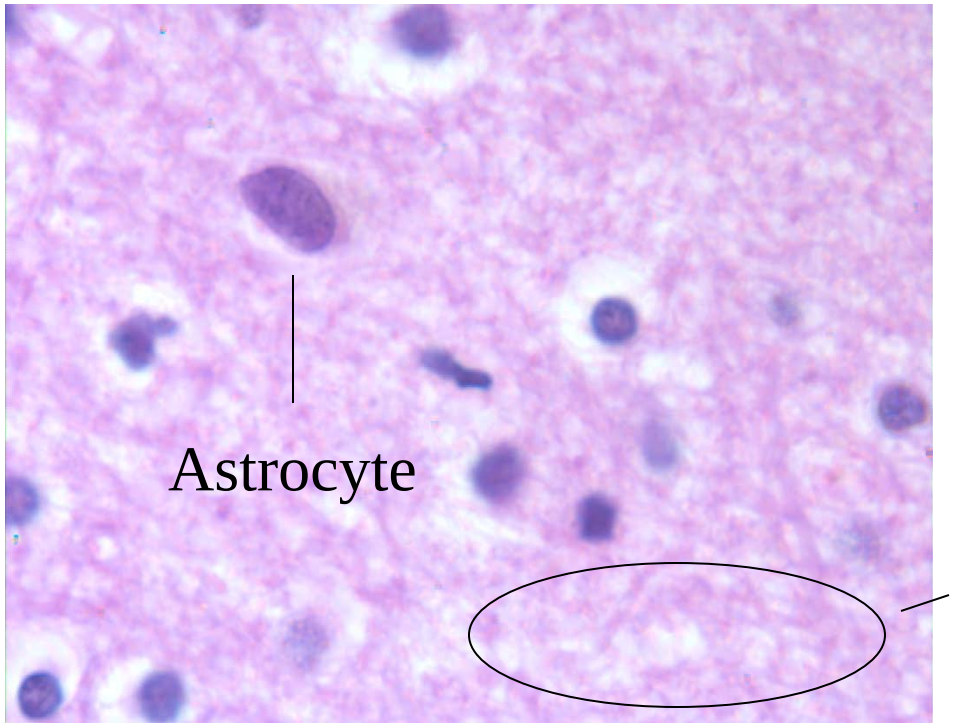


- Can have clear “halos” around cells

Glia - Astrocytes

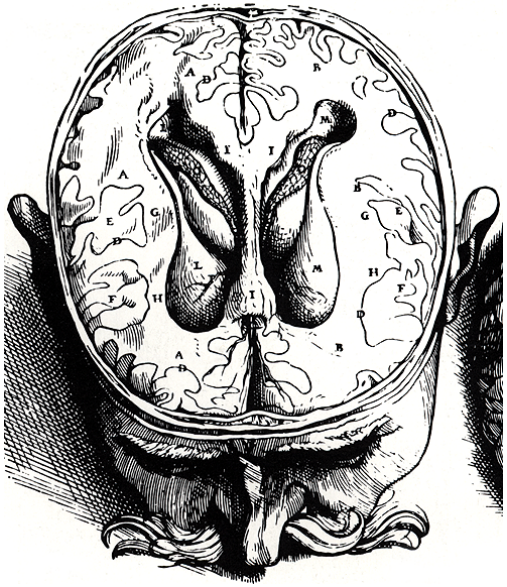
- Branched cells found in both white and grey matter
- Astrocytic processes abut neurons, vessels, the pia and ependyma (glia limitans)
- Act as metabolic buffers, detoxifiers, suppliers of nutrients, and physical barriers





- Astrocytic nuclei are round to oval and slightly larger than those of oligodendrocytes
- Major cell in CNS repair

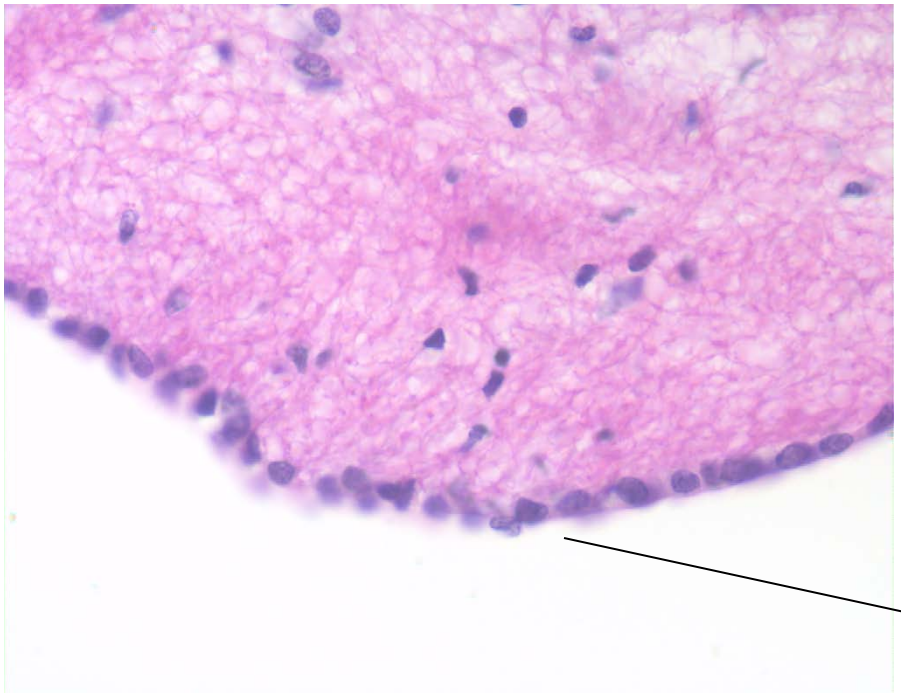
Neuropil = “nerve felt”



Ependyma

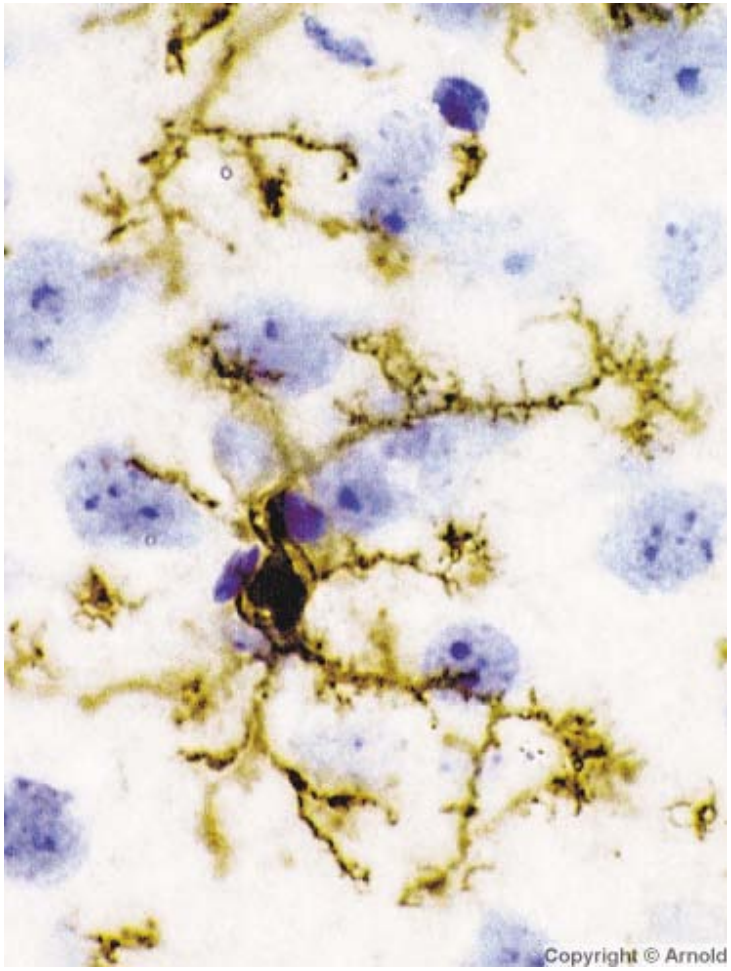
- Cuboidal to columnar cells lining the ventricular system
- Cilia/microvilli on apical surface
- Provide barrier between brain and CSF

Andreas Vesalius
1514-1564



- Thought to be involved in transport between the brain and CSF

Ependymal Cells

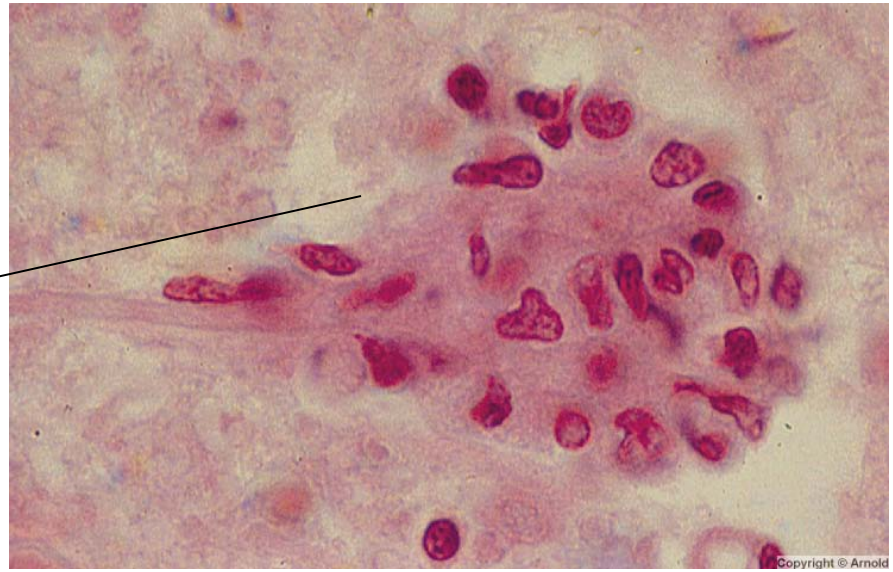


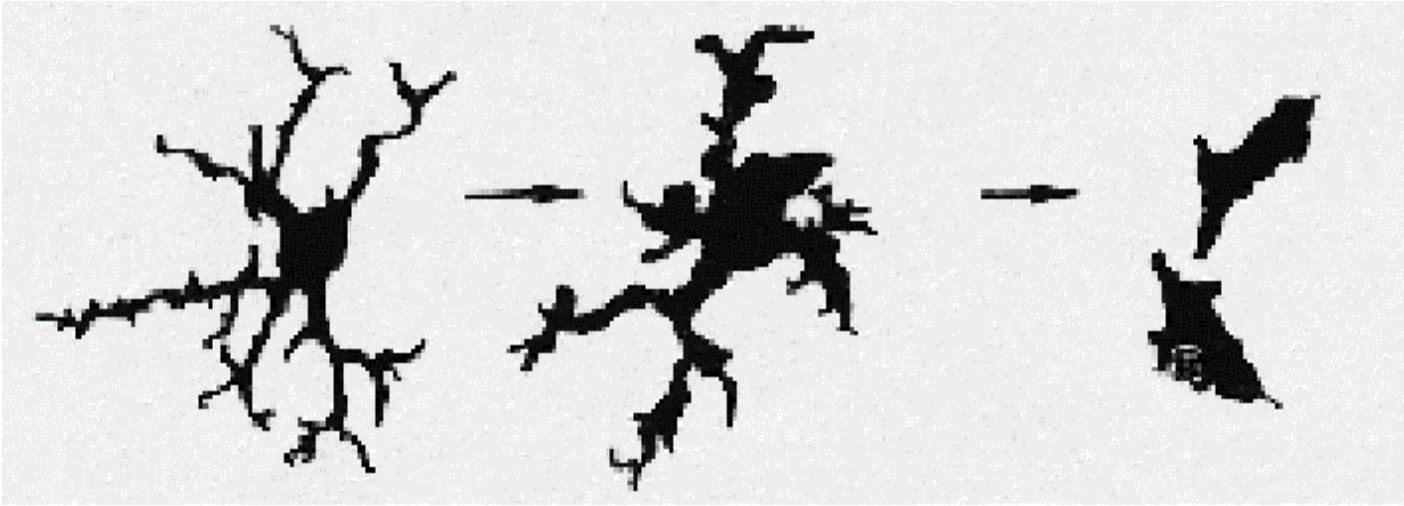
Microglia

- Mesoderm-derived cells that act as a fixed macrophage/ monocyte system in the brain
- Proliferate and migrate in response to infection/injury
- Phagocytic
- Act as CNS antigen-presenting cells

Microglia

Neuronophagia

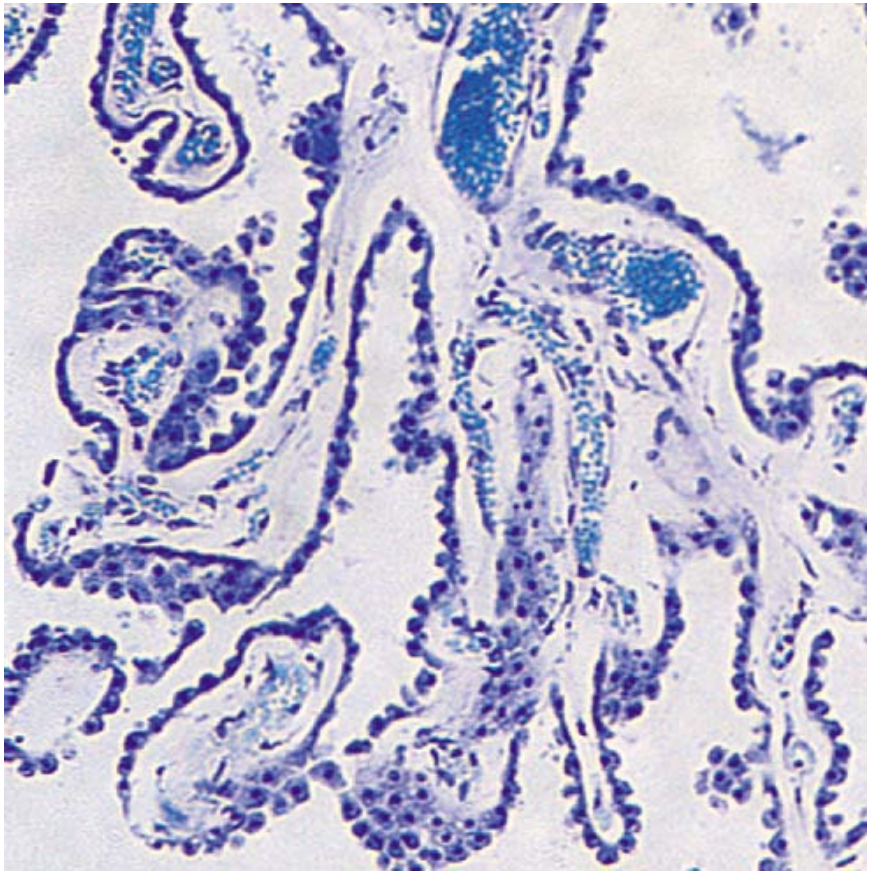




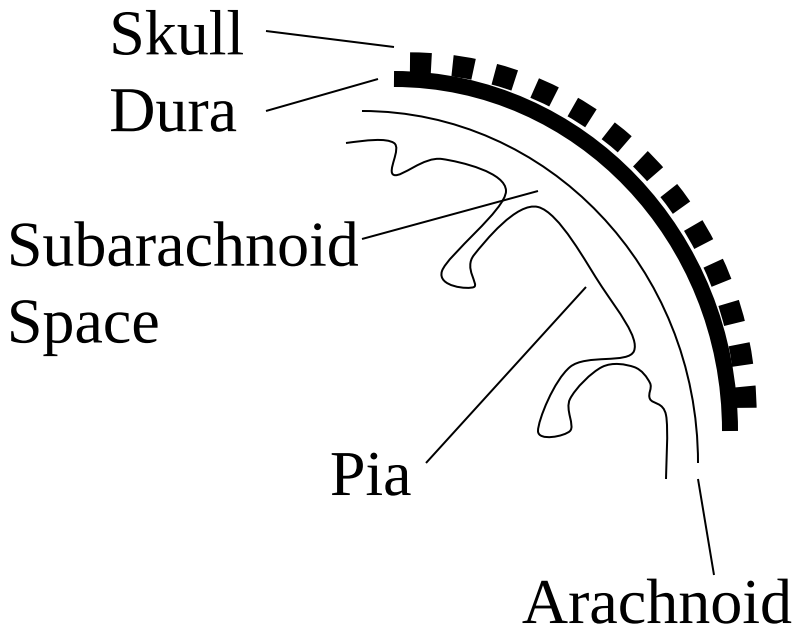
Resting Activated Phagocytic

Choroid Plexus

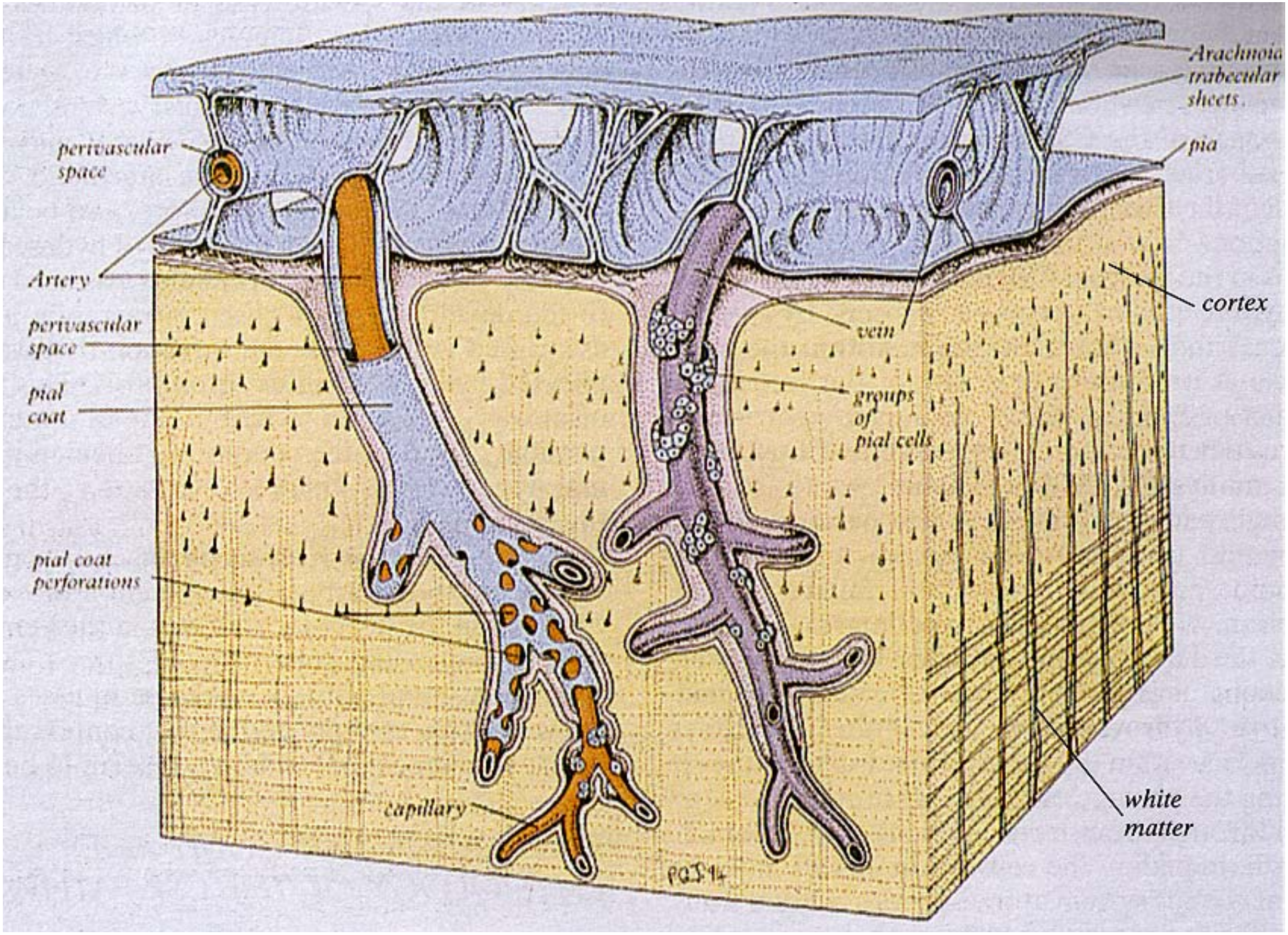
- Specialized cells derived from the ependyma that secrete CSF
- Papillary fronds of cuboidal epithelium covering vascular cores
- Tight junctions maintain blood-CSF barrier
- About 20ml of CSF produced per hour
- Normal CSF volume is ~140ml
- ~25ml in ventricles, the rest in the subarachnoid space



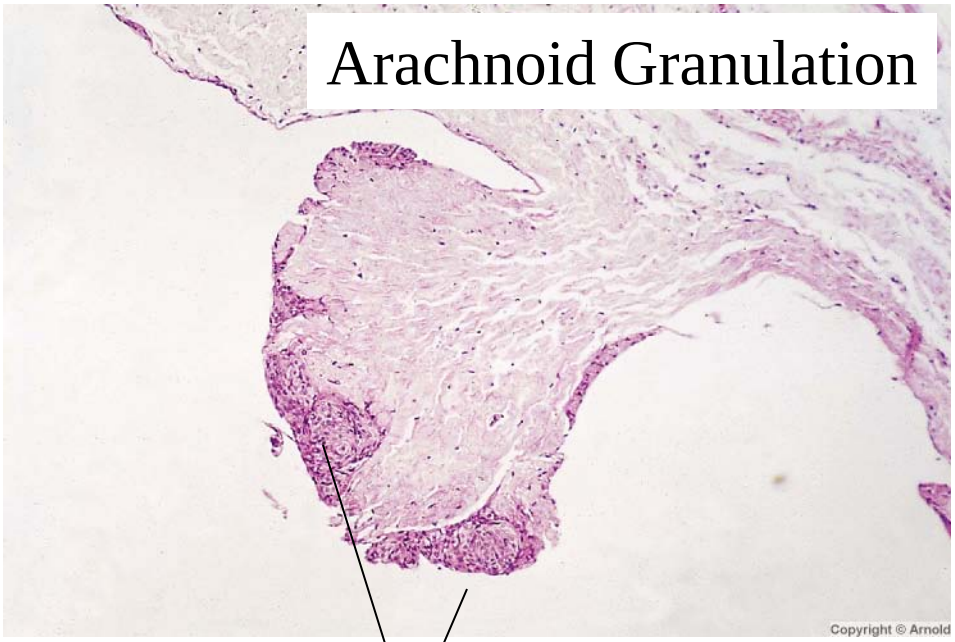
Meninges



- Fibrous dura closely attached to inner skull periostium
- The leptomeninges (arachnoid and pia mater) are made up of meningothelial cells and connective tissue
- The thin, translucent arachnoid membrane drapes over the brain
- The delicate pia mater remains closely attached to the entire cortical surface, and invests arteries as they penetrate the brain
- CSF circulates in the “subarachnoid” space between the arachnoid and pia


Arachnoid trabecular sheets
pia
perivascular space
Artery
perivascular space
pial coat
cortex
vein
groups of pial cells
pial coat perforations
capillary
white matter

CSF flows out of the sub-arachnoid space into the dural sinuses through the arachnoid granulations protruding into the sinuses



Arachnoid cap cells attached to the sinus endothelium

The Black Stain “la reazione nera” formulated by Golgi in 1873

Fixation of CNS tissue in potassium bichromate with application of silver nitrate

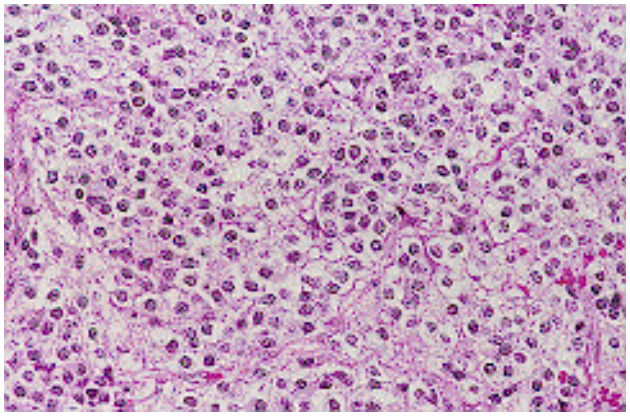
Camillo Golgi (1843-1923), Pavia, Italy

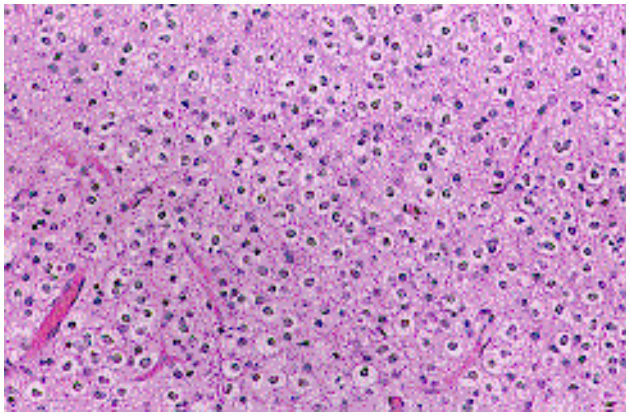
Ramon y Cajal improved on Golgi's silver stain, and developed a gold chloride-mercury stain for astrocytes

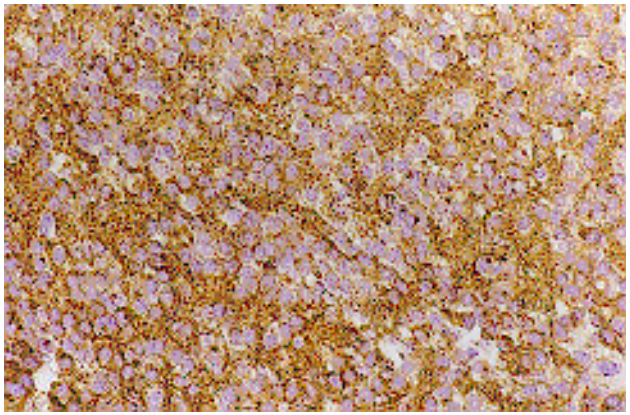
Golgi and Ramon y Cajal shared the 1906 Nobel Prize for Medicine In recognition of their Work on the structure Of the nervous system

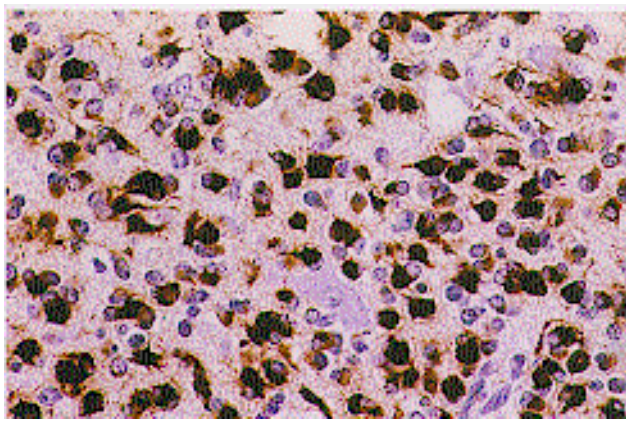
Santiago Ramon y Cajal (1852-1934), Barcelona and Madrid, Spain

Special Stains In Neuropathology Today









Synaptophysin
(Neuronal)

GFAP
(Glial)

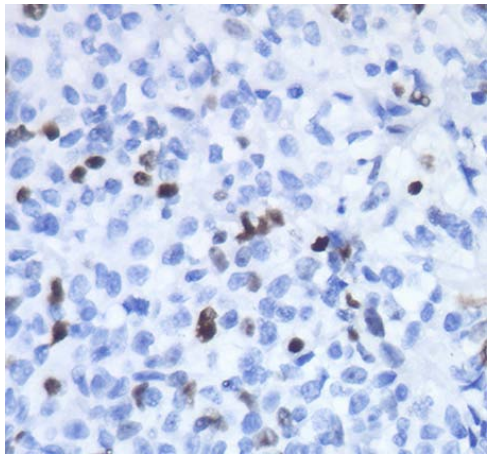
Commonly Used Special Stains

Immunohistochemical Stains

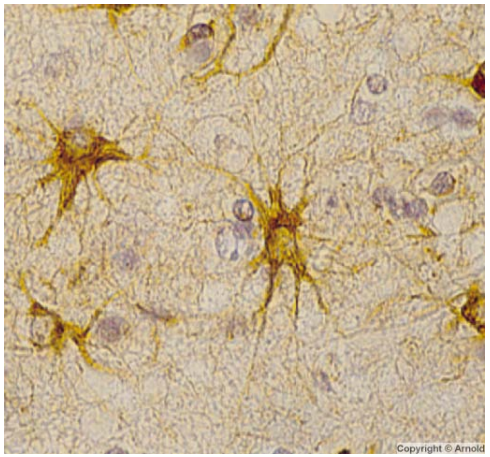
- Glia - GFAP (Glial Fibrillary Acidic Protein)
- Neurons - Synaptophysin, NeuN
- Proliferation – Ki67 (MIB-1)
- Microglia/Macrophages – CD68 (KP1), HAM56
- Lymphoid Cells – CLA, CD3 (T Cells), CD20 (B Cells)
- Infectious Agents – Toxoplasma, Adenovirus, JC Virus
- Inclusion Bodies – Ubiquitin, α-synuclein, Tau

<u>Other Stains</u>

Myelin – Luxol Fast Blue
Alzheimer Dz - Hirano Silver
Fungi – Methenamine silver (GMS)



MIB-1



GFAP

Johns Hopkins Department of Pathology

Patient: John Doe Procedure Date: 1/1/2002

Part 1-3: Temporal Mass (Biopsy):

Frozen Section Diagnosis: Low grade neoplasm

Final Diagnosis: Ganglioglioma, WHO Grade I, See Comment

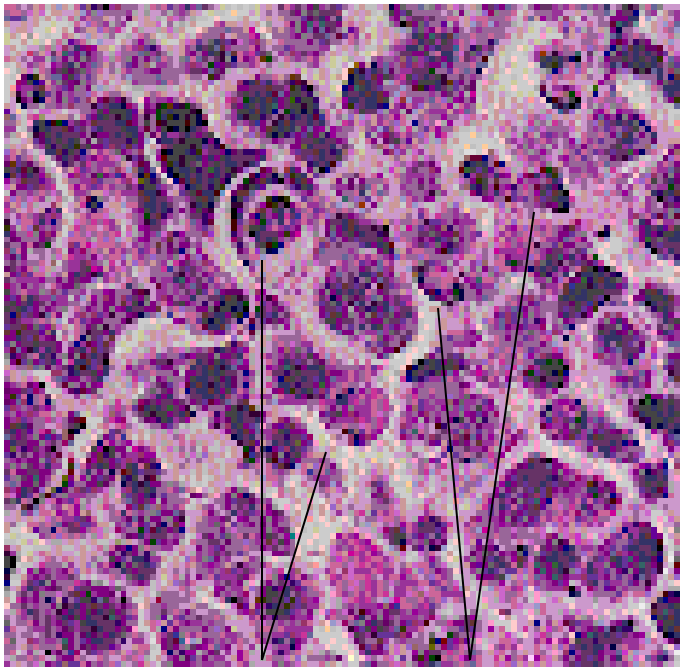
Comment: The tumor has a solid, non-infiltrating architecture, with no intra-tumoral axons detected using SM31 immunostains. Atypical neuronal and glial cells are present in the lesion, as evidenced by positive synaptophysin and GFAP immunostains. The MIB-1 proliferation index is low (1-2%)

Pathology of Neurons

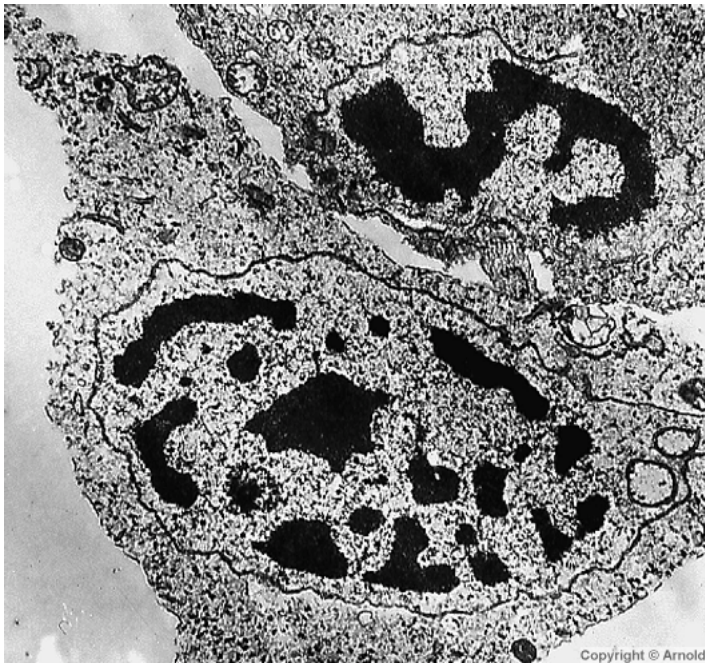
- Apoptotic neuronal cell death
- Hypoxic/ischemic neuronal necrosis
- Neuronal loss in neurodegenerative disease
- Axonal pathologies
  - Axonal degeneration following neuronal death
  - Neuronal changes following axonal damage
- Neuronal Inclusions

Neuronal Apoptosis

- Plays a major role in pruning neurons during CNS development
- Often caused by withdrawal of trophic factors
- DNA fragmentation (karyorrhexis) and condensation into “apoptotic bodies”
- Commonly seen in brain tumors



Apoptosis in Neuroblastic Tumor

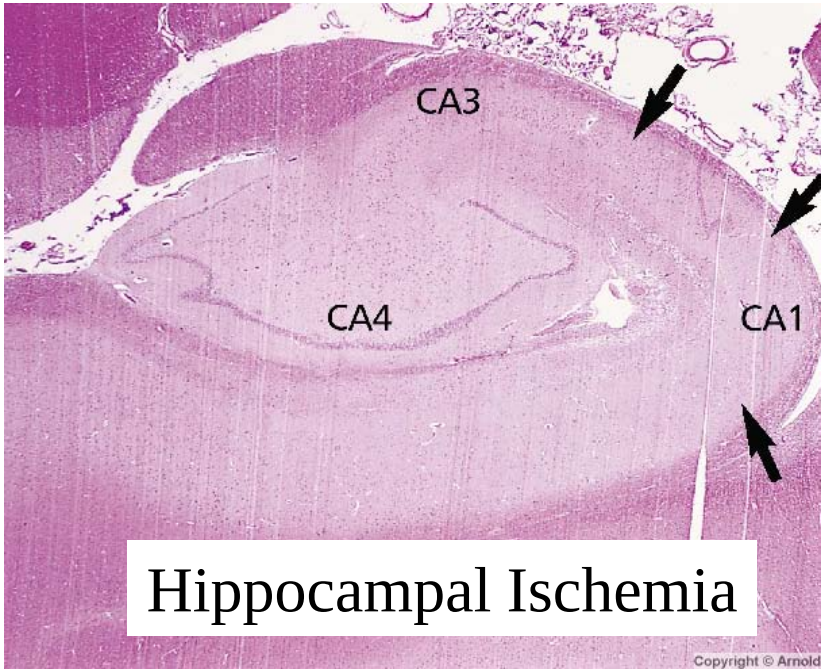


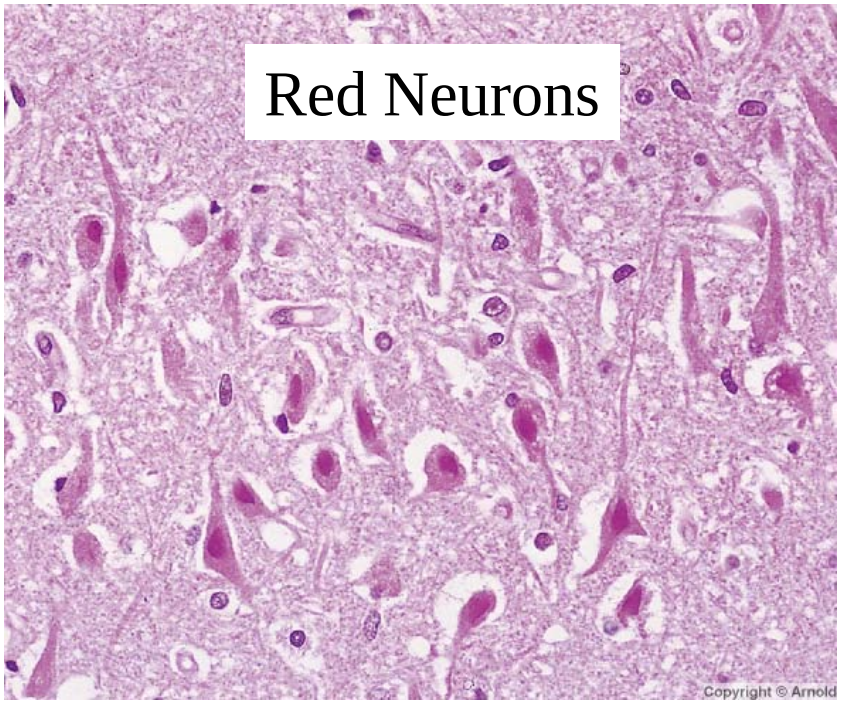
Fragmented Chromatin in Dorsal Root Ganglion Neuron

Necrosis
(Injury Induced Cell Death)

Heat, Toxic Agents, Hypoglycemia, <u>Hypoxic/Ischemic Damage</u>

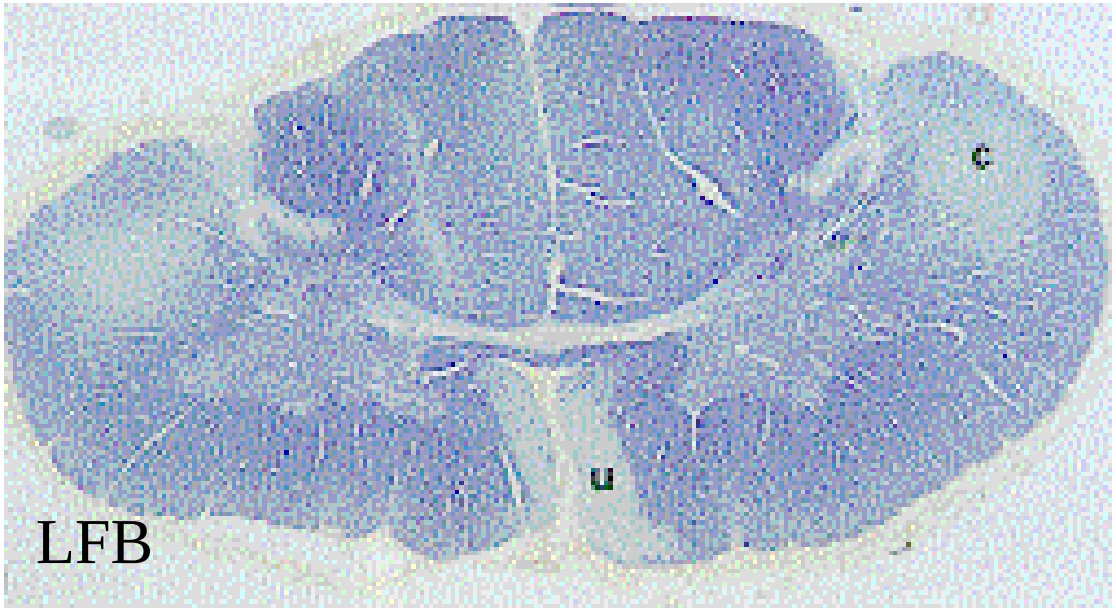
- Neurons in Region CA1 (hippocampus), Cortical layers 3 & 5, and Purkinje Cells are especially vulnerable
- See eosinophilic (red) discoloration within approximately 12 Hours
- If ischemia is severe/prolonged glia also die, and the necrotic region is cleared away by macrophages



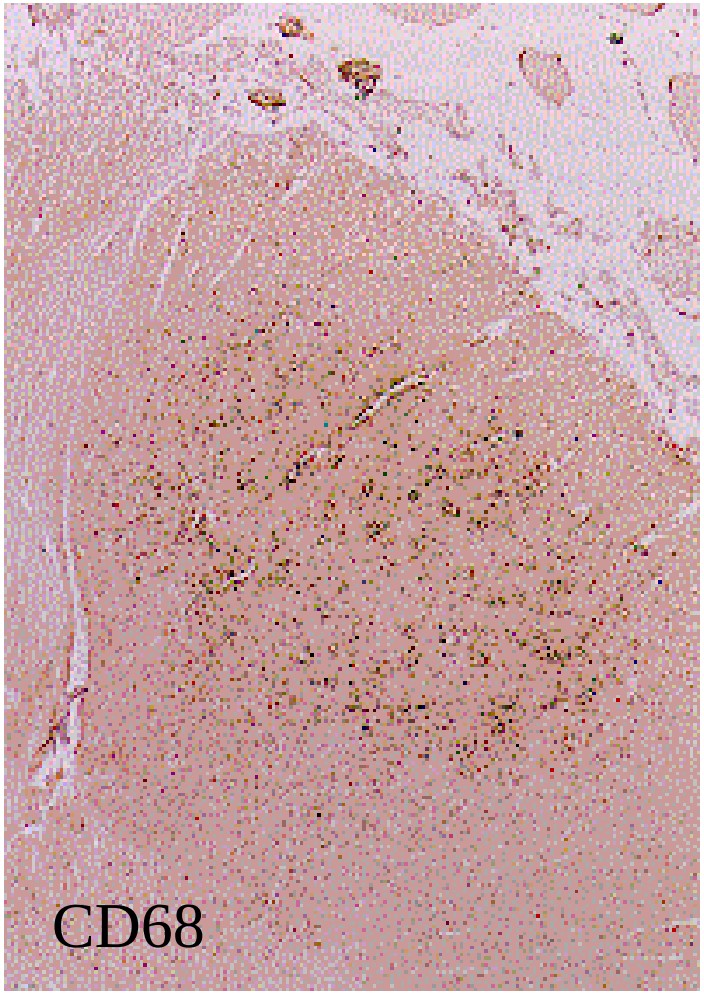


Axonal Degeneration Following Neuronal Loss

A LFB myelin stain and CD68 macrophage immunostain highlight the axonal degeneration in the crossed and uncrossed corticospinal tracts in Amyotropic Lateral Sclerosis (ALS)



LFB


CD68

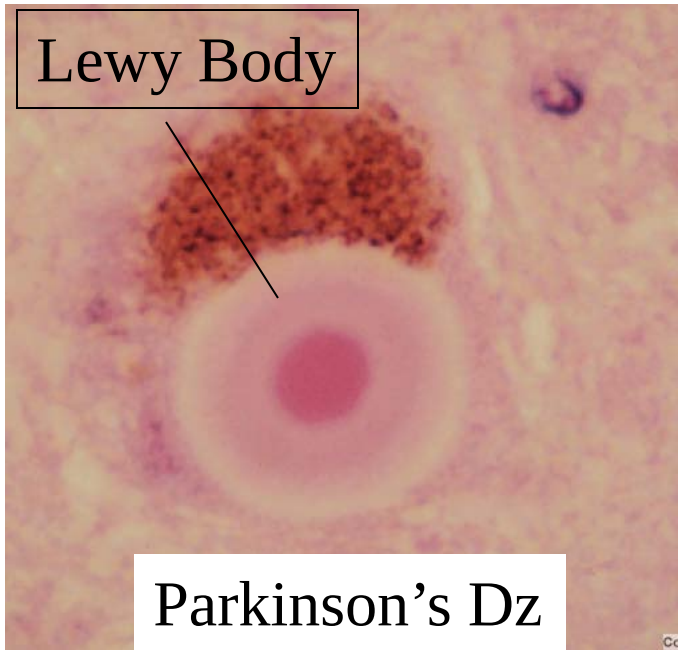
Neuronal Inclusions in Neurodegenerative Disease

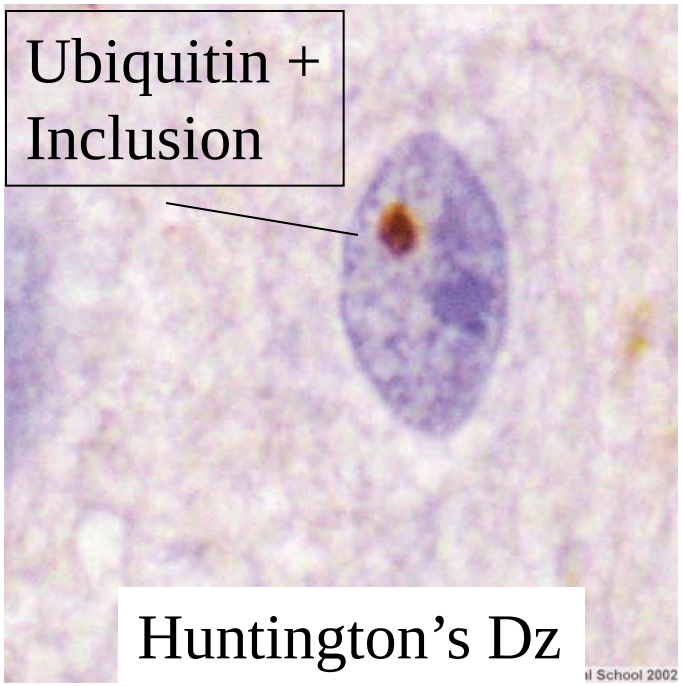
Cytoplasmic

- Alzheimer's – Neurofibrillary Tangles
- Parkinson's - Lewy body
- Pick's – Pick body

Nuclear

- Huntington's



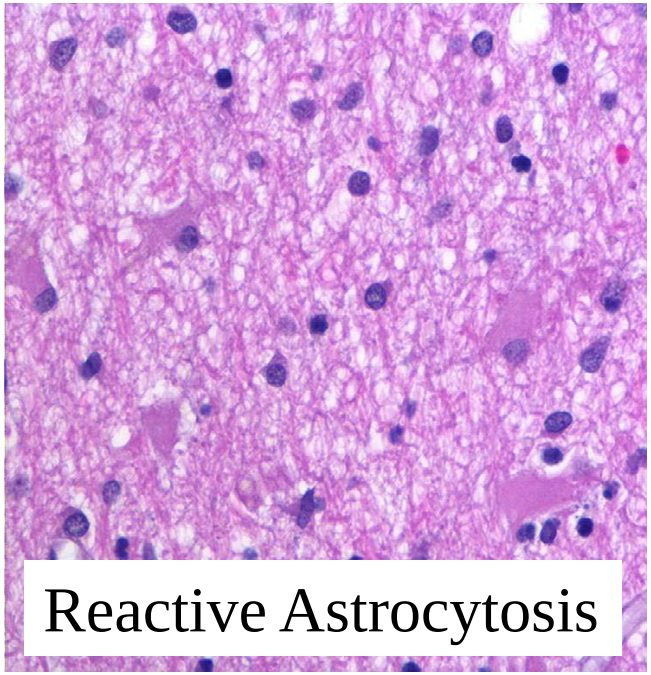


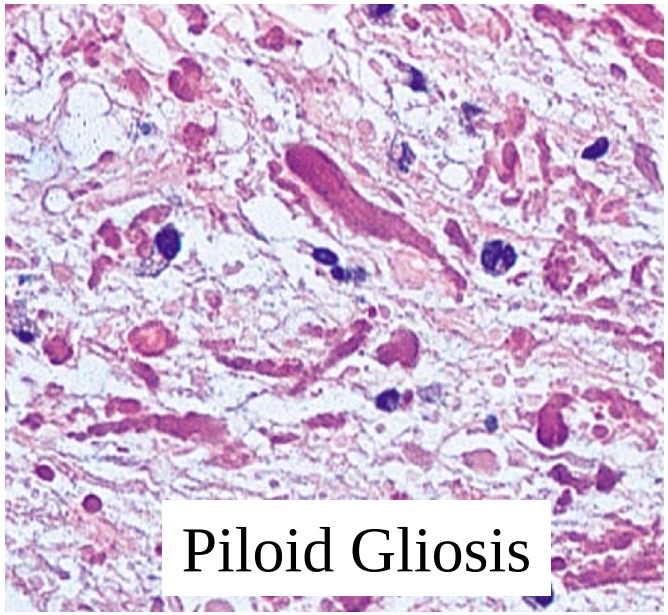
Pathology of Glia

Reactive Astrocytosis
A non-specific reaction to infection, seizures, autoimmune disease, infarction, etc

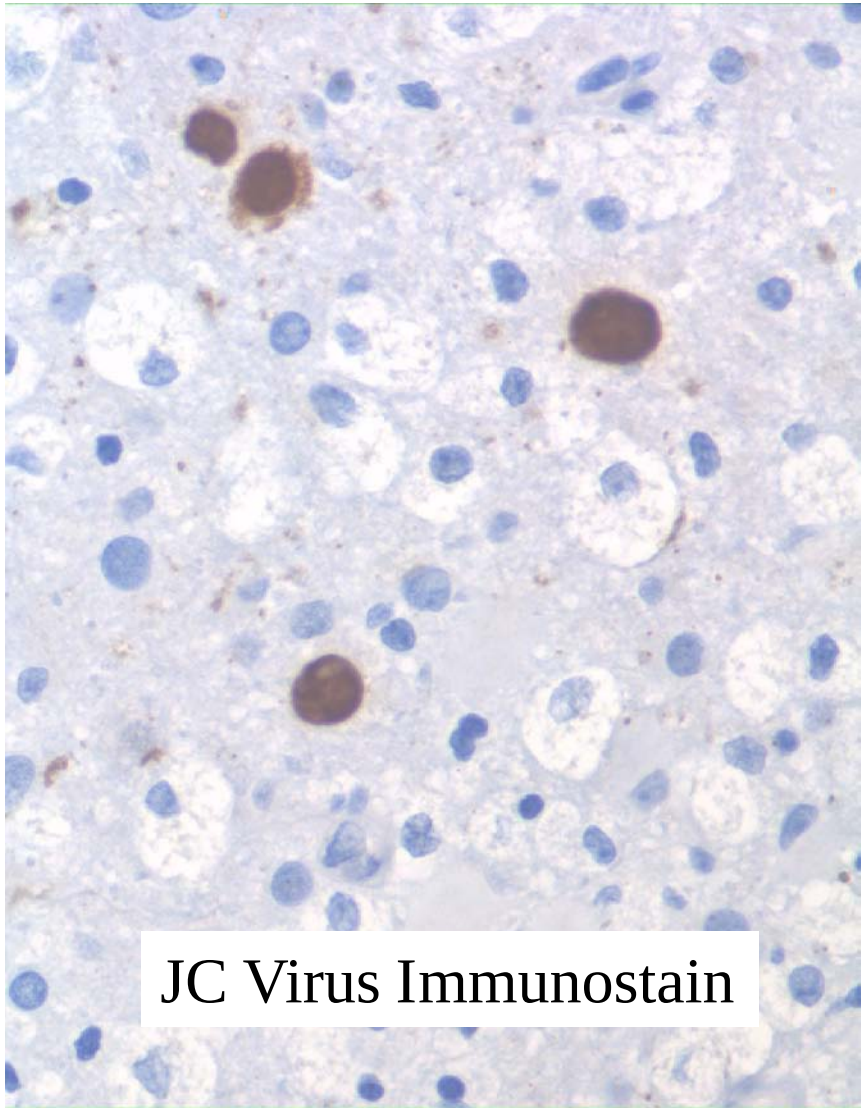
Fibrillary Gliosis
Proliferation of reactive astrocytes

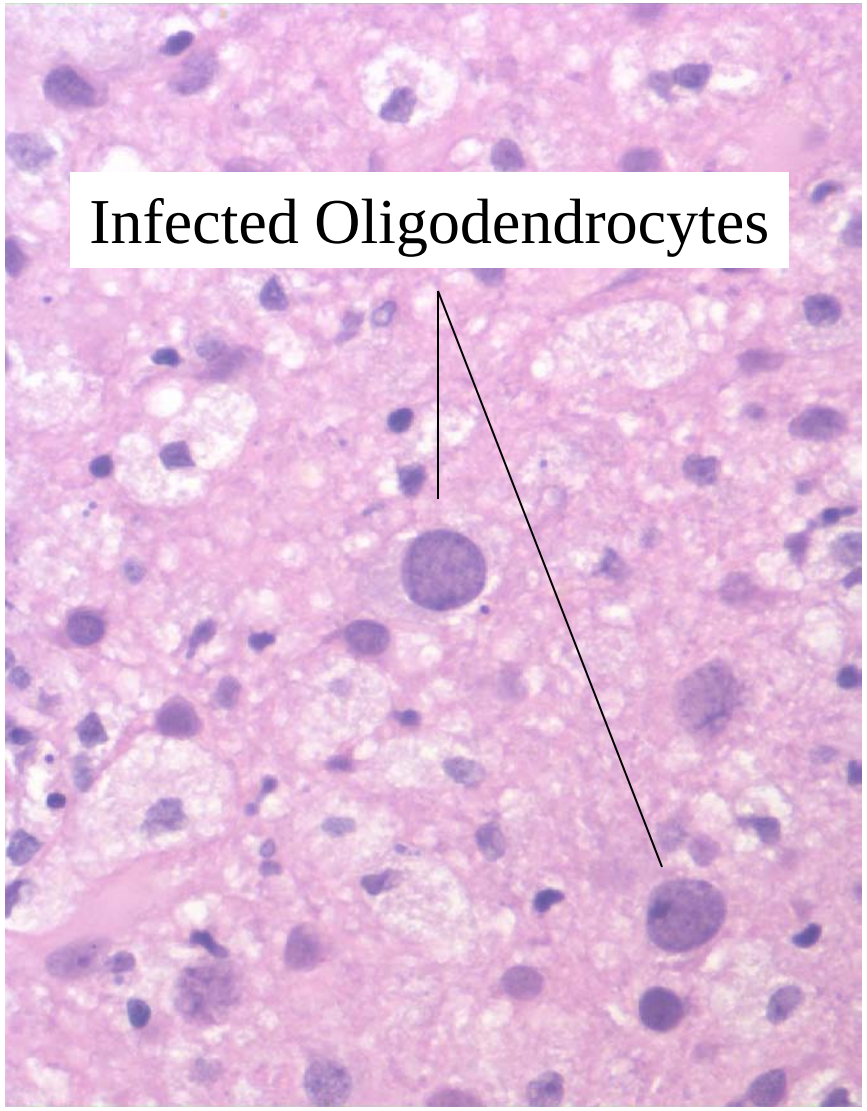
Piloid Gliosis
Seen around spinal cord cavities (syrinx)
And other long-standing reactive gliosis
In cerebellum and hypothalamus. Also
In Alexander's disease


Reactive Astrocytosis


Piloid Gliosis

Glial Nuclear Changes in Progressive Multifocal Leukoencephalopathy

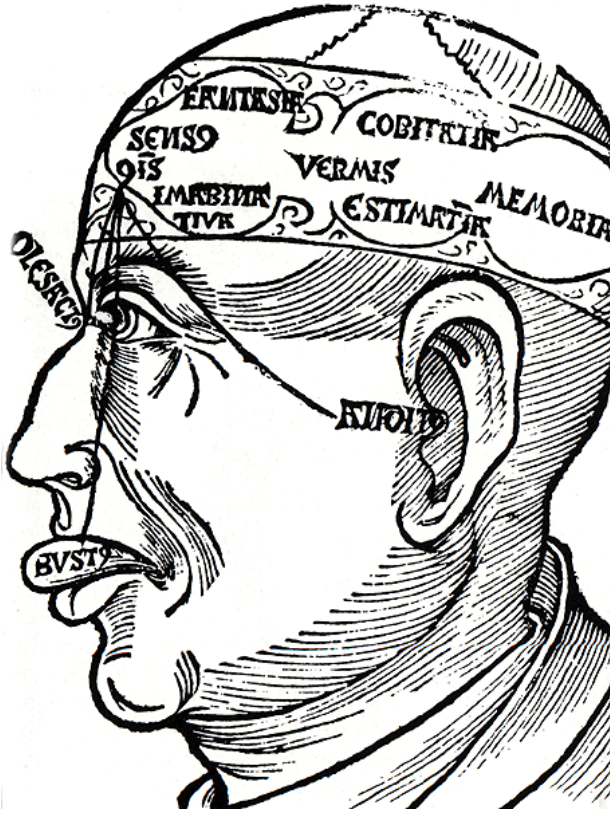




Overview of CNS Pathology

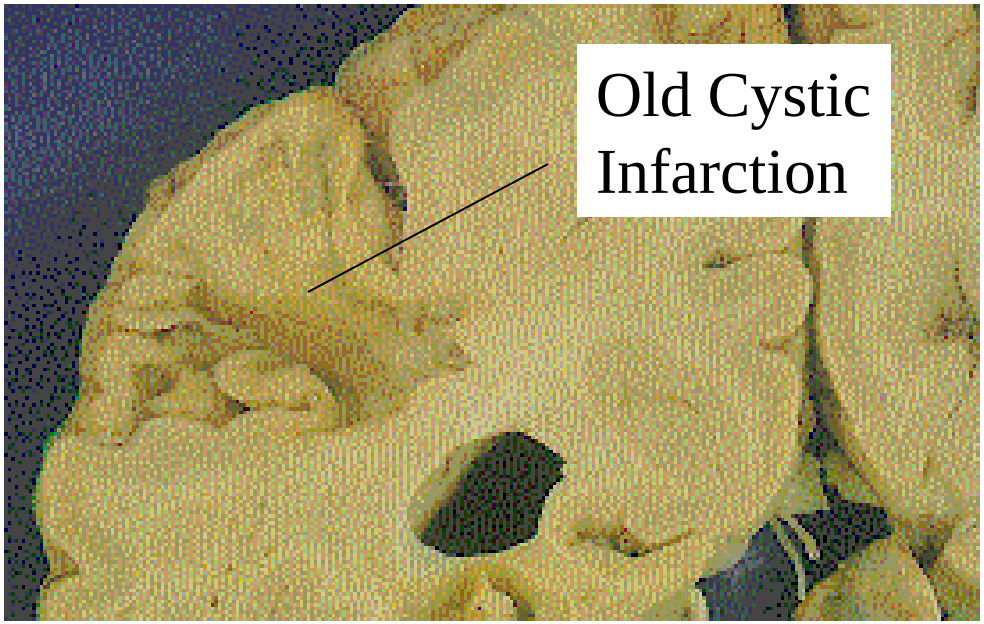
This last section in intended to introduce you to the microscopic appearance of several common CNS diseases. More detailed examples and explanations will be provided in later lectures.

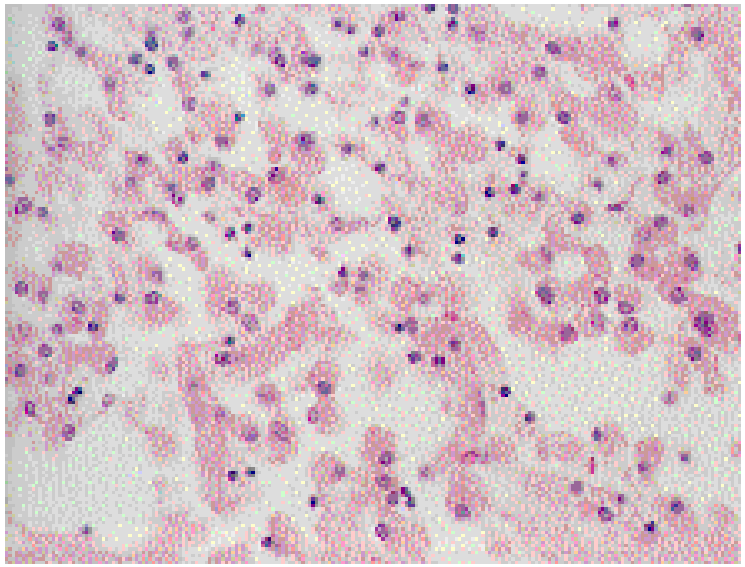
- Ischemic damage/stroke
- Infection – viral, bacterial, fungal
- Neurodegenerative disease
- Demyelinating disease
- Trauma
- Tumors



Infarction

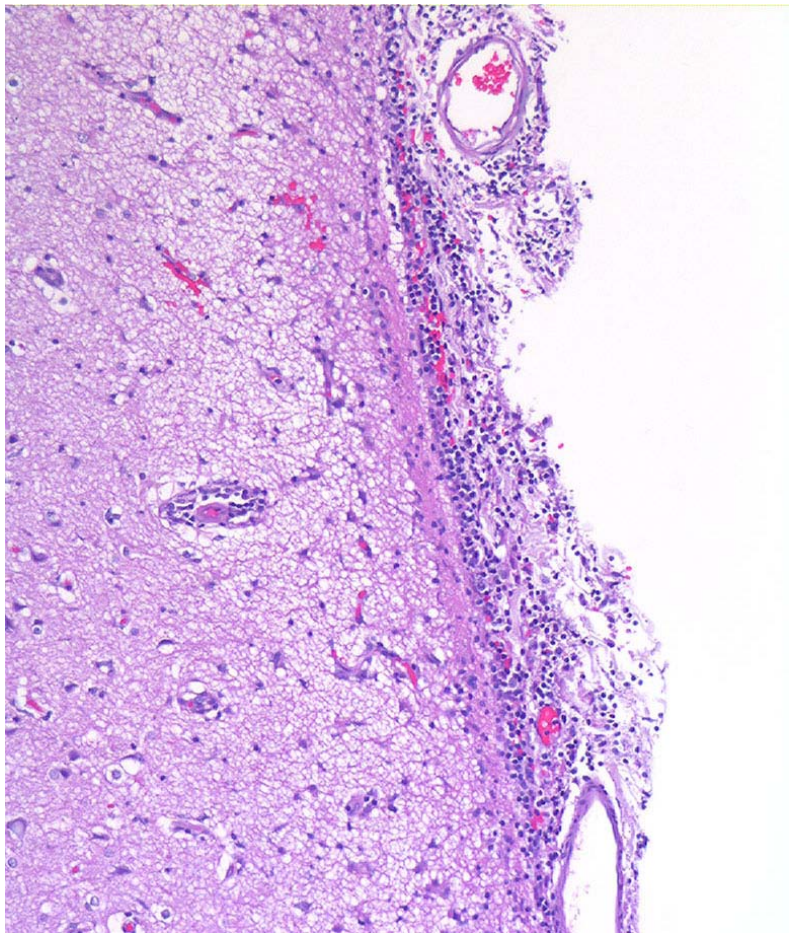
Hours – Days: Neurons become eosinophilic and shrunken
Neutrophils infiltrate the lesion
Days - Weeks: Neurons gone, macrophages infiltrate lesion
Reactive astrocytosis around edge
Weeks – Months: Cystic cavity





Macrophages

Bacterial Infection

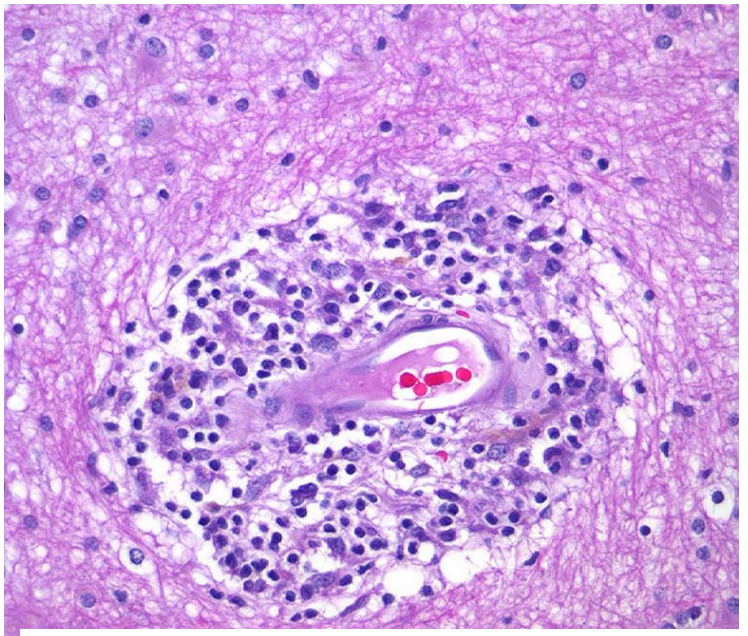


Meningitis

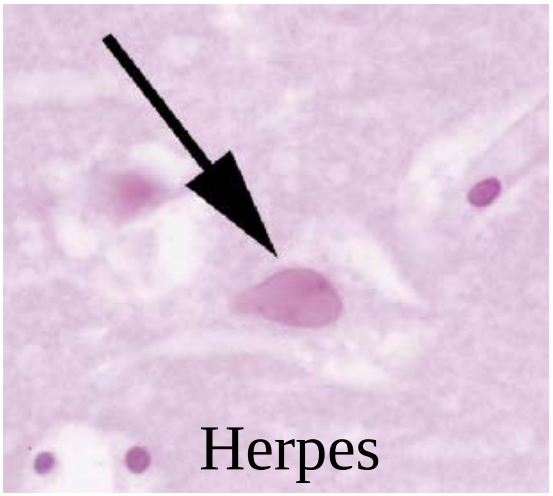
Abcess

Viral Infection

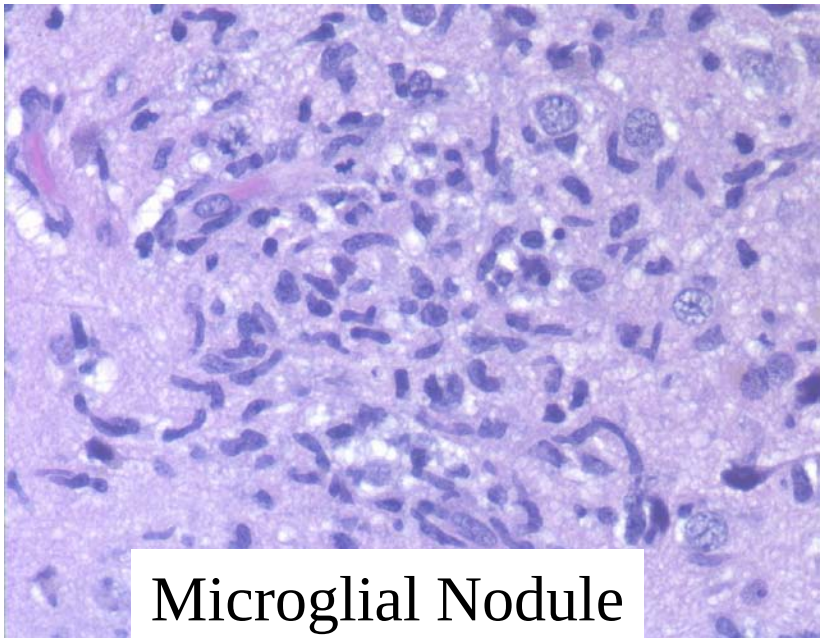
- Viral agents involving CNS include echo, coxsackie, herpes, mumps, measles adenovirus, polio, VZV, EBV, CMV, rabies, arboviruses, JC, HIV
- Can cause meningitis or encephalitis
- Often see perivascular and intraparenchymal lymphocytes
- Elongated microglial “rod” cells and microglial nodules also commonly present



Perivascular Lymphocytes



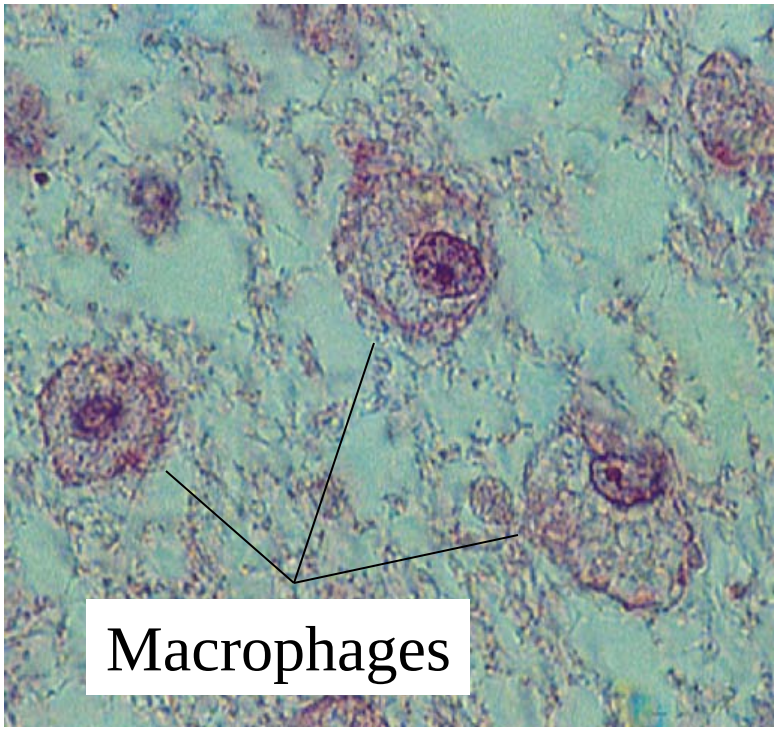
Herpes

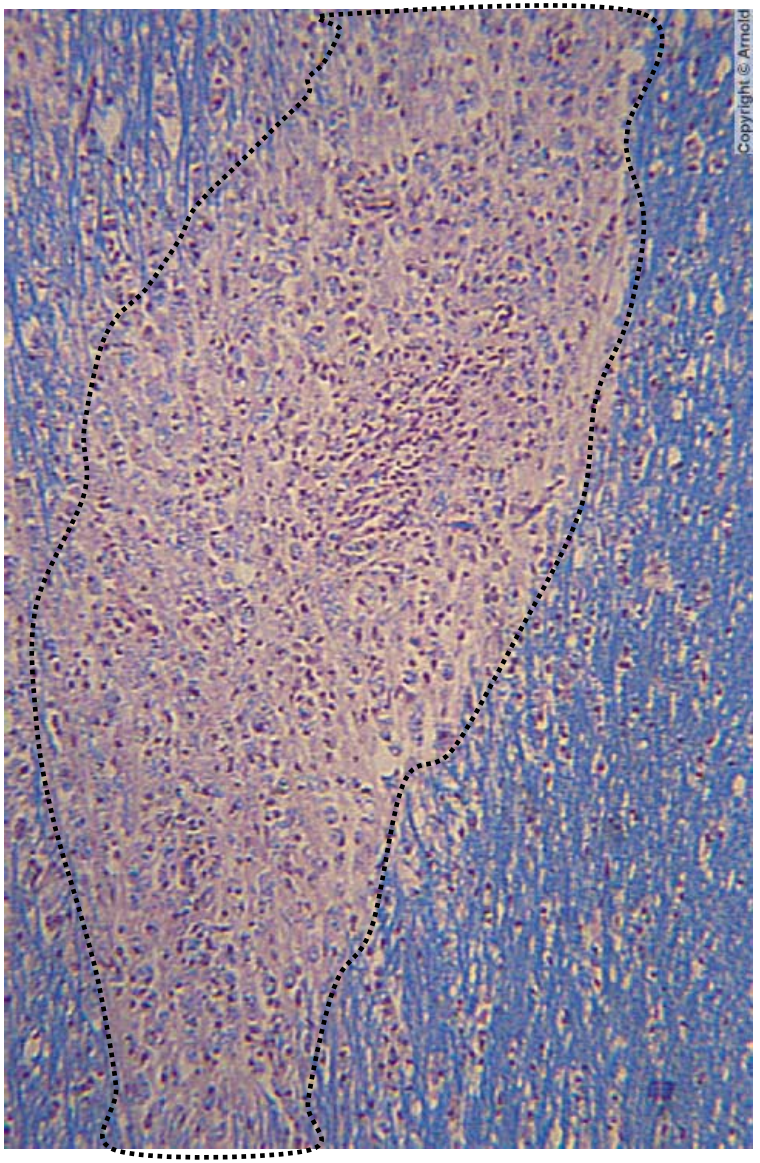


Microglial Nodule

Demyelinating Disease

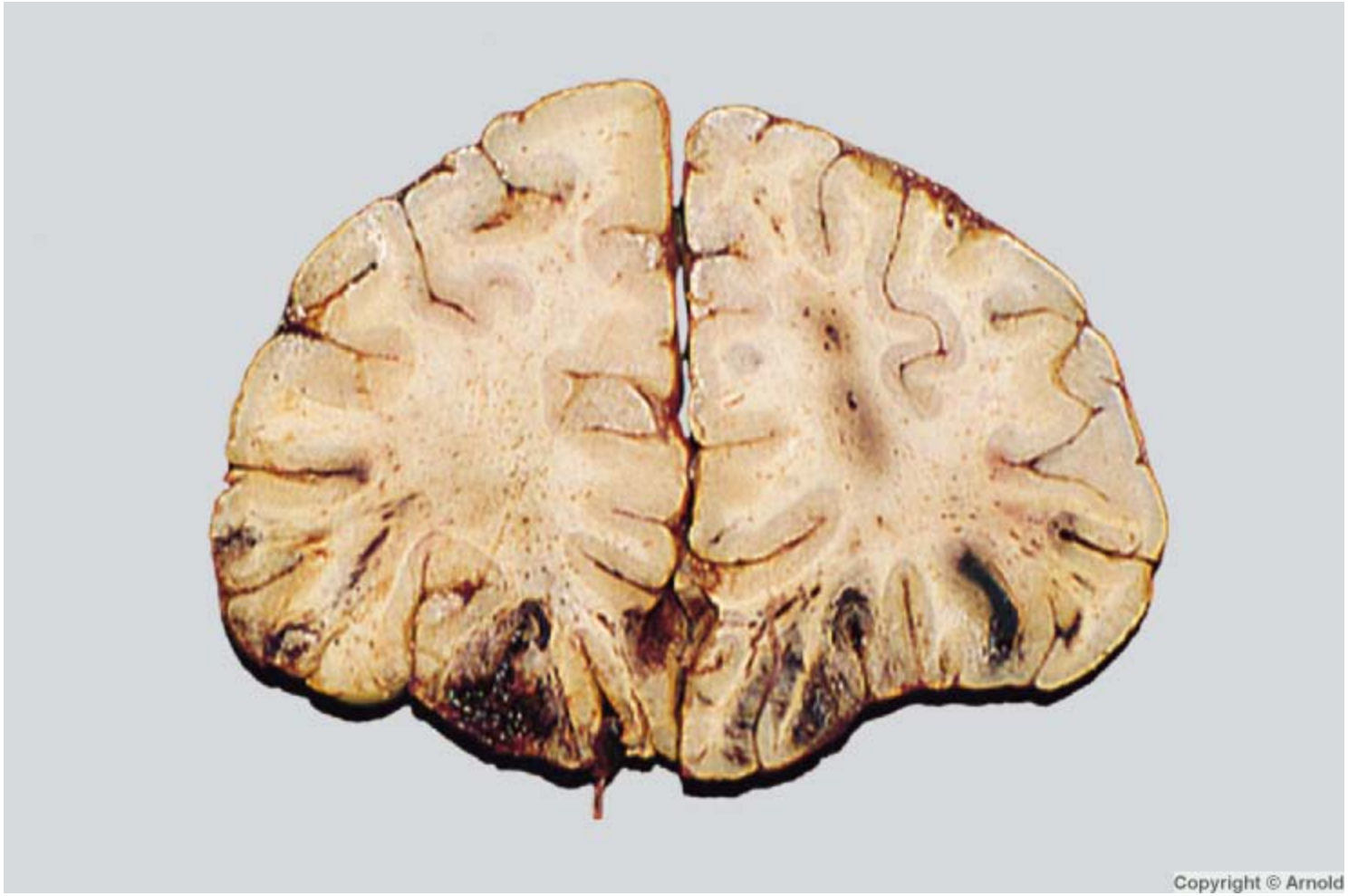
- Myelin loss seen as region of pallor on LFB stain
- Demyelinated regions tend to have sharp borders
- Numerous macrophages and reactive astrocytes found in plaque





Loss of myelin on HE/LFB stain

Trauma - Contusions

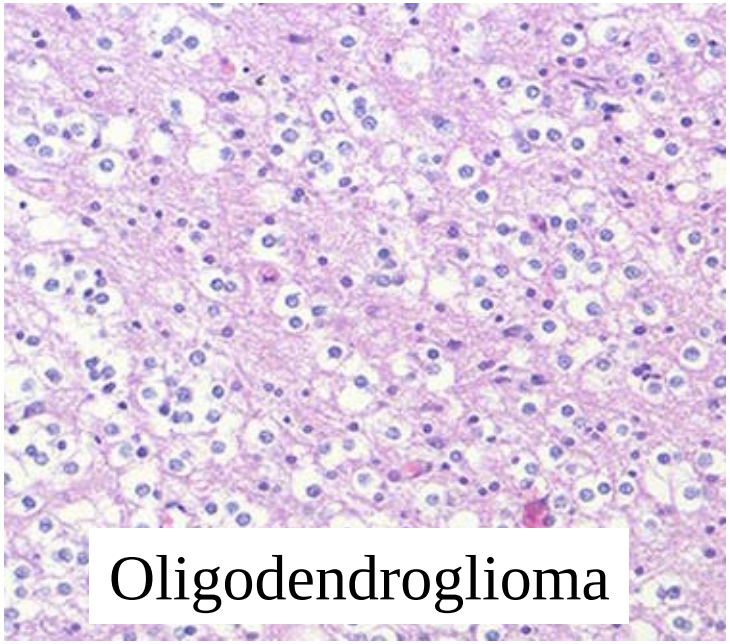


CNS Tumors

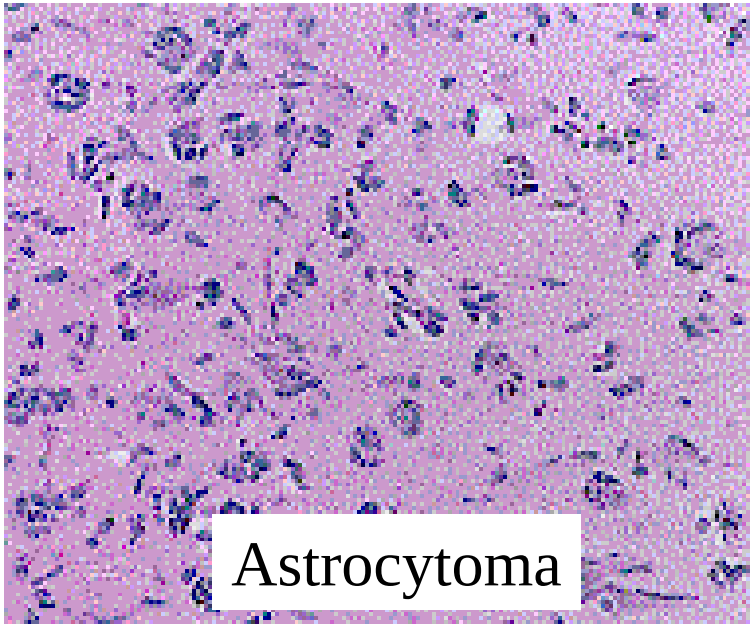
All of the cell types in the brain
Can give rise to tumors

- Astrocytoma
- Oligodendroglioma
- Ependymoma
- Choroid Plexus Tumor
- Meningioma
- Neurocytoma
- Gangliocytoma
- Medulloblastoma (Embryonal)

Glial tumors are the most common
Malignant lesions



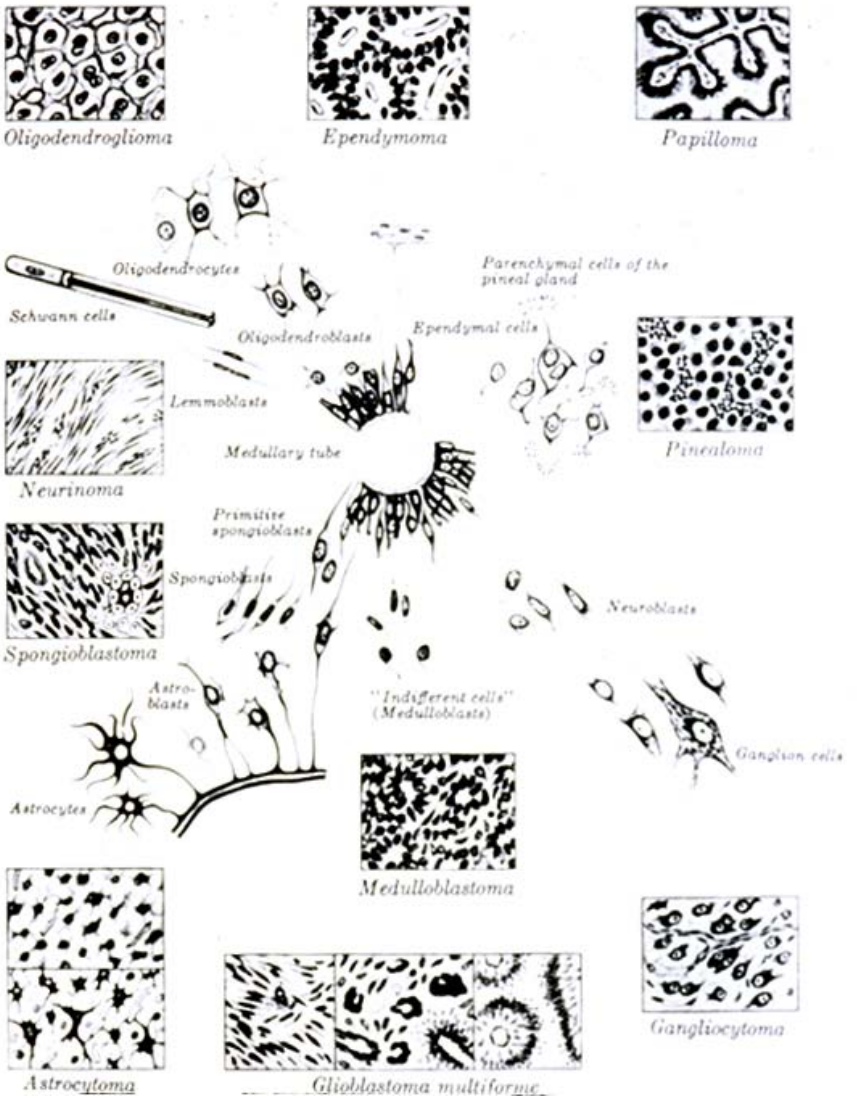
Oligodendroglioma



Astrocytoma

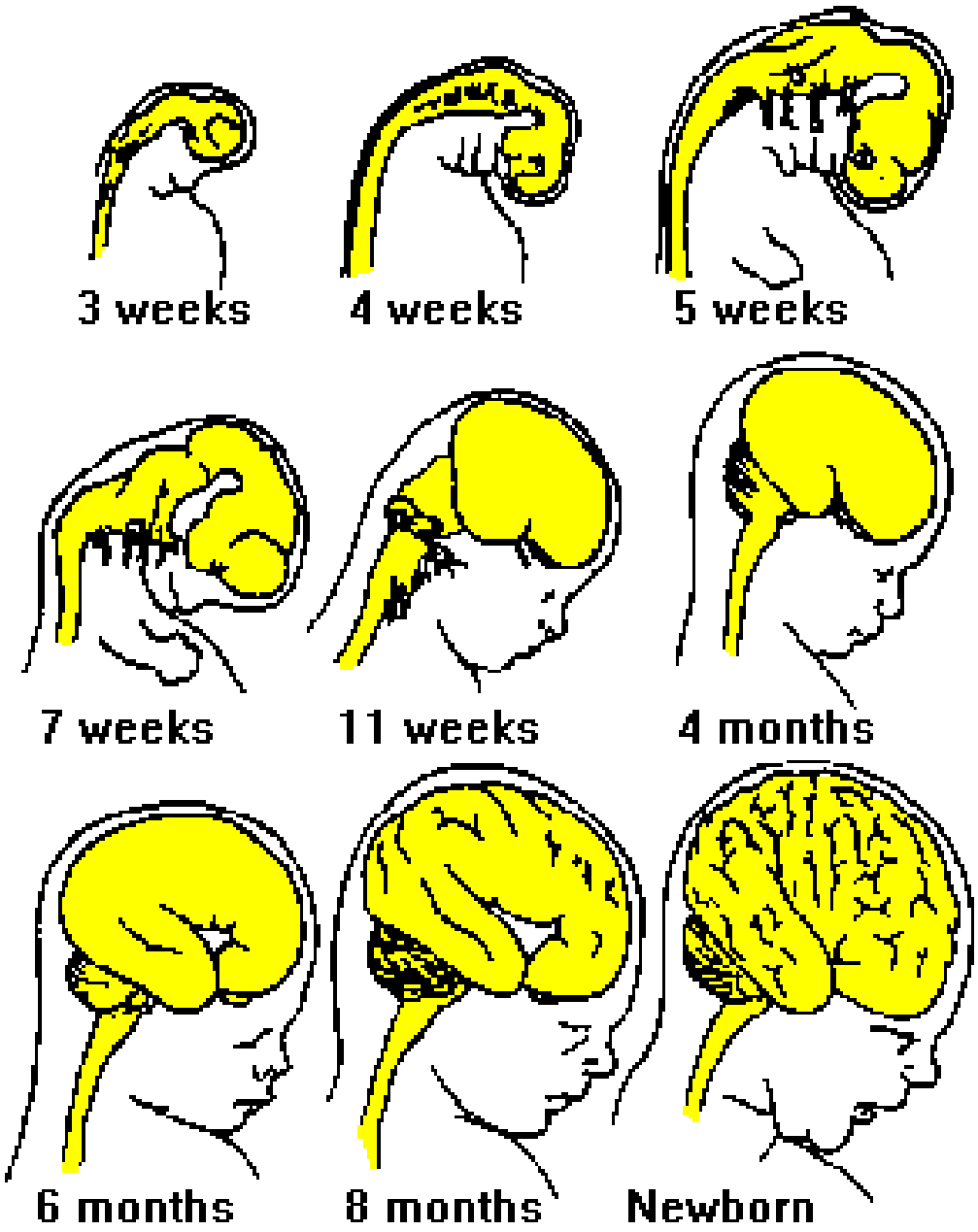
Shifting Gears….
A very brief introduction to CNS development and imaging

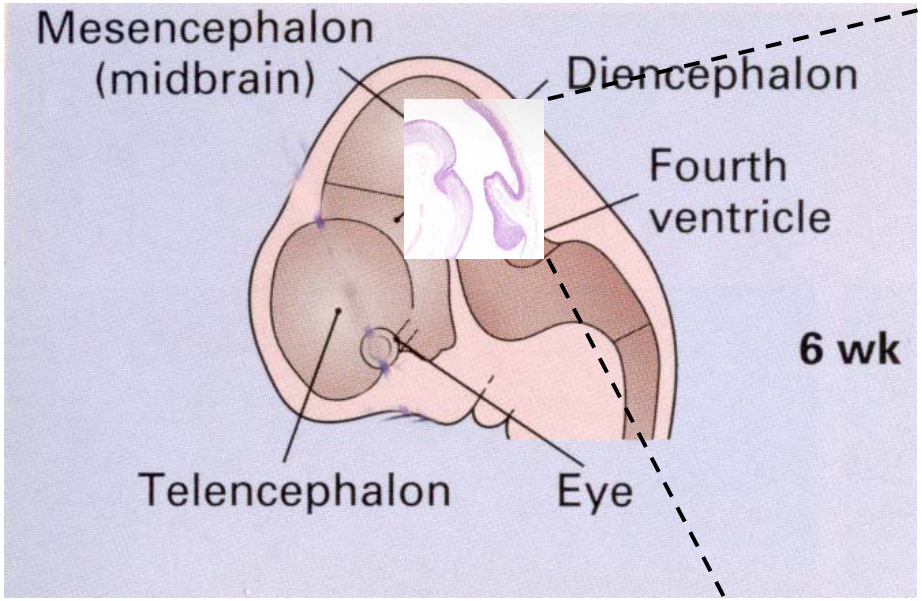
It has long been thought that brain tumors resemble (and perhaps arise from) stem/precursor cells

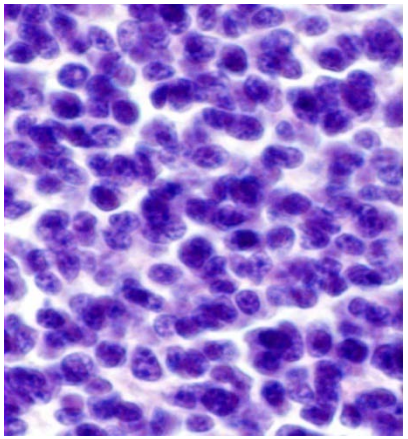


A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis. (1926)

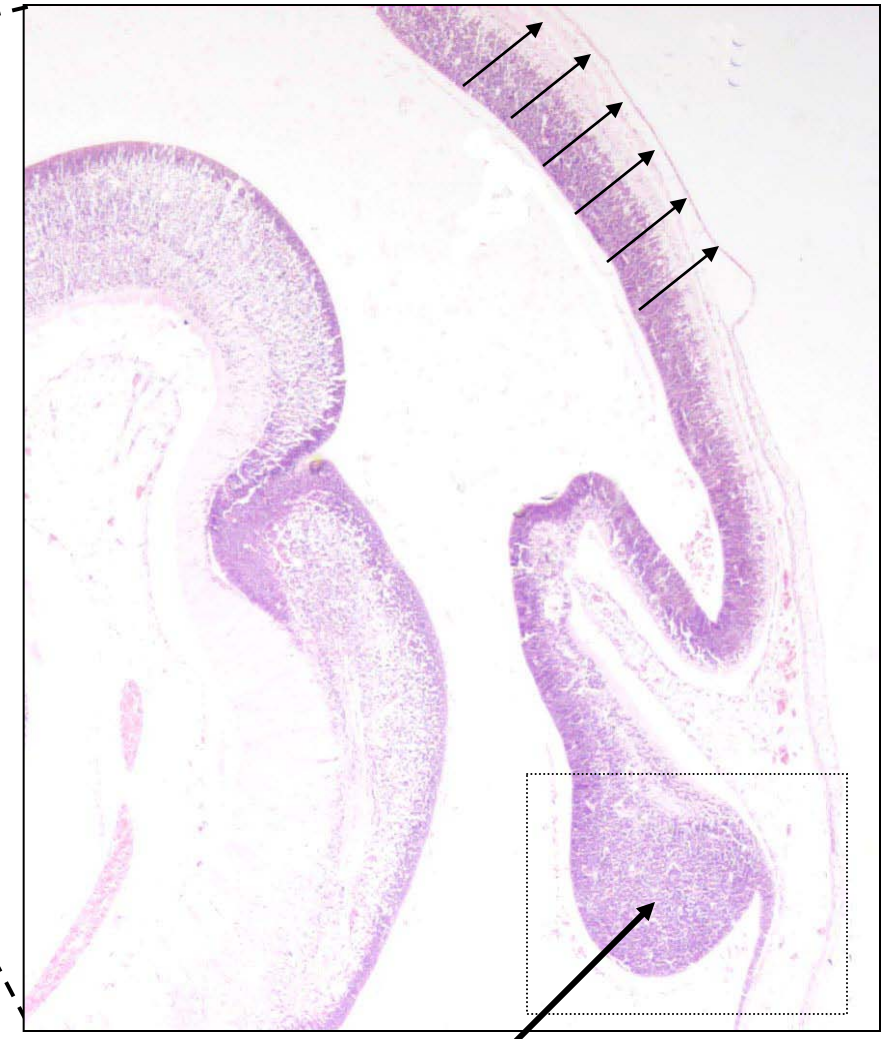
Harvey Cushing


3 weeks
4 weeks
5 weeks
7 weeks
11 weeks
4 months
6 months
8 months
Newborn





VZ



Cerebellar Anlage

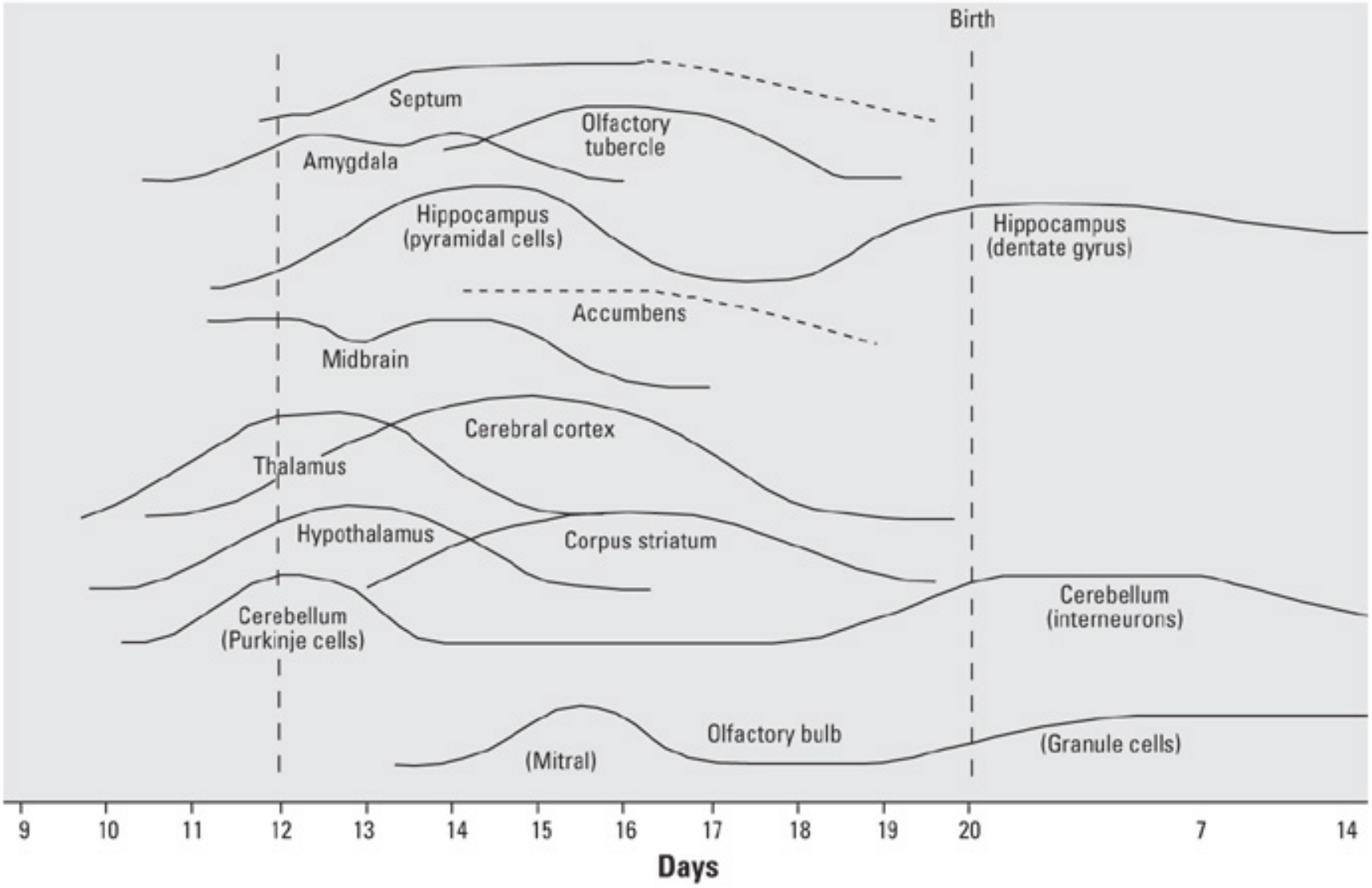
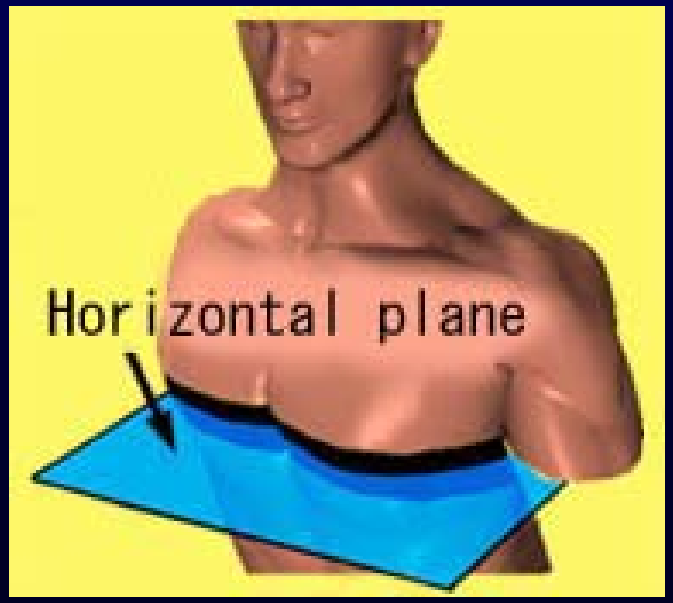
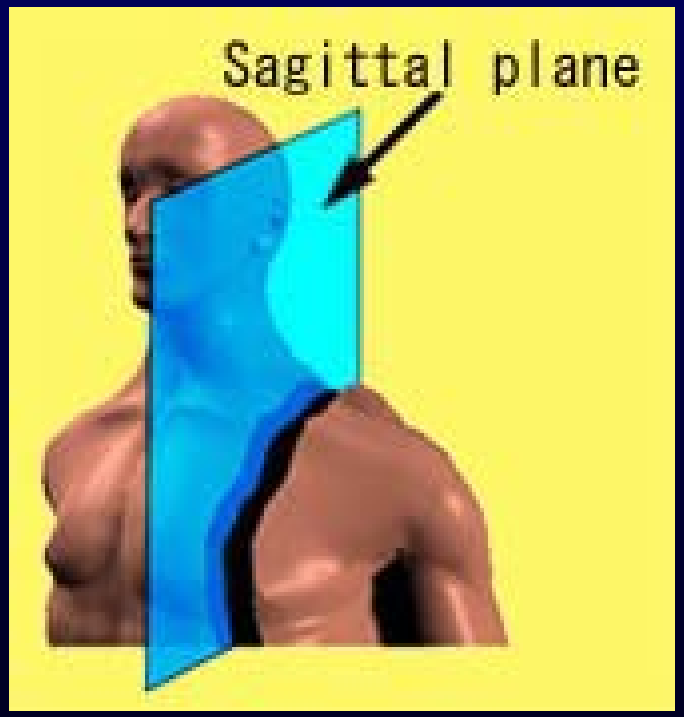


Figure 8. Patterns of neuronal proliferation in specific brain regions of mice. Illustration of overall mouse brain development showing critical windows of peak neuroepithelial cell proliferation (neurogenesis) within specific brain regions and nuclei throughout gestation. Figure reproduced from Rodier (1977) and reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Conventions & Terminology

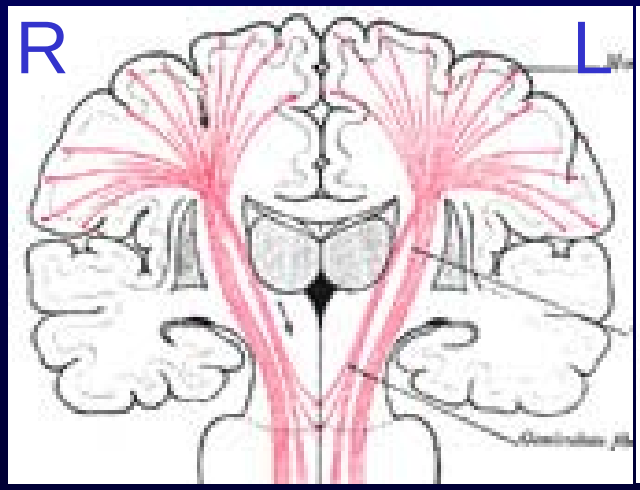
Body Planes





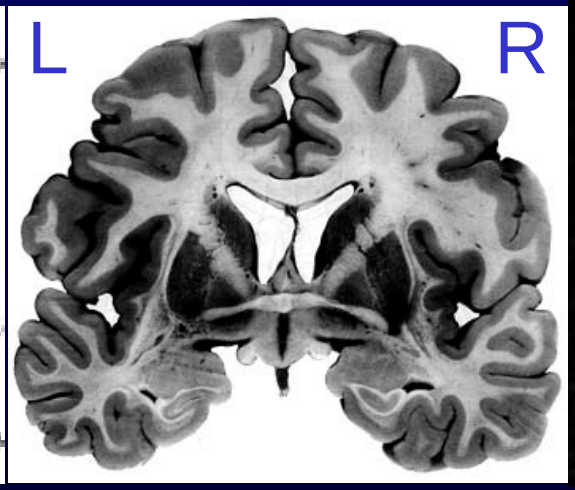
Conventions & Terminology
Right-Left Confusion

As If From Front



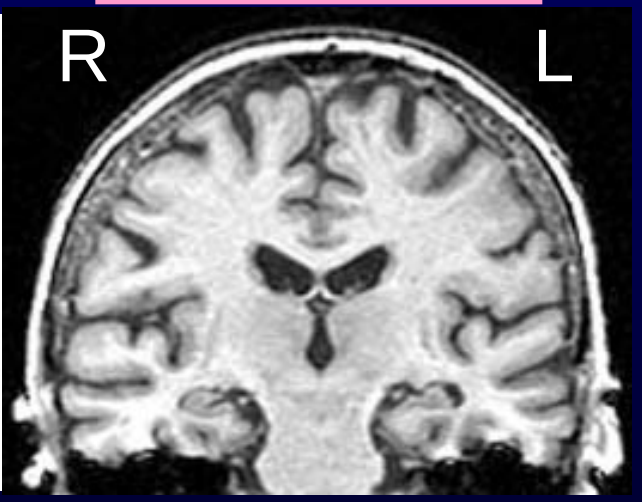
Diagram

As If From Back



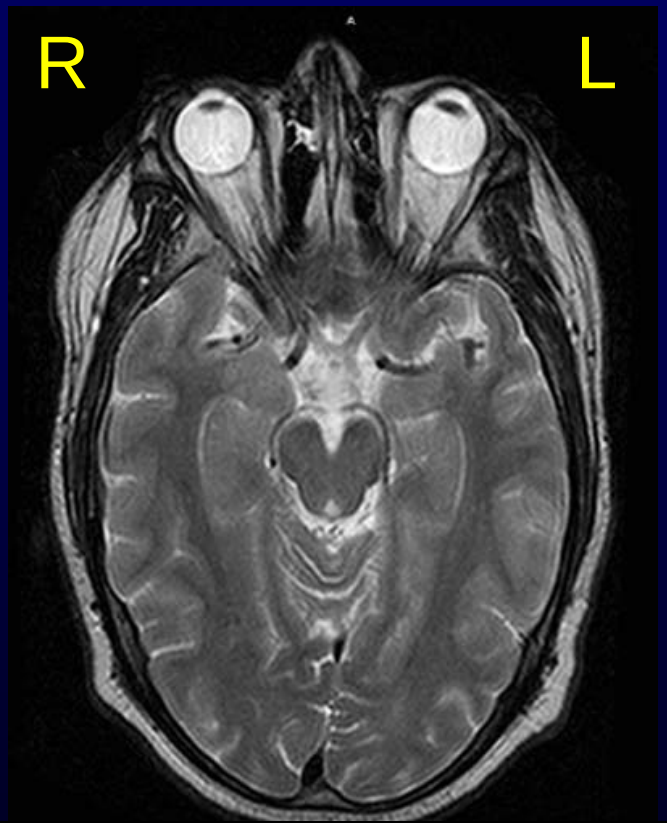
Pathology Specimen

As If From Front



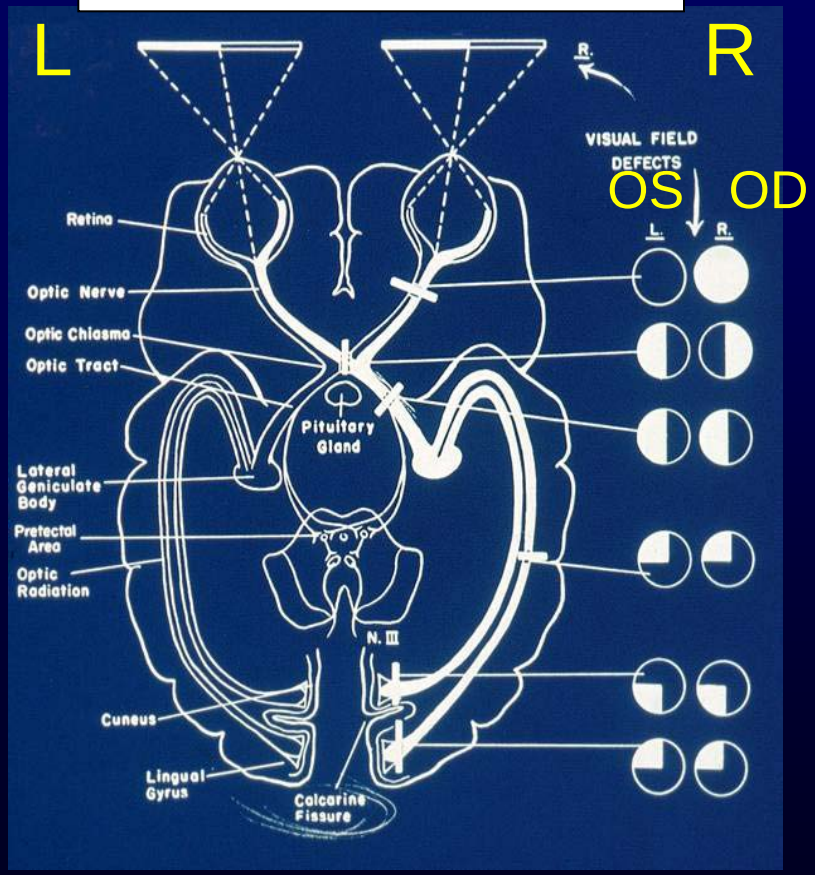
MRI-CT-Radiograph

Conventions & Terminology
More Right-Left Confusion

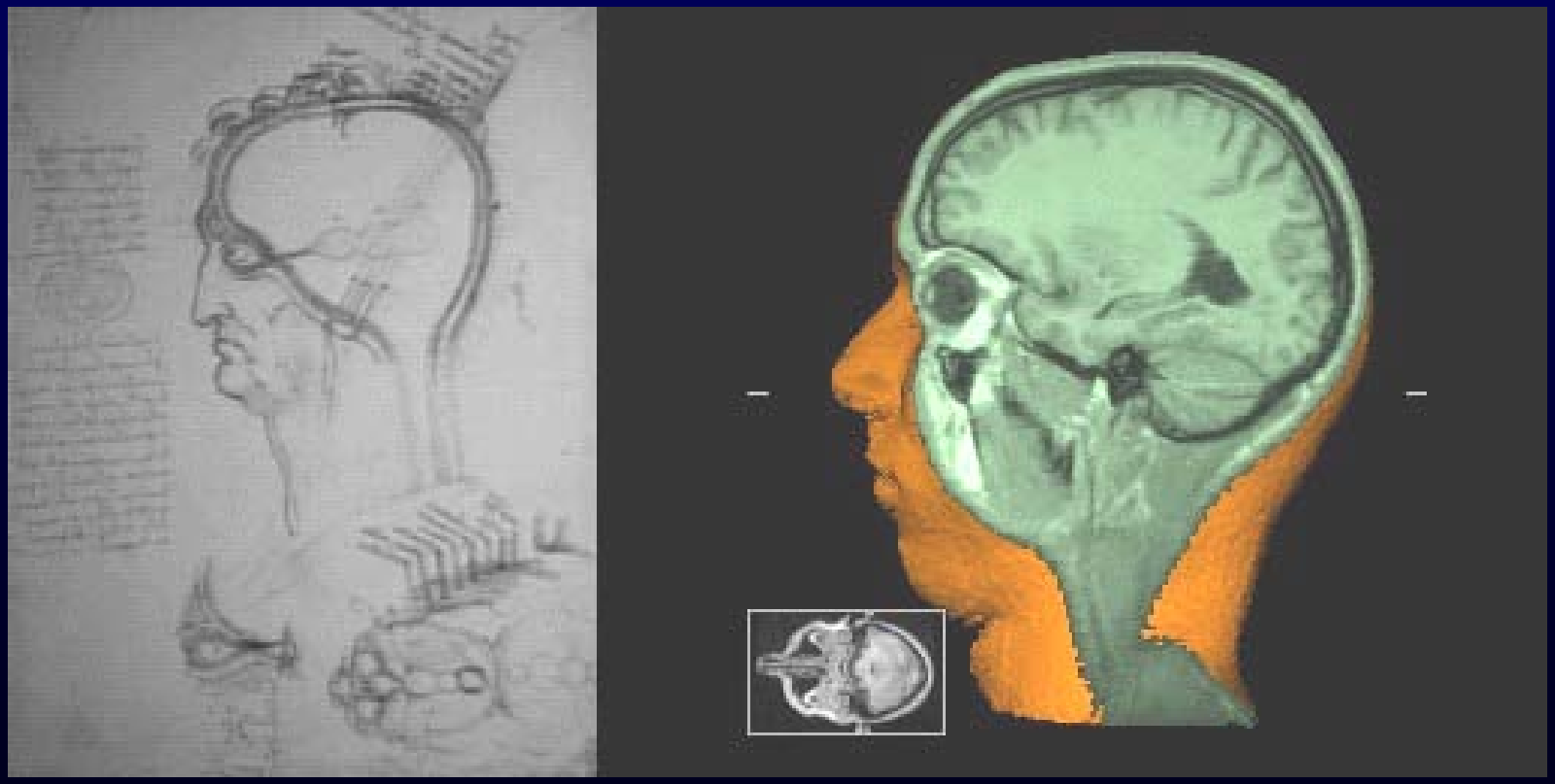


MRI As If From Bottom Of Feet

Visual Field Pathways
As If From Top Of Head



Brief Review of Neuroradiology

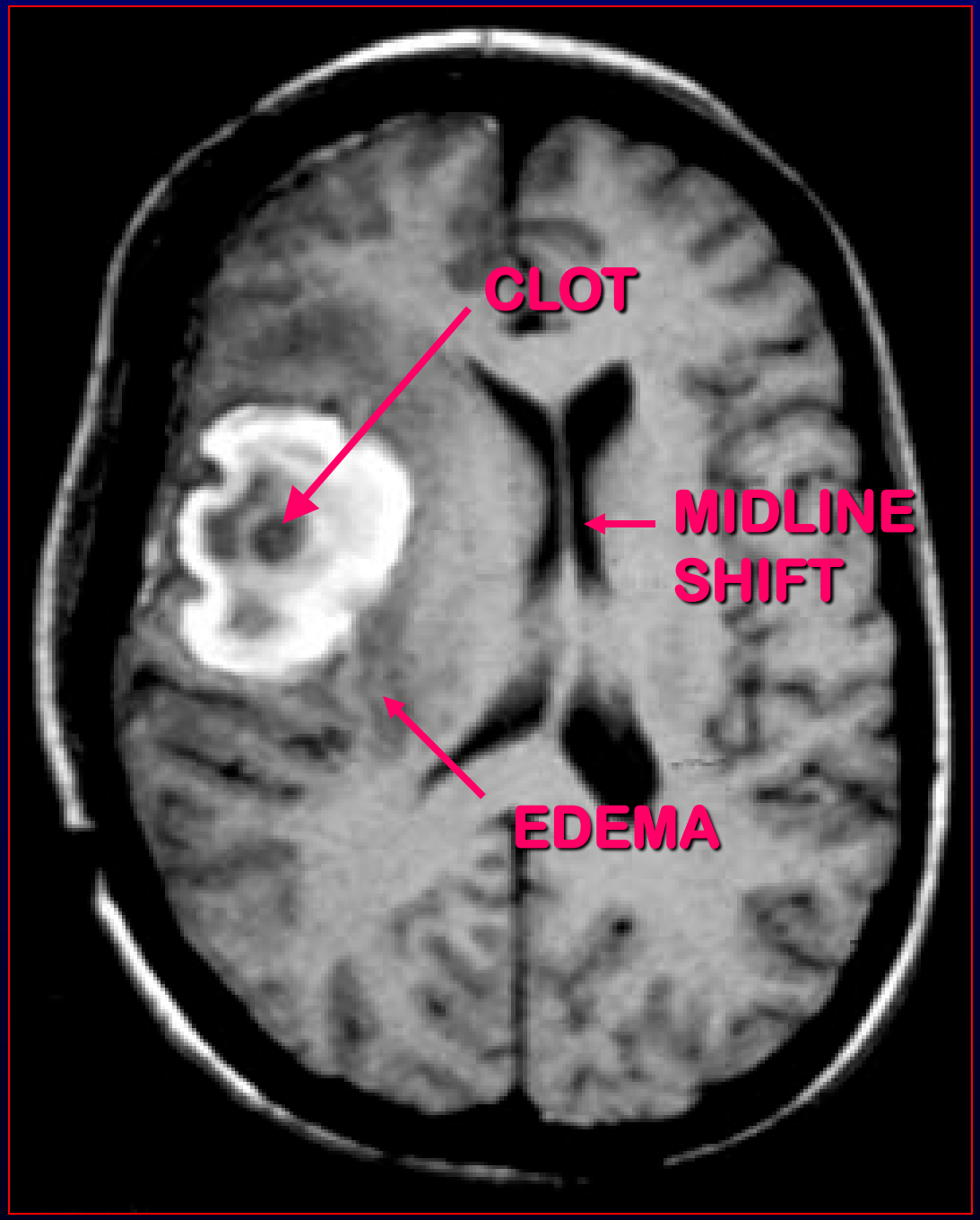


IMAGING:

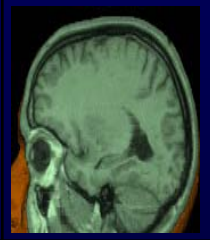
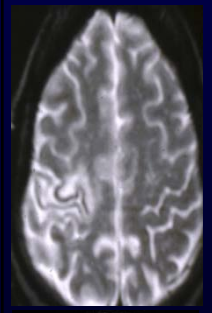
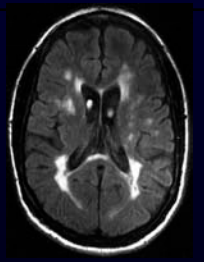
MRI Brain with intraparenchymal hemorrhage from mycotic aneurysm

Elucidates…

1) pathoanatomy,
2) pathology,
3) pathophysiology
4) clinical risk



Non contrast or plain imaging appearances

Scan	Uses	CSF	Lesion	Blood	Bone	
CT	Rapid screen	Dark	Dark	White	White	
T1 MRI	Anatomy	Dark	Dark	White	Dark	
T2 MRI	Lesion ident.	White	White	Varies with age of bleed	Dark	
FLAIR	Lesion ident.	Dark	White	Varies with age of bleed	Dark	

CT is useful for...

- Quick look
  - Major mass effect with midline shift
  - (Obstructive) hydrocephalus
- Blood
  - E.g., Subarachnoid, Intraparenchymal
- Bone
  - Skull fractures
  - Bone erosion from infection
- Bullets
  - Bullets and other metal
- Imaging vessels acutely
  - CT Angiography (e.g. for acute stroke)
- Imaging when the patient cannot get an MRI
  - Pacemaker or other paramagnetic retained foreign body
  - Severe claustrophobia
  - None available

CT, Noncontrast (soft tissue window)

CT: skull is white

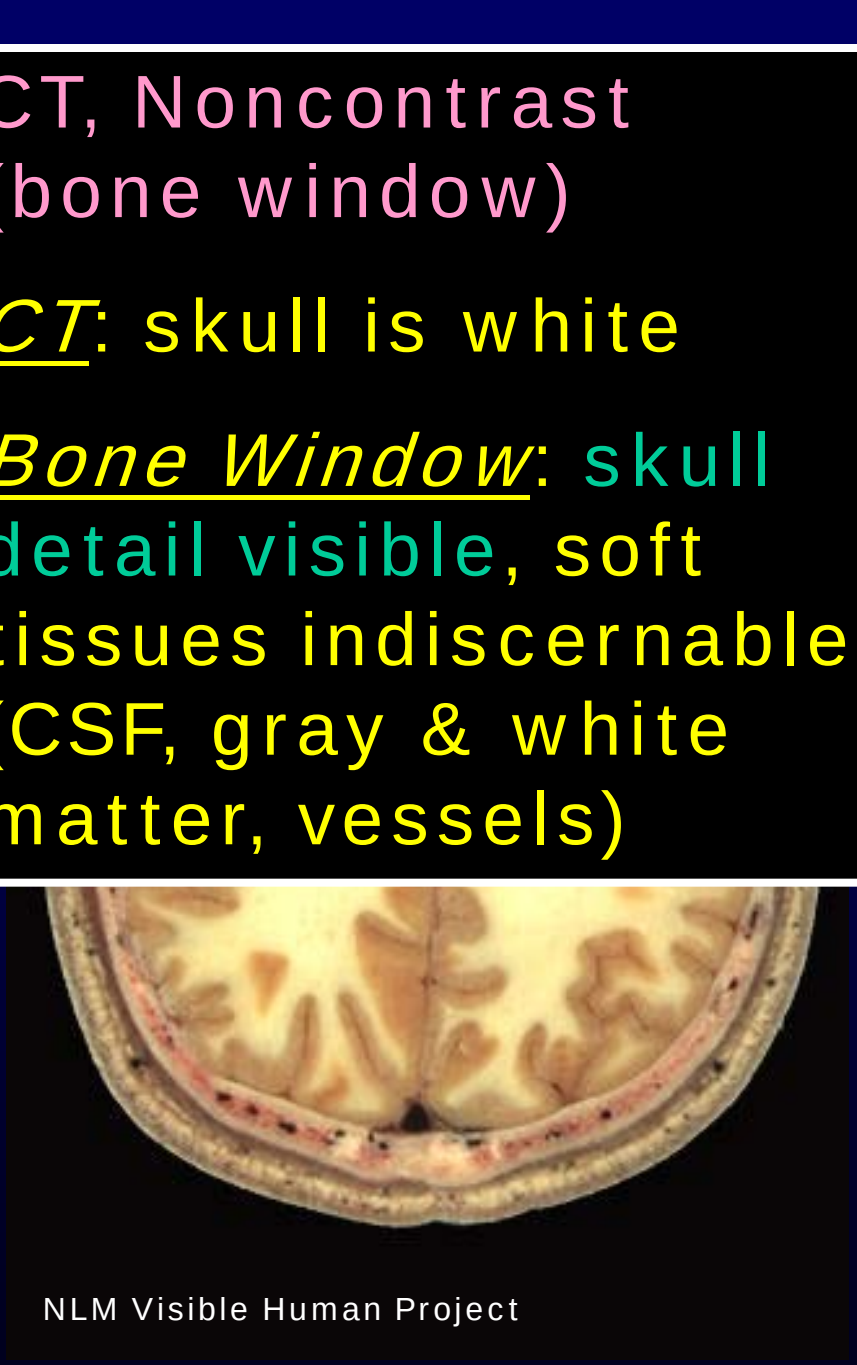
Soft Tissue Window: skull detail not visible, CSF black, gray vs. white matter discrimination fuzzy

Noncontrast: vessels are inapparent

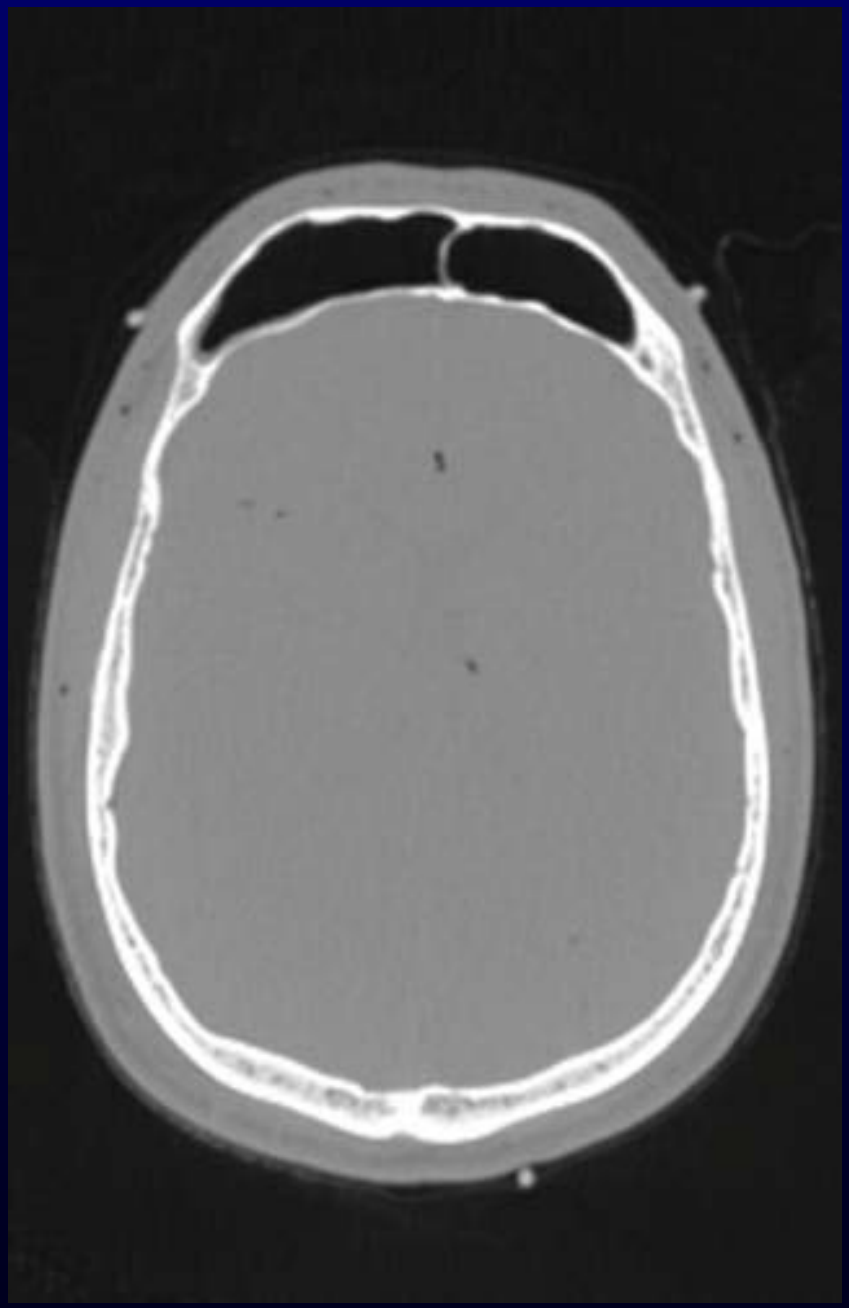
CT, Noncontrast (bone window)

CT: skull is white

Bone Window: skull detail visible, soft tissues indiscernable (CSF, gray & white matter, vessels)

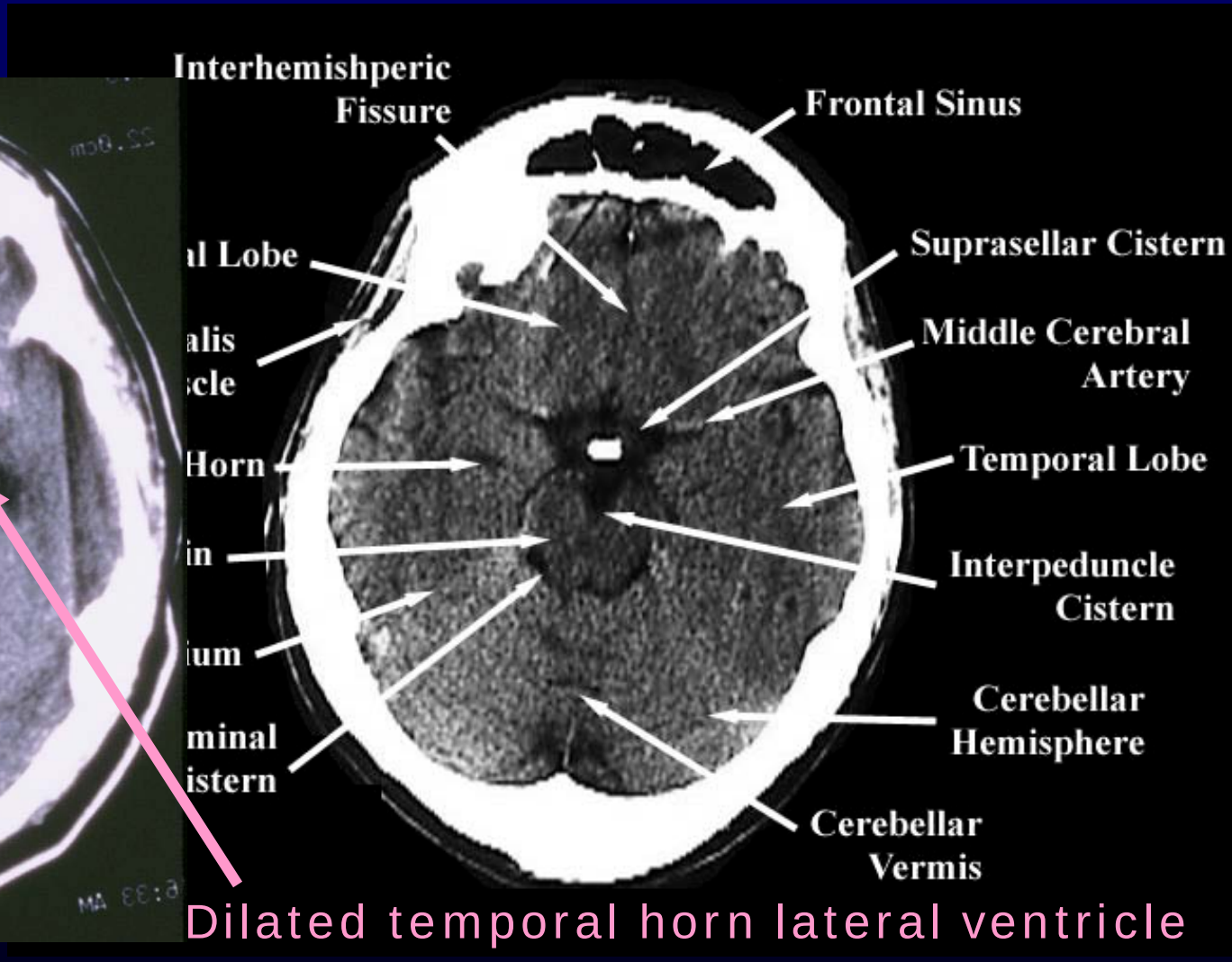


NLM Visible Human Project



CT Subarachnoid Hemorrhage

Normal CT

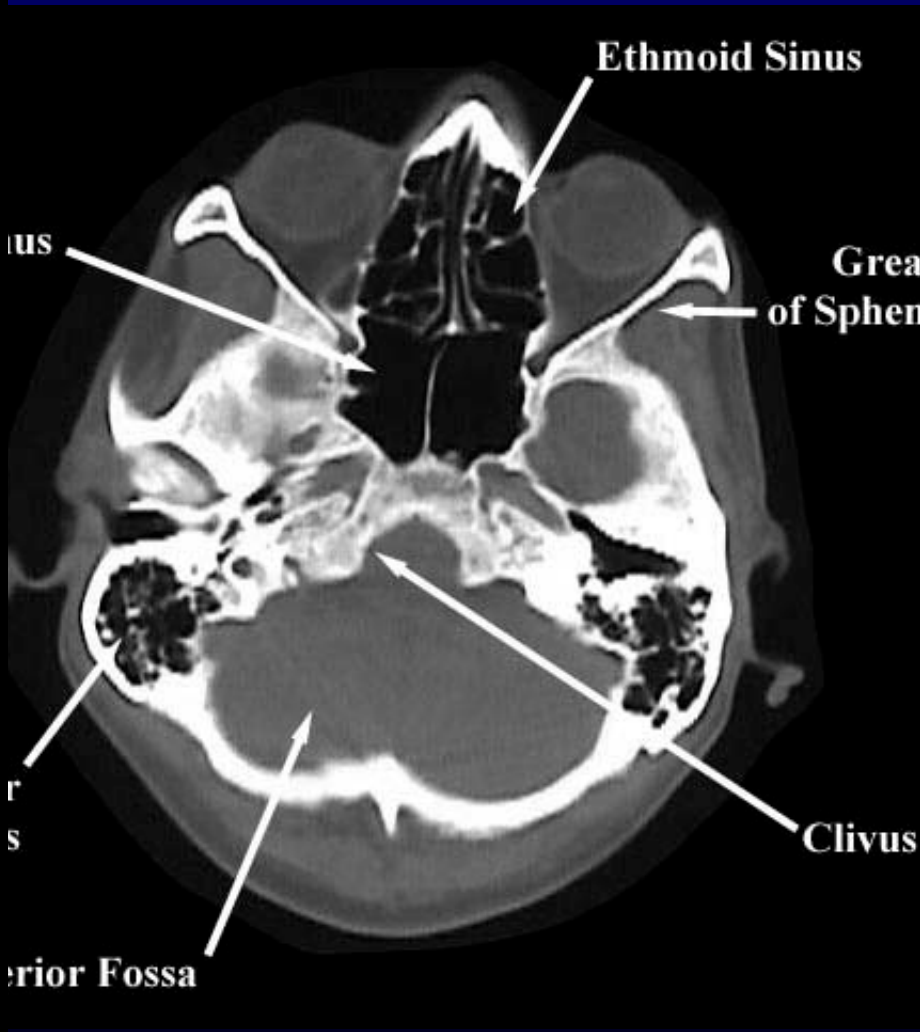


Dilated temporal horn lateral ventricle

Bright BLOOD in the peri-mesencephalic SA spaces

Normal MRI T1 contrast @ lvl. of ear

Normal CT Bone Windows @ lvl. ear



Note that MRI is useless for imaging bone rel. to CT

MRI is useful for...

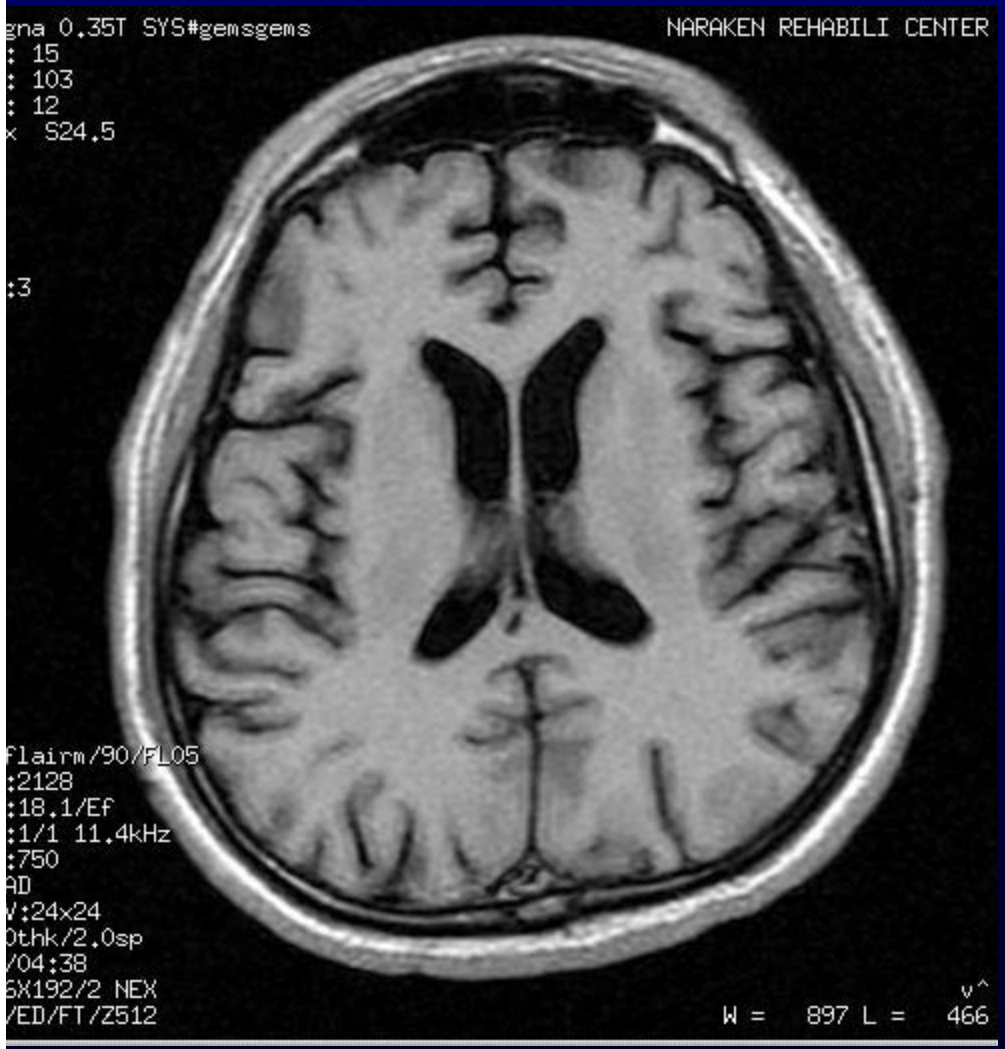
- Anatomic detail
- Subtle or small pathology
  - including lesions without large mass effect (esp. white matter disease)
- Posterior fossa lesions
- Acute stroke (Diffusion Weighted Imaging [DWI])
- Imaging Vessels (MR angiogram or venogram [MRA/V])

MRI, T1, noncontrast

MRI: skull is black (scalp fat & bone marrow white)

TI: CSF black, & differentiation of gray vs. white matter good

Noncontrast: vessels inapparent

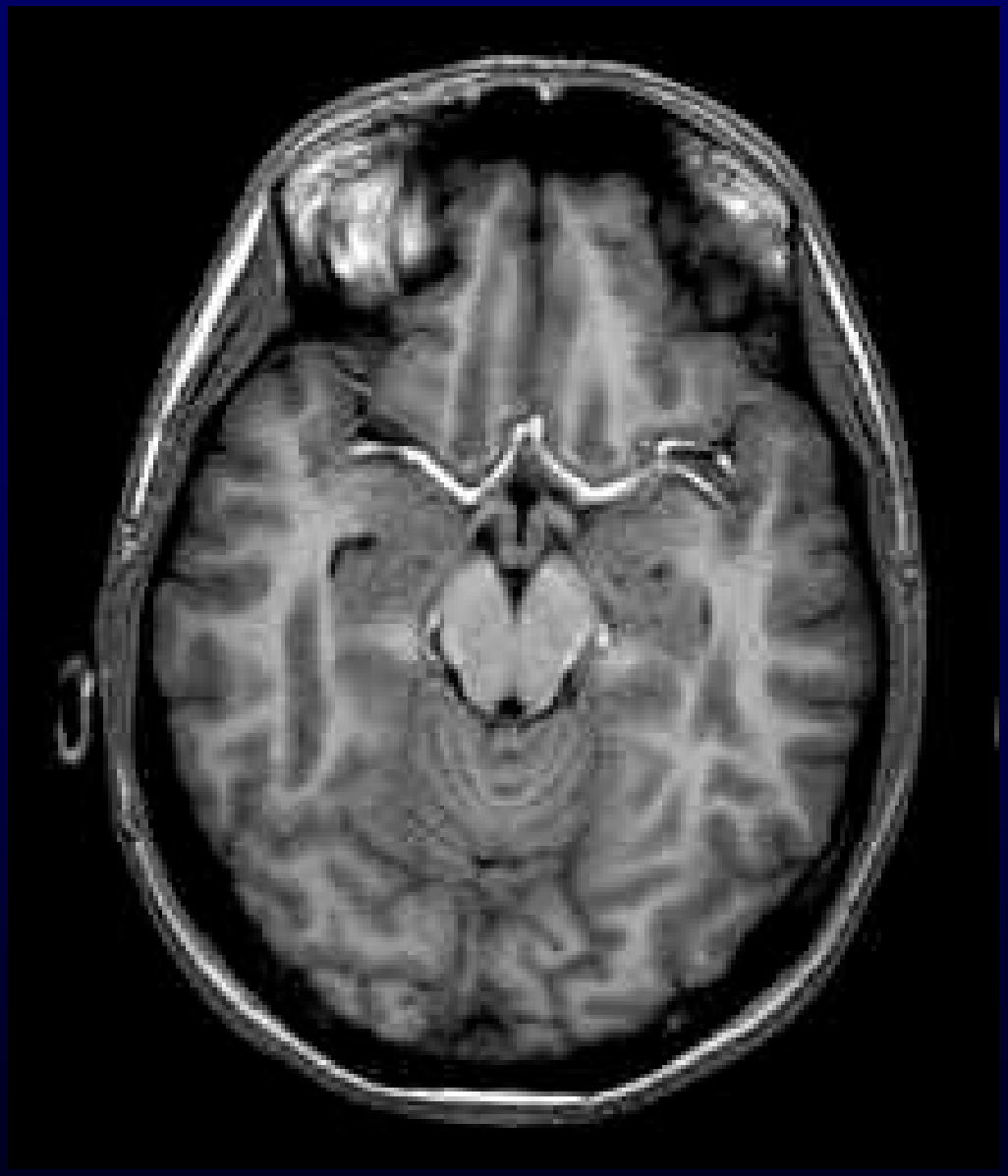


MRI, T1, Contrast

MRI: skull is black (scalp fat & bone marrow white)

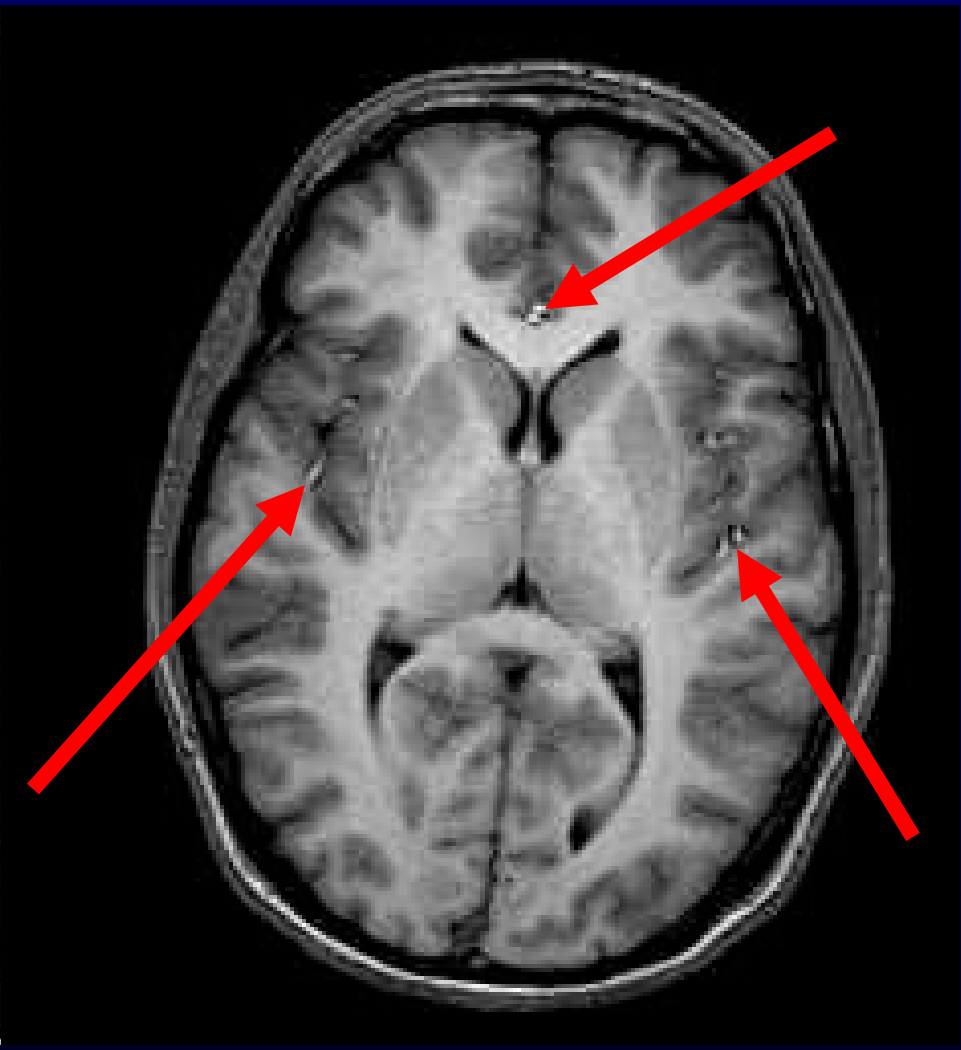
TI: CSF black, & differentiation of gray vs. white matter good; gray matter darker than white matter

Contrast: vessels white



T1 Noncontrast

T1 Contrast



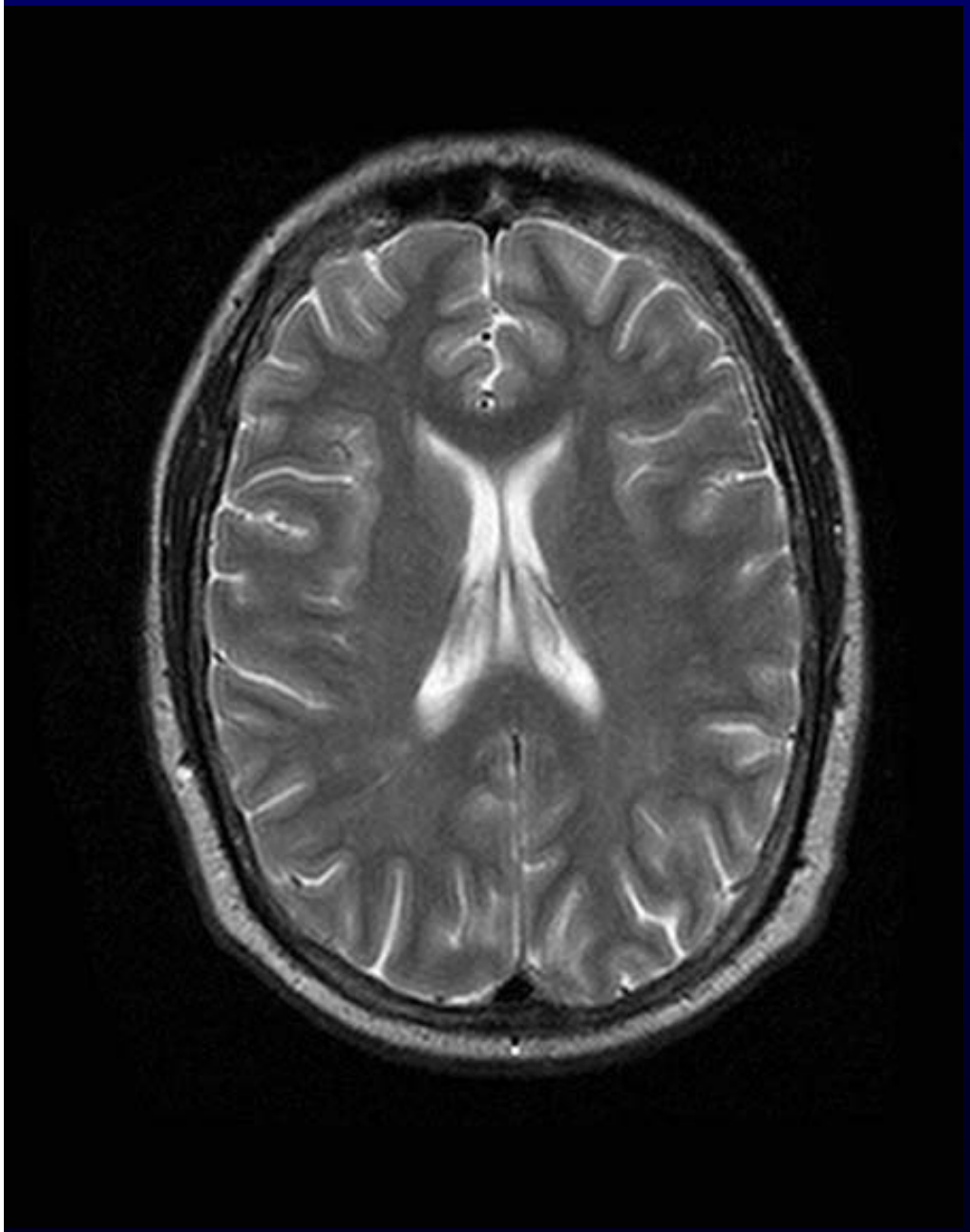
Note subtle appearance of contrast in blood vessels

MRI, T2, noncontrast

MRI: skull is black (scalp fat & bone marrow white)

T2: CSF white, & differentiation of gray vs. white matter fair; white matter darker than gray matter

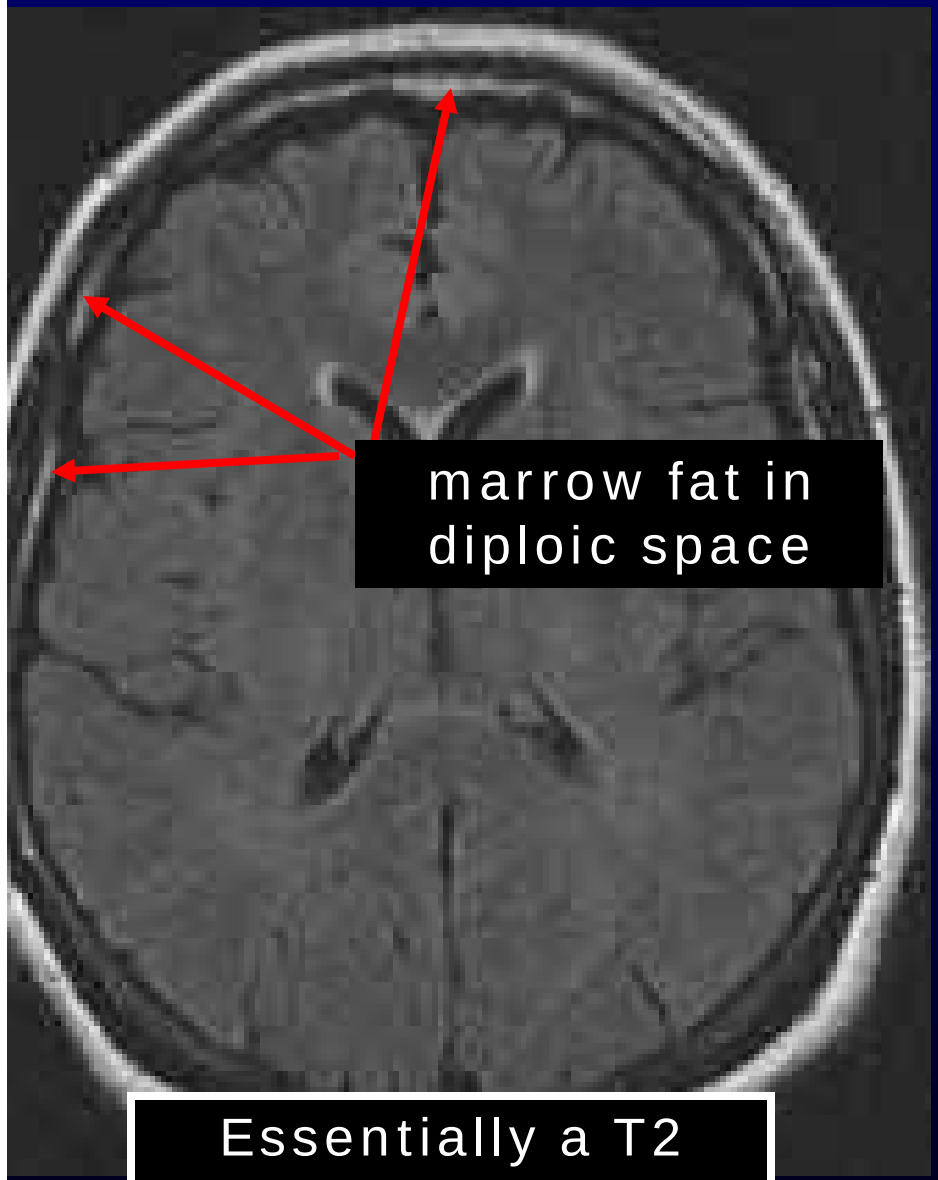
Non Contrast: vessels inapparent (small black flow voids)



MRI FLAIR (fluid attenuated inversion recovery)

MRI: skull is black (scalp fat & bone marrow white)

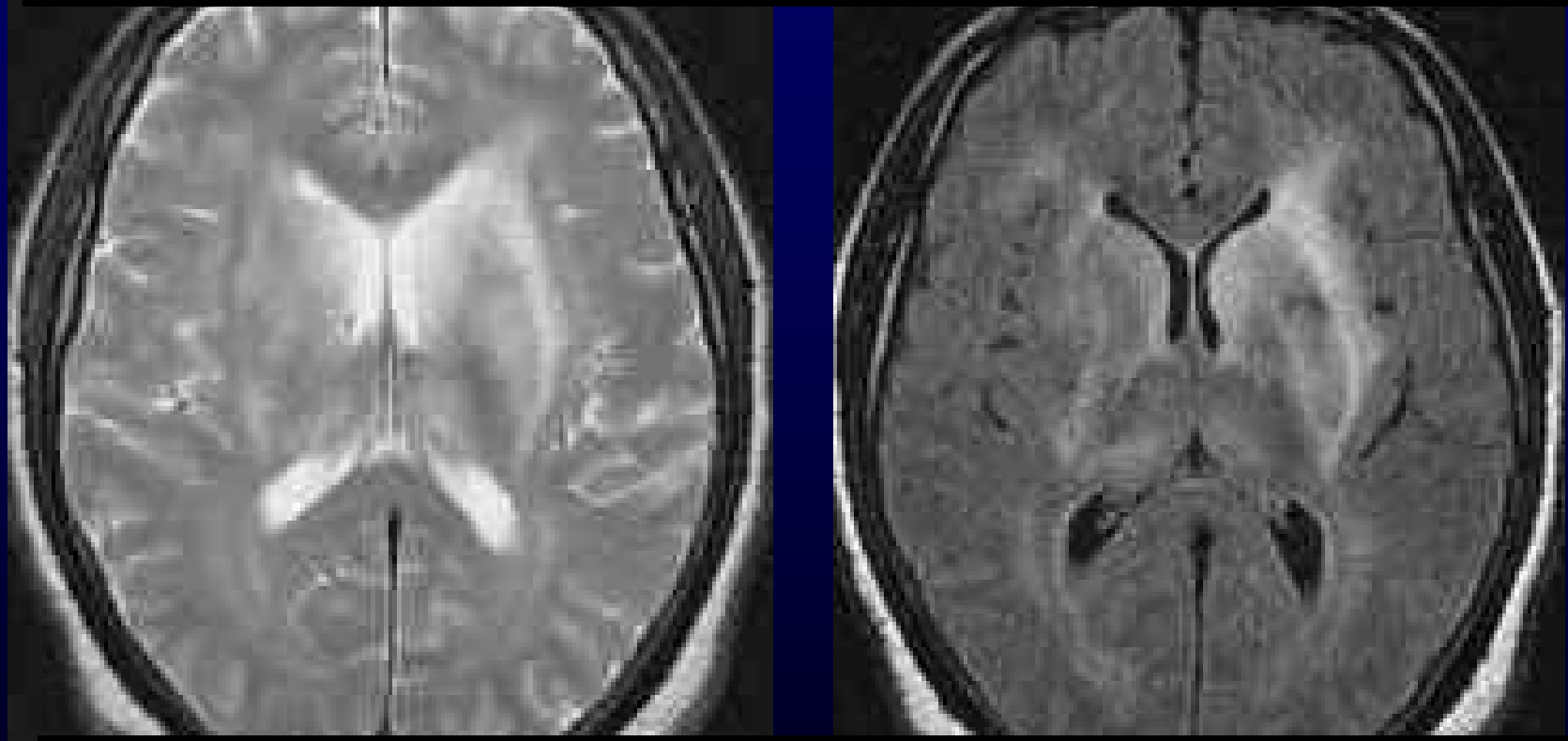
FLAIR: CSF black, & differentiation of gray vs. white matter poor; white matter darker than gray matter



Essentially a T2 image with the CSF 'averaged' out

MRI scan: T2 vs. FLAIR – Why use FLAIR?

As a result, FLAIR images end up being more sensitive, but less specific



Note that pathology ‘stands out’ when CSF is ‘averaged out’ of the image