The Central Nervous System

Reaction to Injury

APPROVED

This is the first CNS lecture, so she is going to give some background info

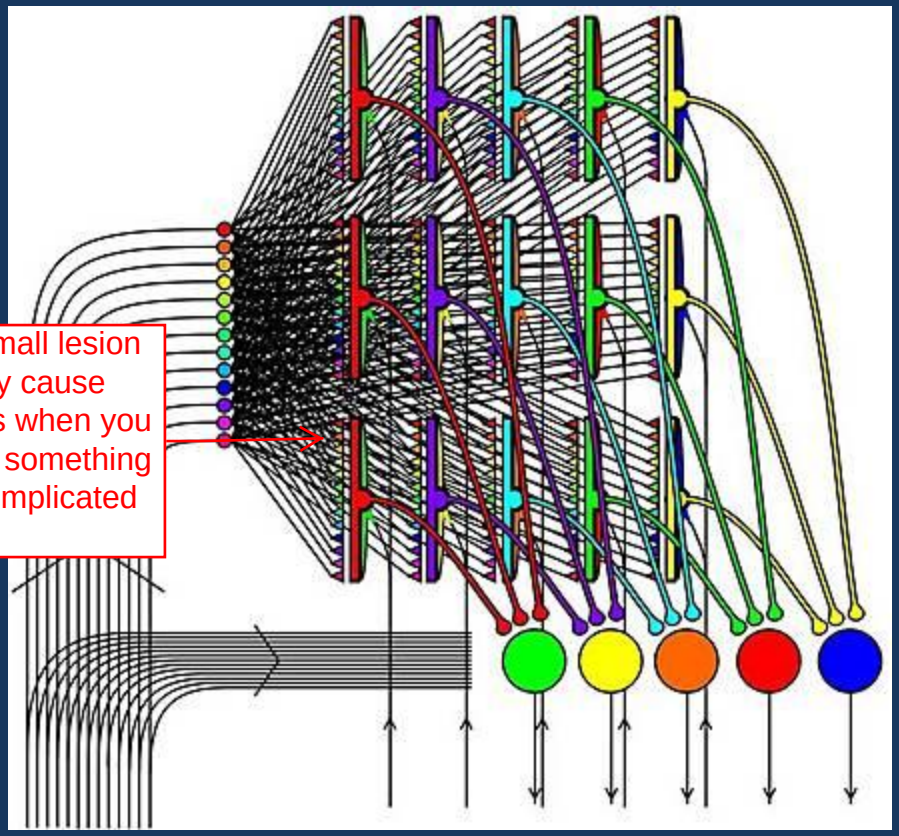
Anne Buckley MD PhD
Neuropathology

Unique features of CNS that influence its response to injury

-cell types unique to CNS
-complex neural circuit architecture
-little internal structural support
-very limited room to expand
-no typical lymphatic drainage

Brain is like Jello, no internal structure, it can't support itself. Only the skull keeps it together

joepastry.com



A very small lesion can really cause problems when you mess up something in this complicated circuit.

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R&C Chapter 28: The CNS

- Cellular Responses to Injury
- Cerebral Edema, Hydrocephalus, Raised Intracranial Pressure & Herniation
- Perinatal Brain Injury
- Trauma

Developing brains respond differently to injury

R&C Chapter 28: The CNS

- **Cellular Responses to Injury**
- **Cerebral Edema, Hydrocephalus, Raised Intracranial Pressure & Herniation**
- **Perinatal Brain Injury**
- **Trauma**

The cells of the CNS

Neuroectodermal origin

Neurons

Glia (astrocytes, oligodendroglia, ependymal/choroid plexus cells)

Stem/progenitor cells

Glia means glue. They are the supporting cells that hold everything together, physically and functionally. They may also modulate neuronal synapses

Mesodermal origin

Resident microglia

Act as macrophages

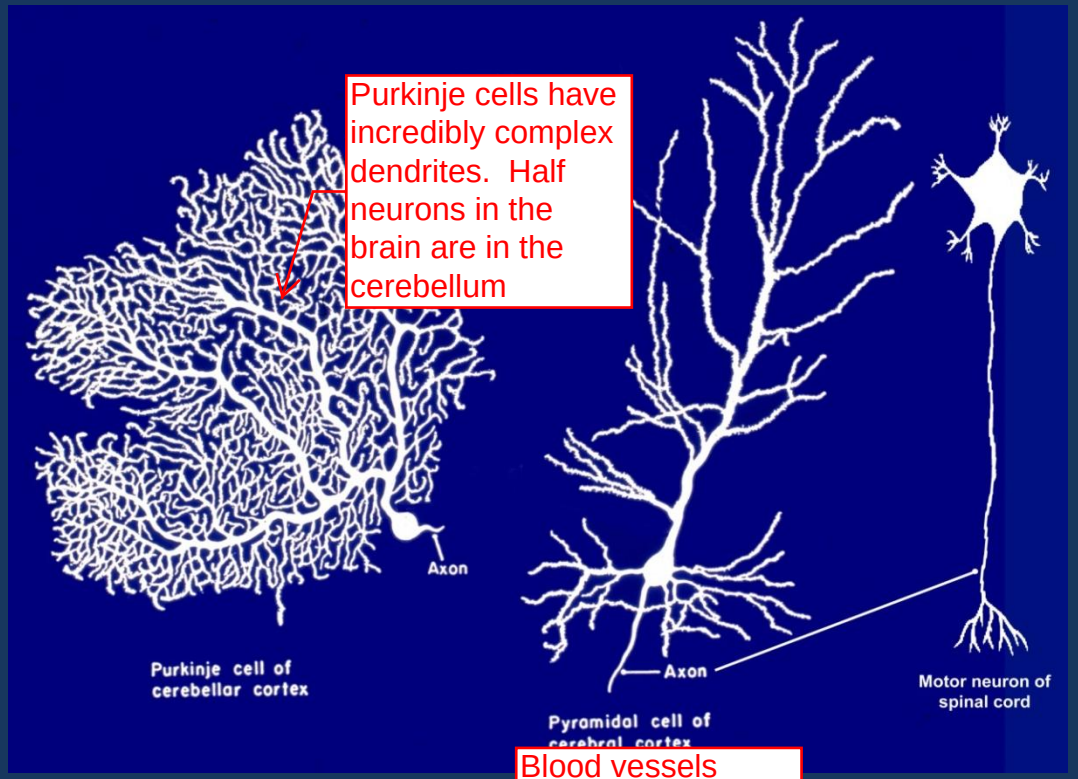
Meningial cells

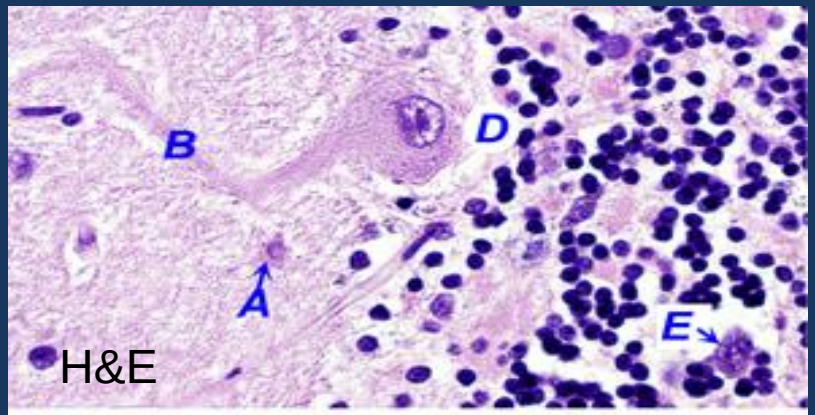
Blood vessels and blood cells

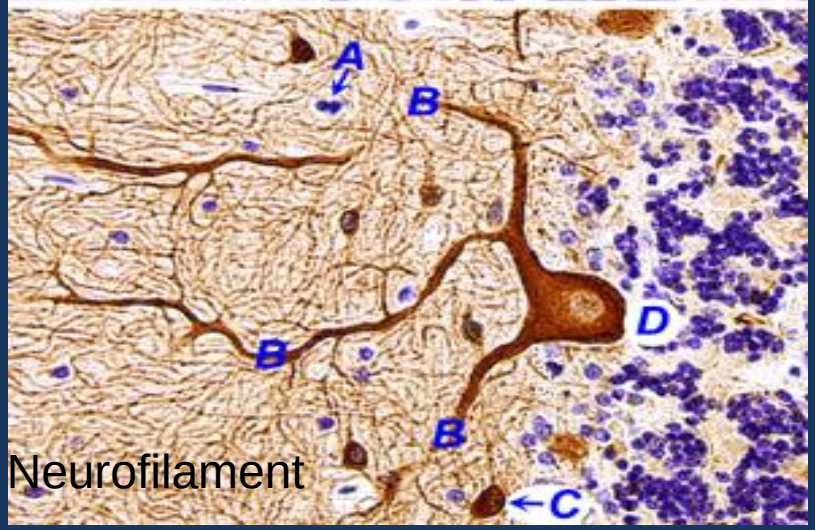
Most cells in the CNS are unique to the CNS. Blood vessels are not unique.

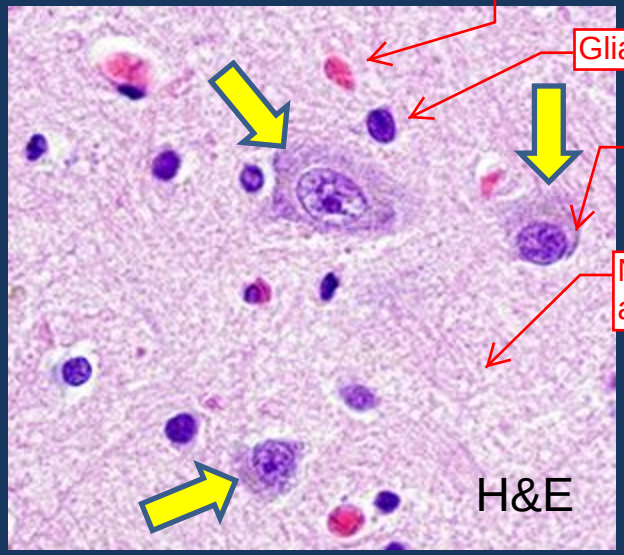
Up to 150 different kinds of neurons, not just the few kinds we normally learn about.

Neurons









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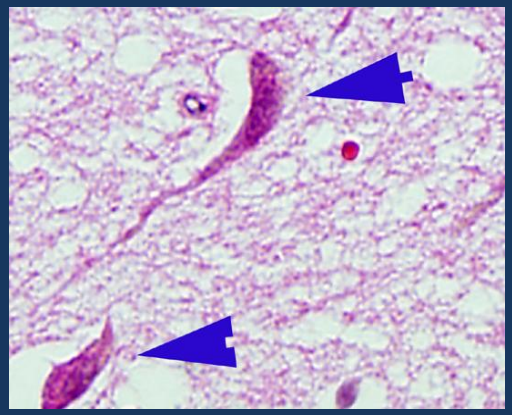
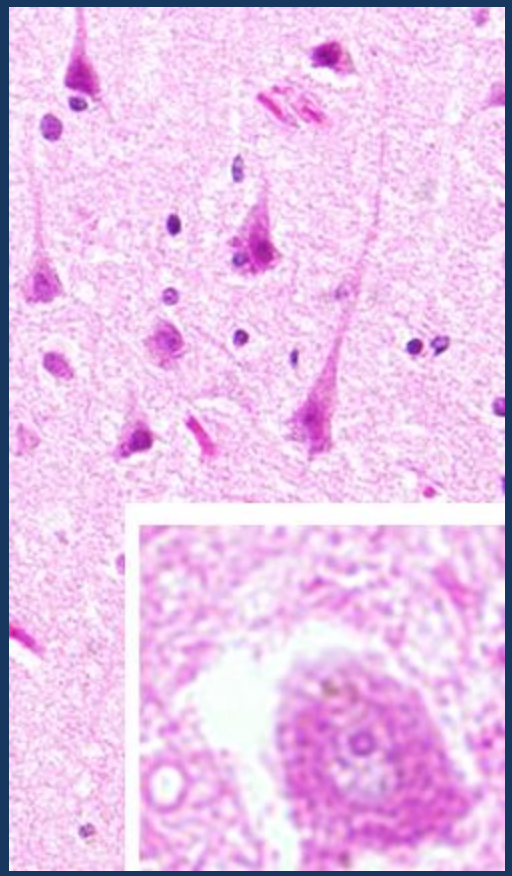
Neurons are very vulnerable and are some of the first cells to be lost with injury, especially Purkinje cells. Glial cells are much more resilient.

Neuronal reaction (acute)

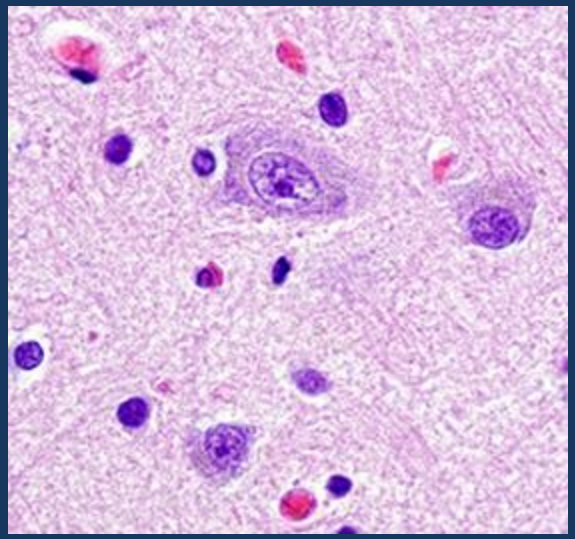
- **"Red neurons" in hypoxia/ischemia**
- **Selective vulnerability**

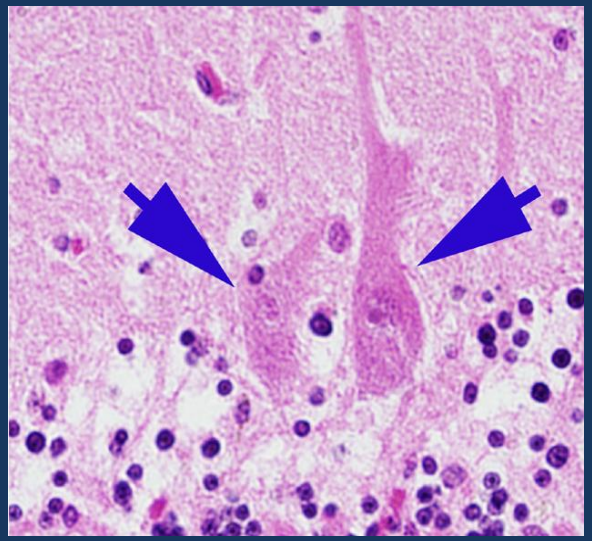
Red neurons are dying neurons, show up within first day of hypoxia.





Normal cortical neurons





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Neuronal reaction (subacute/chronic)

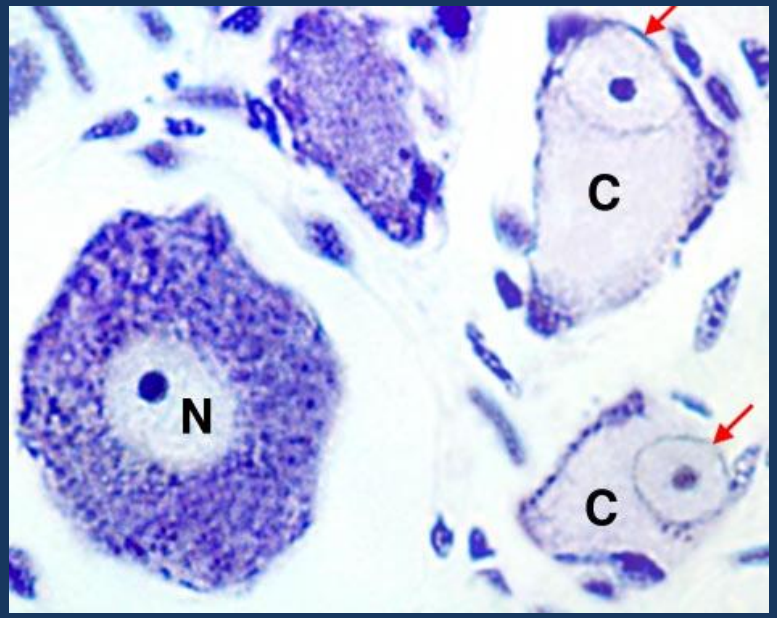
- **Apoptosis (in situ and trans-synaptic)**

Neuron itself can die from insult or downstream neurons can die due to lack of signalling

Neuronal reaction (subacute/chronic)

- **Apoptosis (in situ and trans-synaptic)**
- **Regeneration: axonal reaction (central chromatolysis)**

Neurons labeled C are bad, they are trying to recover from an insult, it is producing a lot of protein. They should normally look like the neuron labelled N



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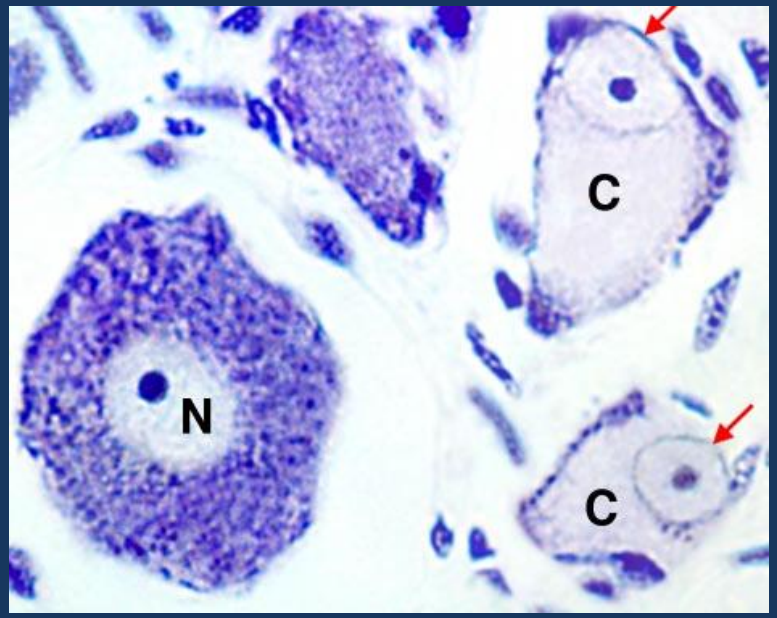
Nissl stain (cresyl violet)

Neuronal reaction (subacute/chronic)

- Apoptosis (in situ and trans-synaptic)
- Regeneration: axonal reaction (central chromatolysis)
- Neuronal inclusions (lipofuscin)



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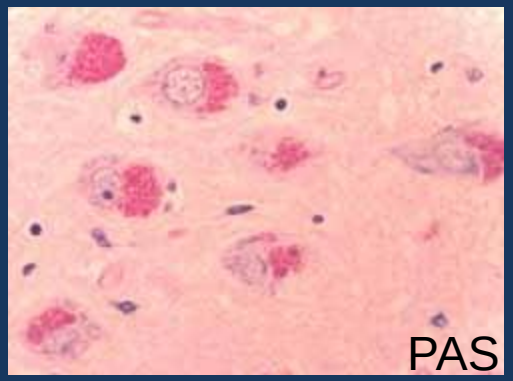
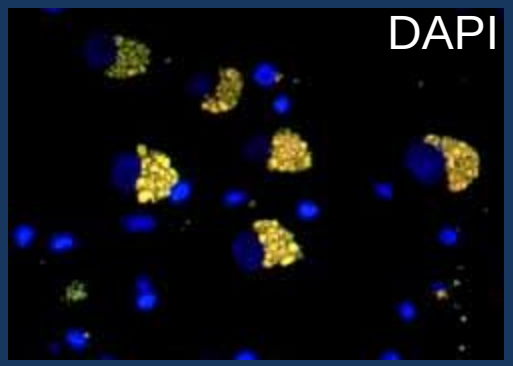
Nissl stain (cresyl violet)





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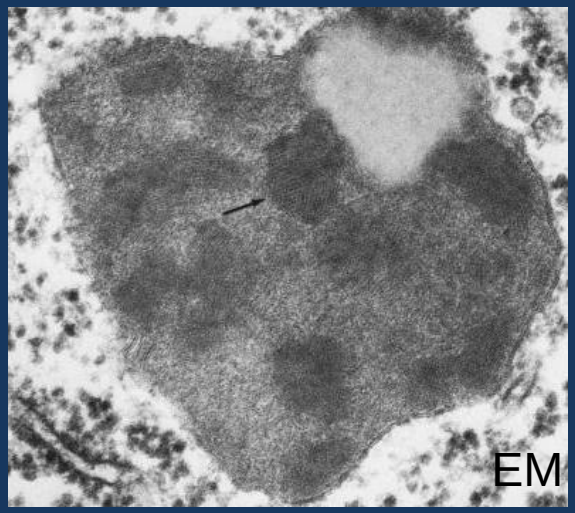

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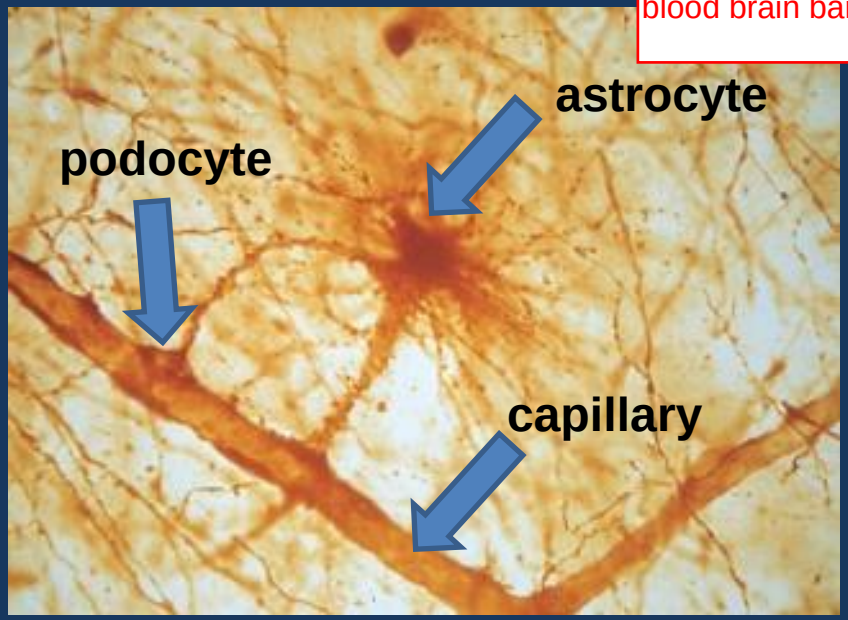
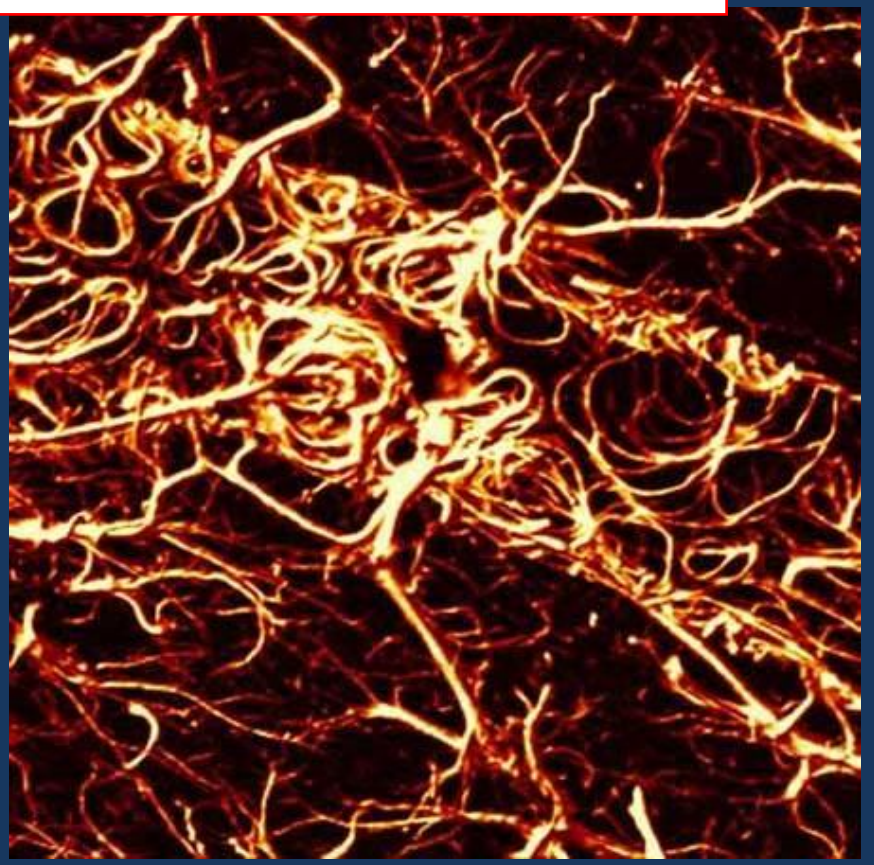
Lipofuscin buildup in normal in aging brains. Sign of wear and tear, accumulates as we age.

Astrocytes

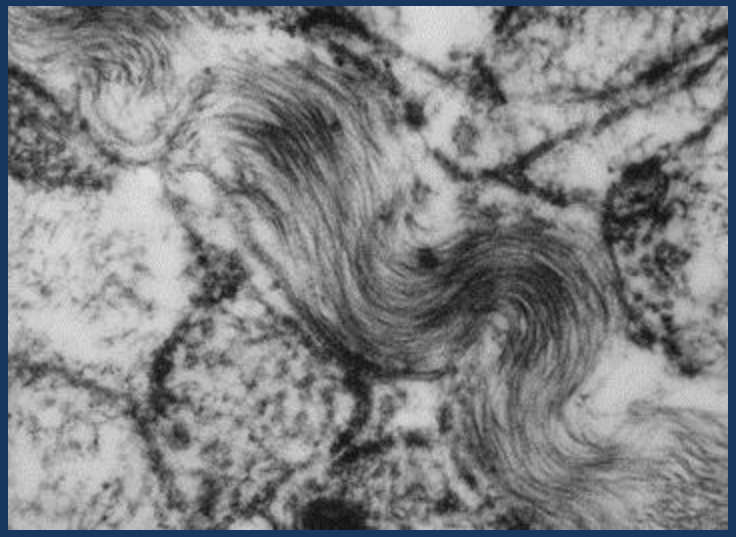
One of the glial cells. Most reactive and most likely to cause problems after an insult. They put their hands on everything. They maintain synapses, nourish neurons, mop up stuff, they form the blood brain barrier on capillaries, they uptake neurotransmitters, etc.



r scan)



C. R. Green/The Biomedical Imaging Research Unit



Glial fibrillary acid protein (GFAP)
(Electron microphotograph)

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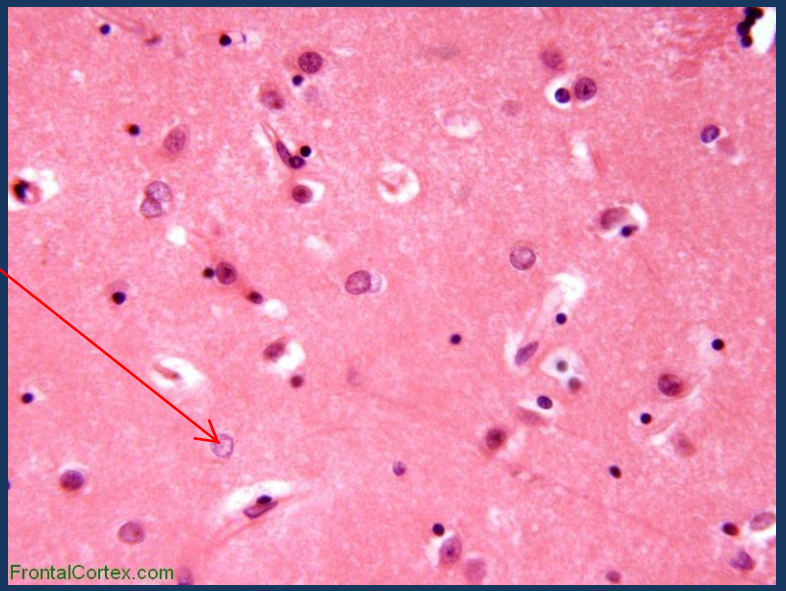
This is not Alzhemiers disease, these are just named after the same guy

Reactive astrocytes

When astrocytes are insulted, there are a number of changes.

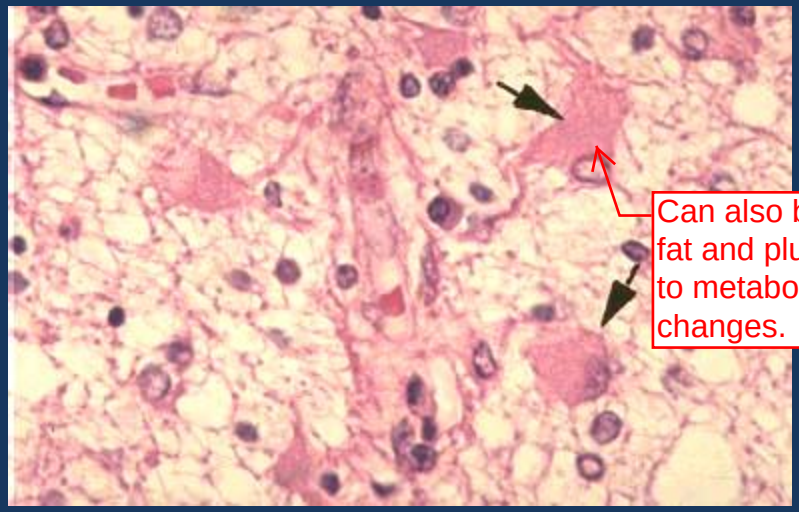
Astrocytes with clear nuclei due to changes in metabolism fromP increased ammonia exposure

Alzheimer type II astrocytes (H&E)



- **Astrogliosis: hypertrophy and hyperplasia**

Gemistocytes (H&E)



Can also become fat and plump due to metabolic changes.

Reactive astrocytes (silver stain)

Pictures of astrocytes like these just tell you that something bad has been happening.

Astrocytosis is both hypertrophy and hyperplasia of astrocytes

Reactive astrocytes (chronic gliosis)

Corpora amylacea

Collections of excretions from astrocytes in areas where there are lots of astrocyte podocytes. Common as we age and in epilepsy.

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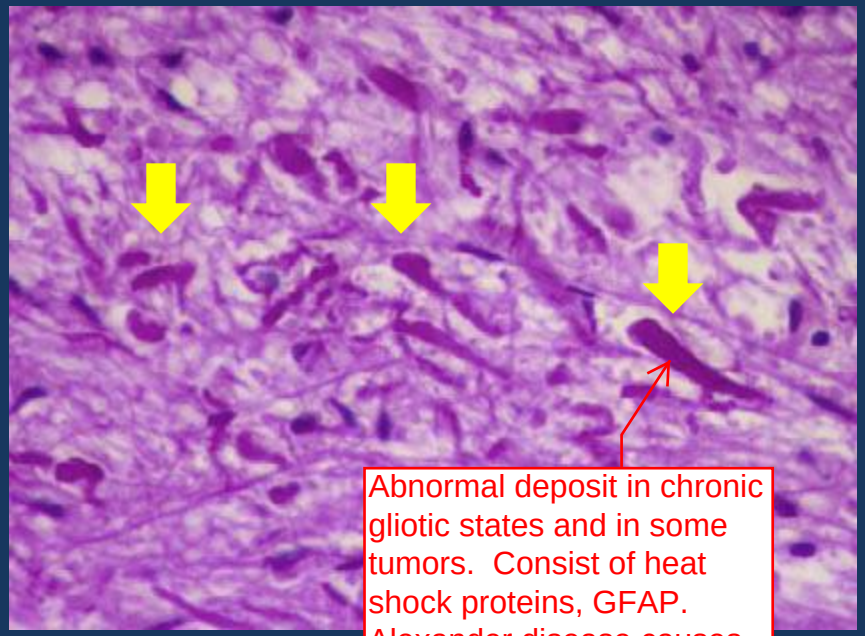
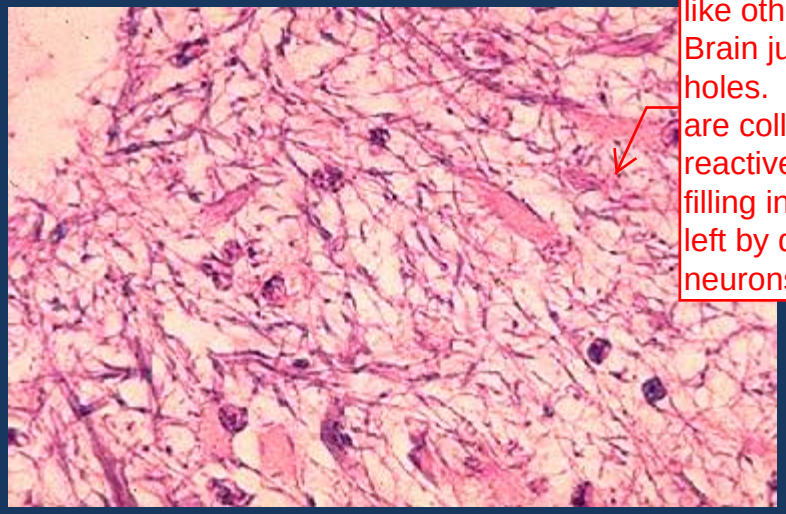
Rosenthal fibers

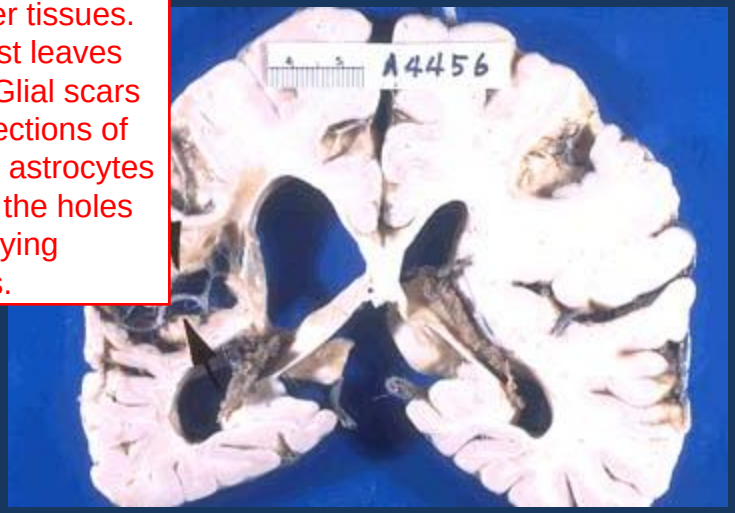


Abnormal deposit in chronic gliotic states and in some tumors. Consist of heat shock proteins, GFAP. Alexander disease causes lots of GFAP buildup and kills children by age 10

Glial "scar"



Brain cant form collagenous scars like other tissues. Brain just leaves holes. Glial scars are collections of reactive astrocytes filling in the holes left by dying neurons.



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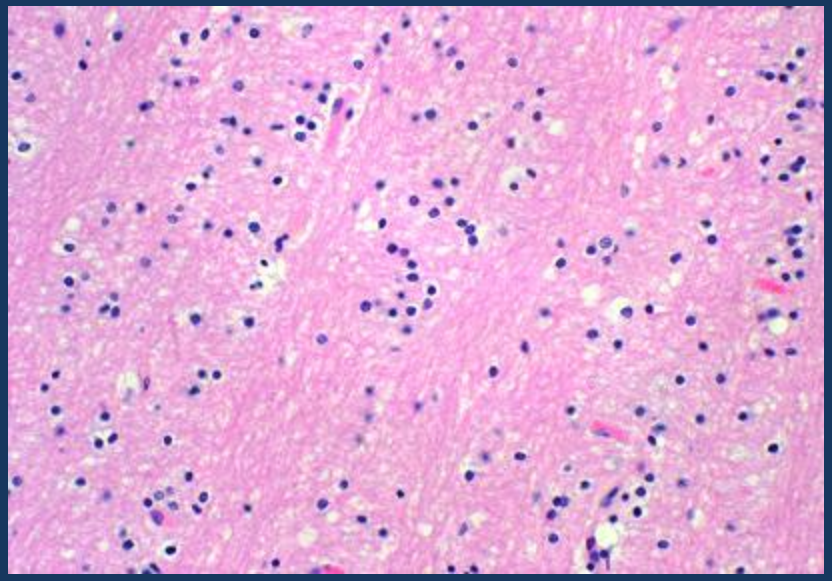
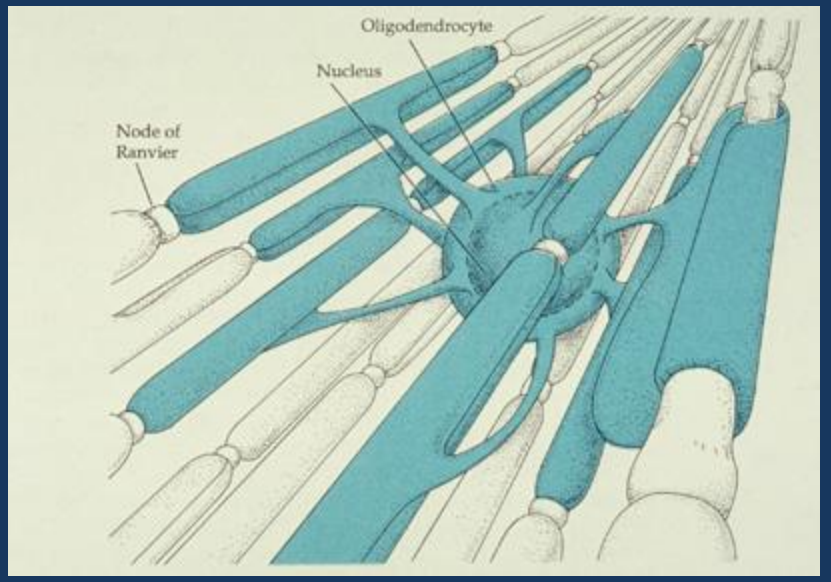
Oligodendrocytes





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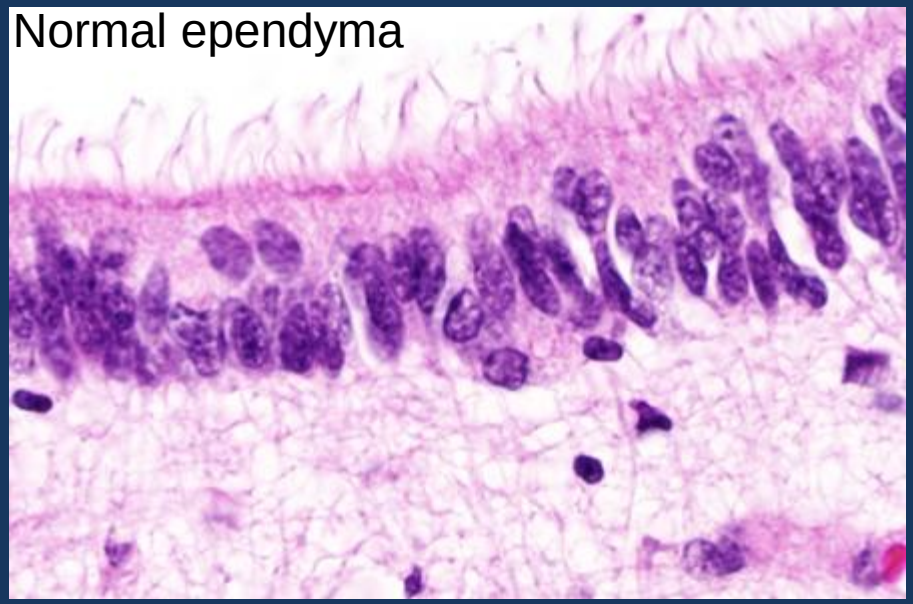
These don't really react much. They just die. When functioning, they insulate the neurons. These are lost in MS

Ependymal cells & choroid plexus

Normal ependyma



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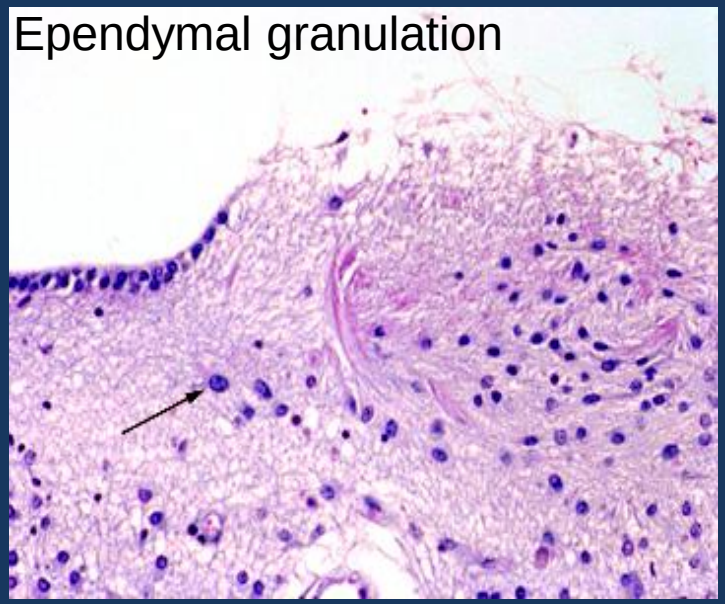
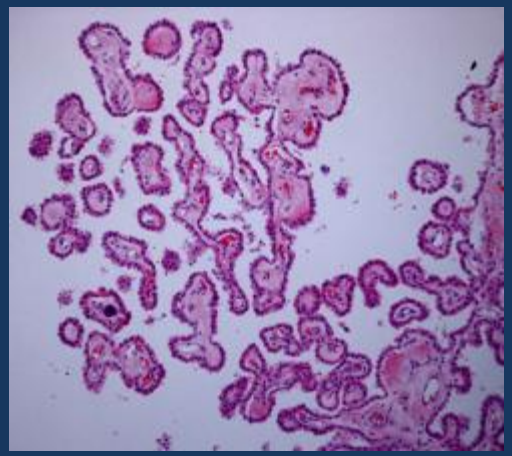
Ependymal granulation



Normal choroid plexus



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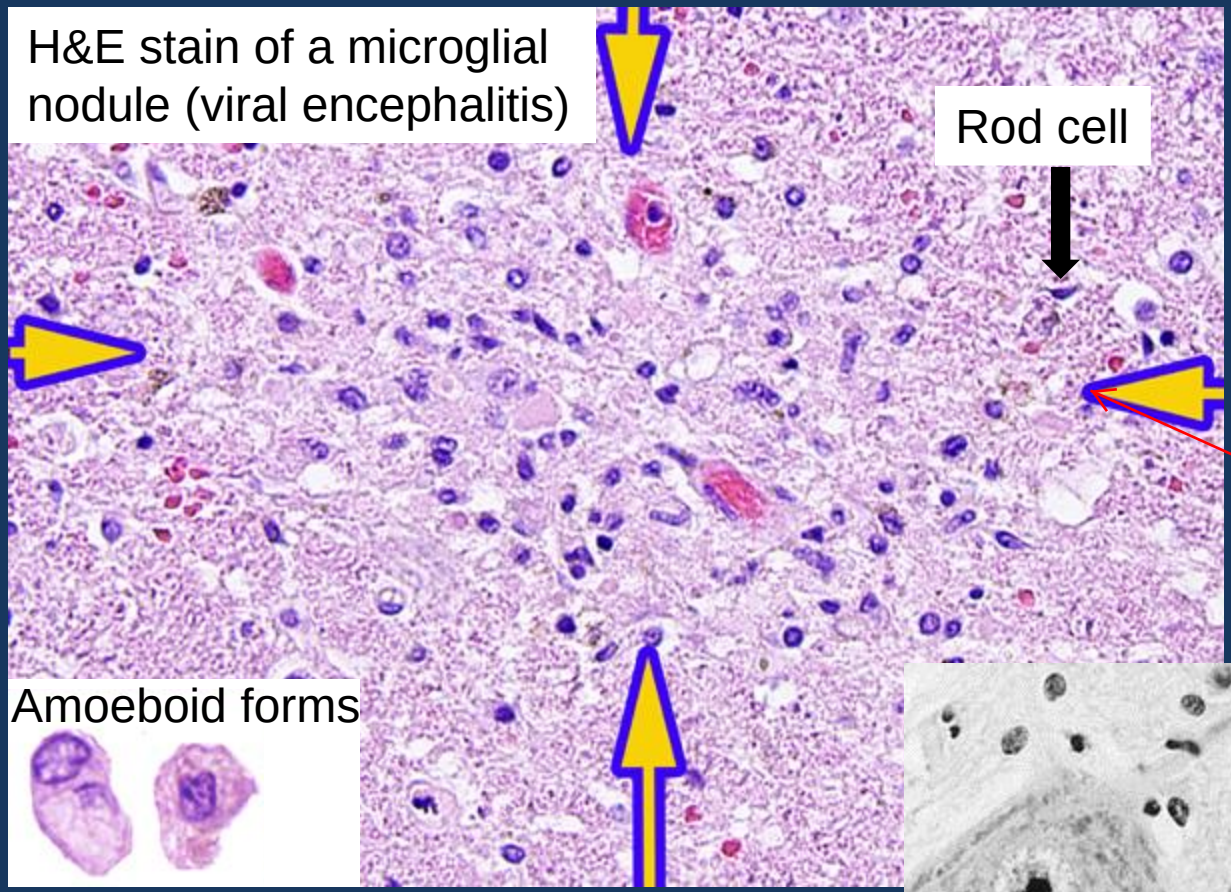
(Scanning EM)

Choroid is specialized ependymal cells that produce CSF in the ventricles

Ependymal cells line the ventricles. They have cilia. Possible stem cells are below this layer. Ependymal granulations occur when it is damages, but it is actually just astrocytes from below this layer reacting.

Microglia

H&E stain of a microglial nodule (viral encephalitis)



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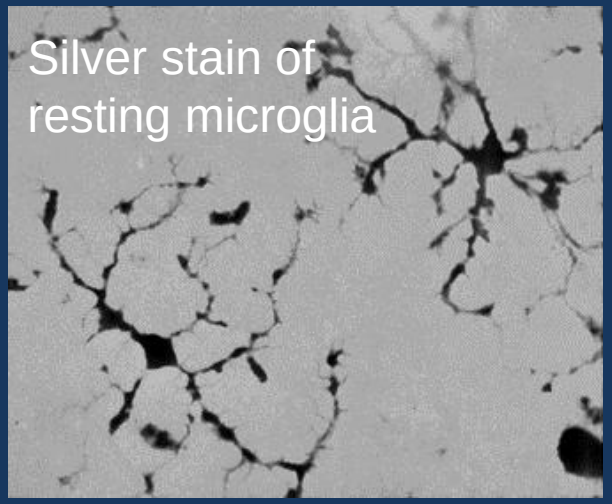
Microglia are the macrophages of the CNS. They are reactive cells when you have infection or insult. They try to clean up the area. Amoeboid forms (actively cleaning up) and rod cell forms.



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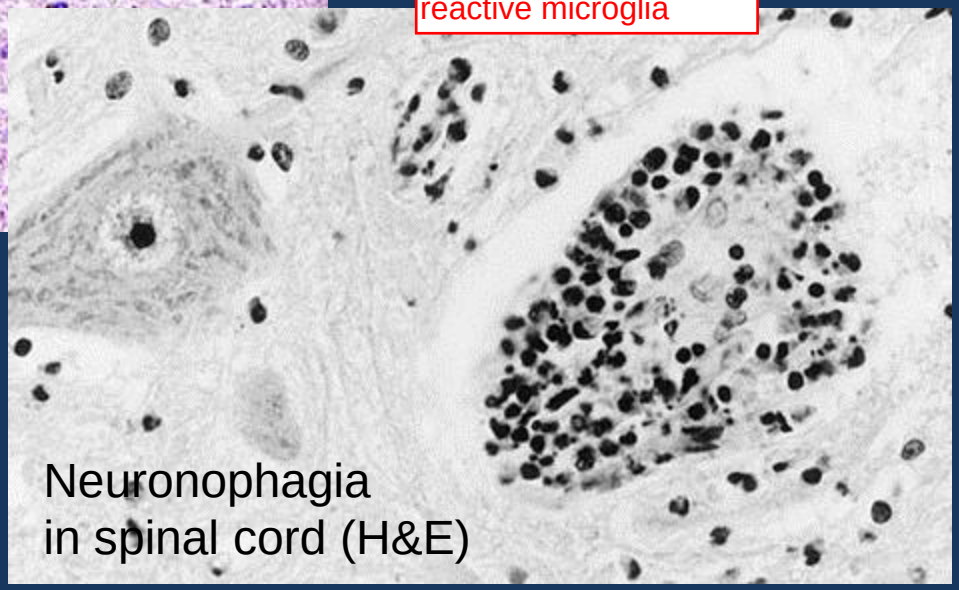
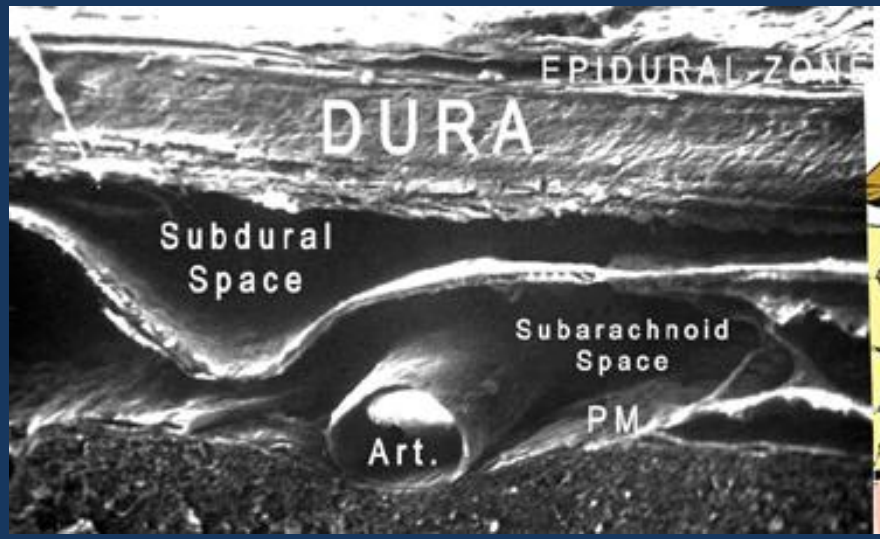
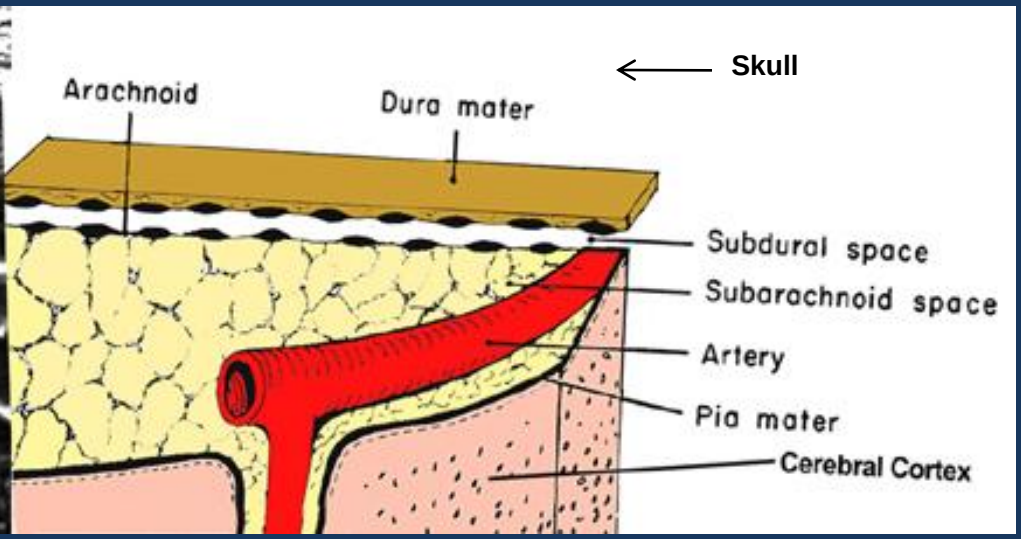
These four arrows define a microglial nodule in a viral infection, which consists of a bunch of reactive microglia



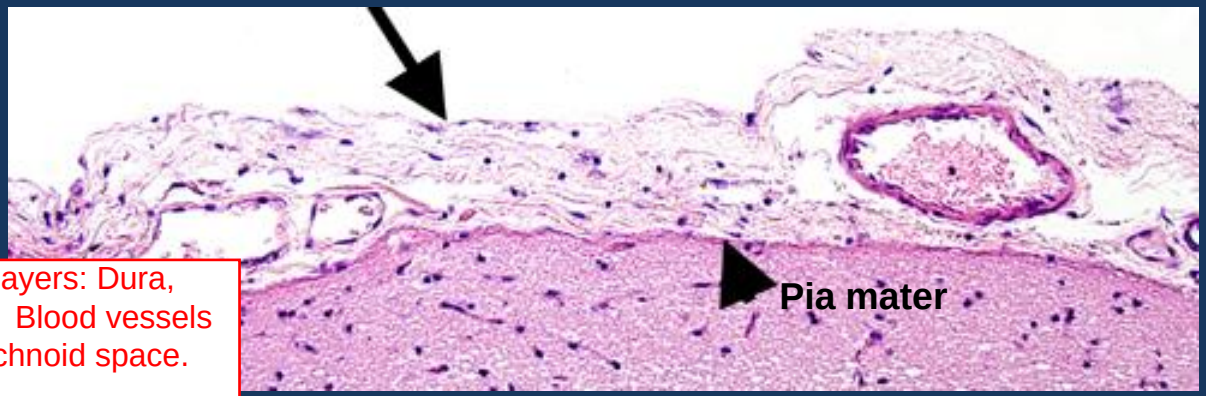
Hsueh (2000) Mod Pathol13:1200

Meninges





Arachnoid surface



Mesodermal in origin. 3 layers: Dura, arachnoid and pia mater. Blood vessels usually run in the subarachnoid space.

R&C Chapter 28: The CNS

- Cellular Responses to Injury
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Cerebral (brain parenchymal) edema

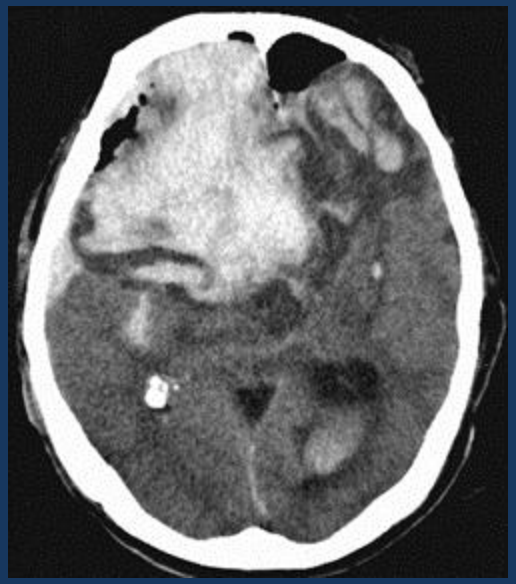
- **Vasogenic:** blood-brain barrier is compromised (e.g. trauma, tumor)

Fluid from blood goes into brain tissue, no lymphatics to drain it

- **Cytotoxic:** cellular injury (e.g. hypoxic or metabolic insult)

Cellular injury can also cause edema

CT scan: hemorrhage



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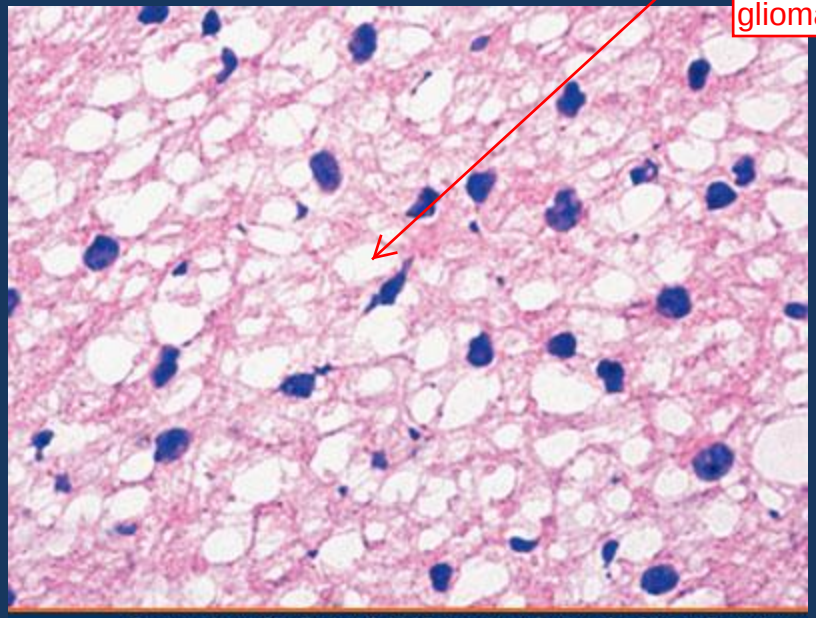
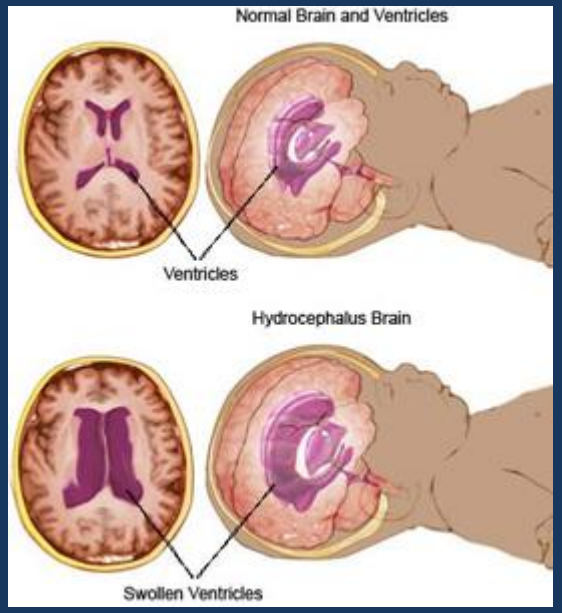
H&E frozen section: glioma

All these wholes are filled with fluid, lots of edema in gliomas



Hydrocephalus

(excess cerebrospinal fluid)



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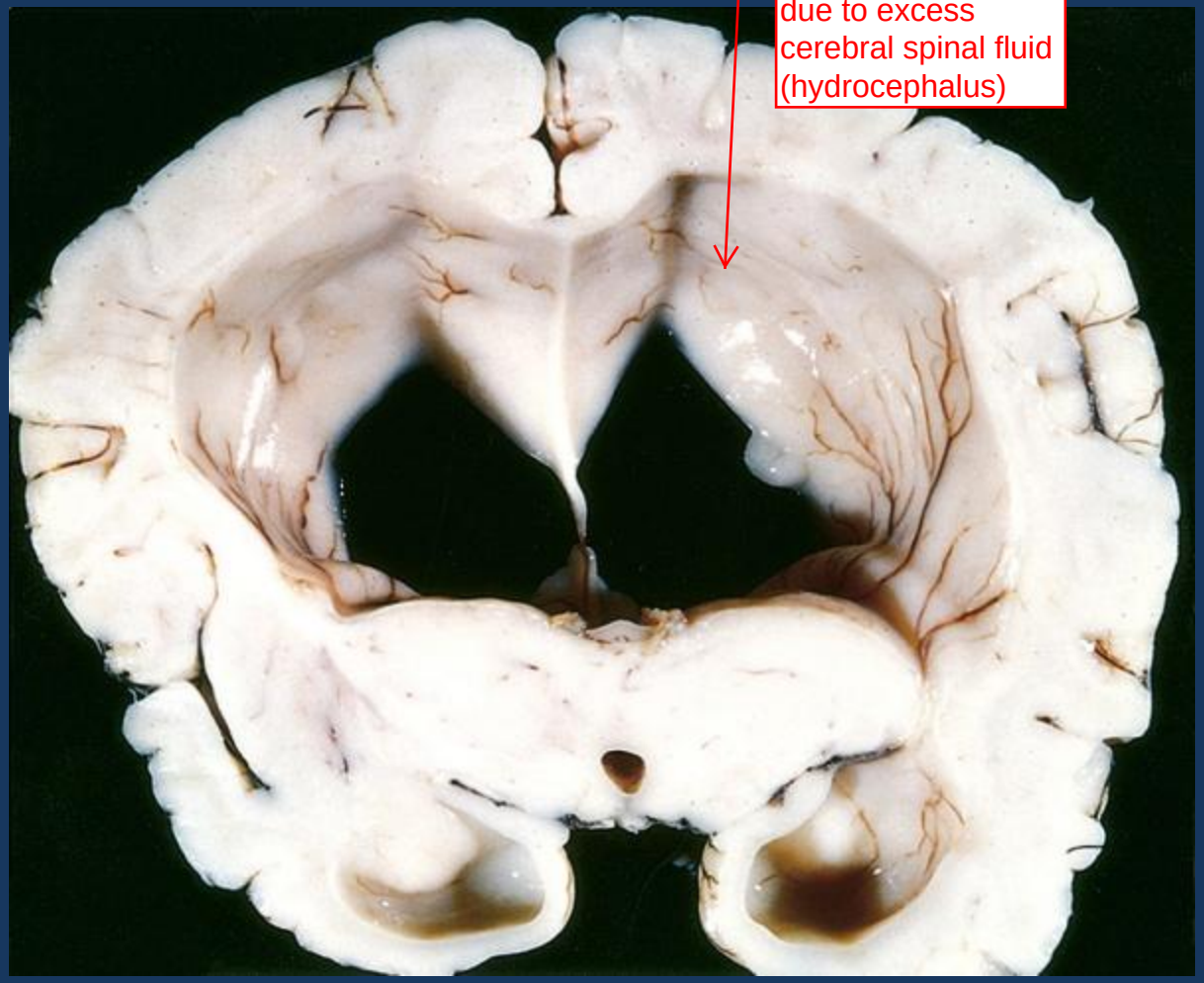
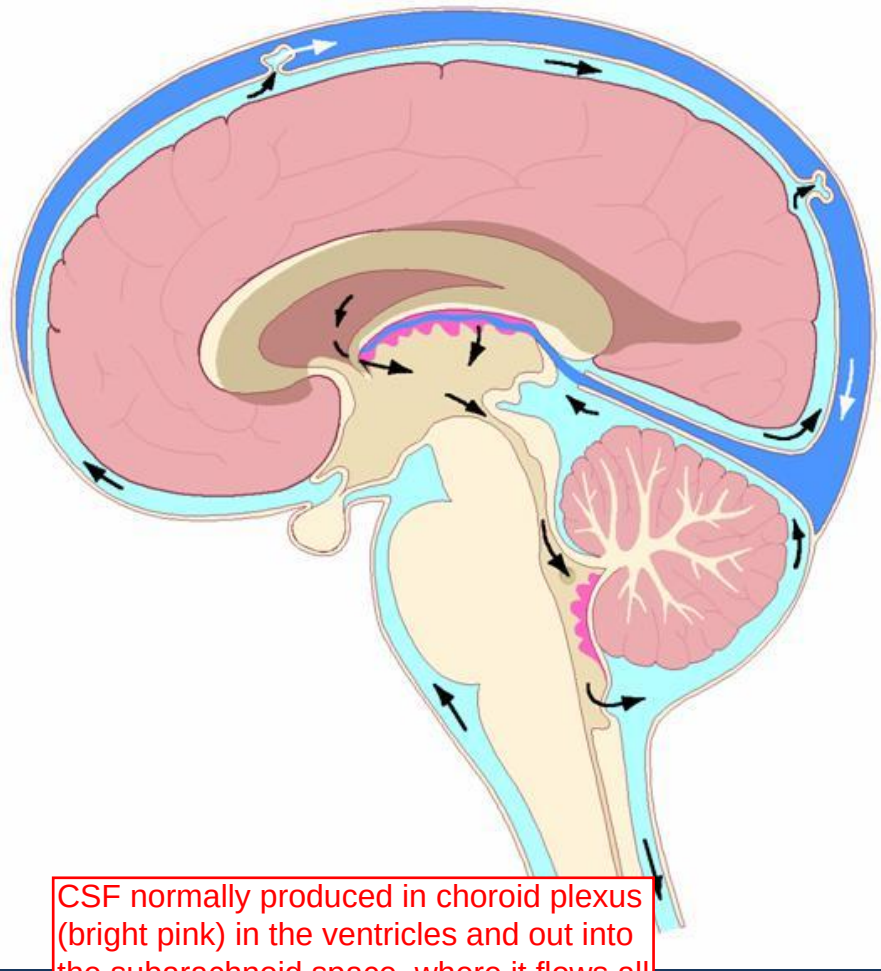


Ventriculomegaly, or enlarged ventricles. This is due to excess cerebral spinal fluid (hydrocephalus)

Cerebrospinal fluid flow



CSF normally produced in choroid plexus (bright pink) in the ventricles and out into the subarachnoid space, where it flows all over the brain. Granulations in subarachnoid space come in contact with venous sinuses, allowing CSF to drain.

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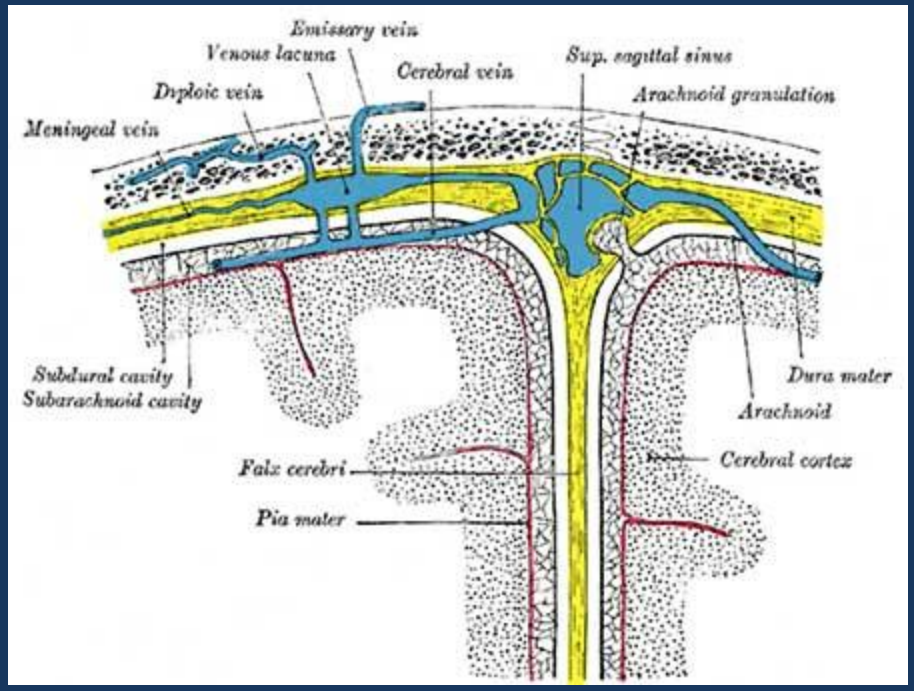


http://embryology.med.unsw.edu.au

Pressure hydrocephalus

Build up of pressure due to excess CSF, cause compression of the brain

- communicating (impaired CSF absorption)

CSF can flow freely between ventricles, so all of brain is compressed

- non-communicating (obstructive)

Obstruction between ventricles cause one region to buildup

- (versus hydrocephalus ex vacuo)

Hydrocephalus ex vacuo is enlarged ventricles due to brain atrophy

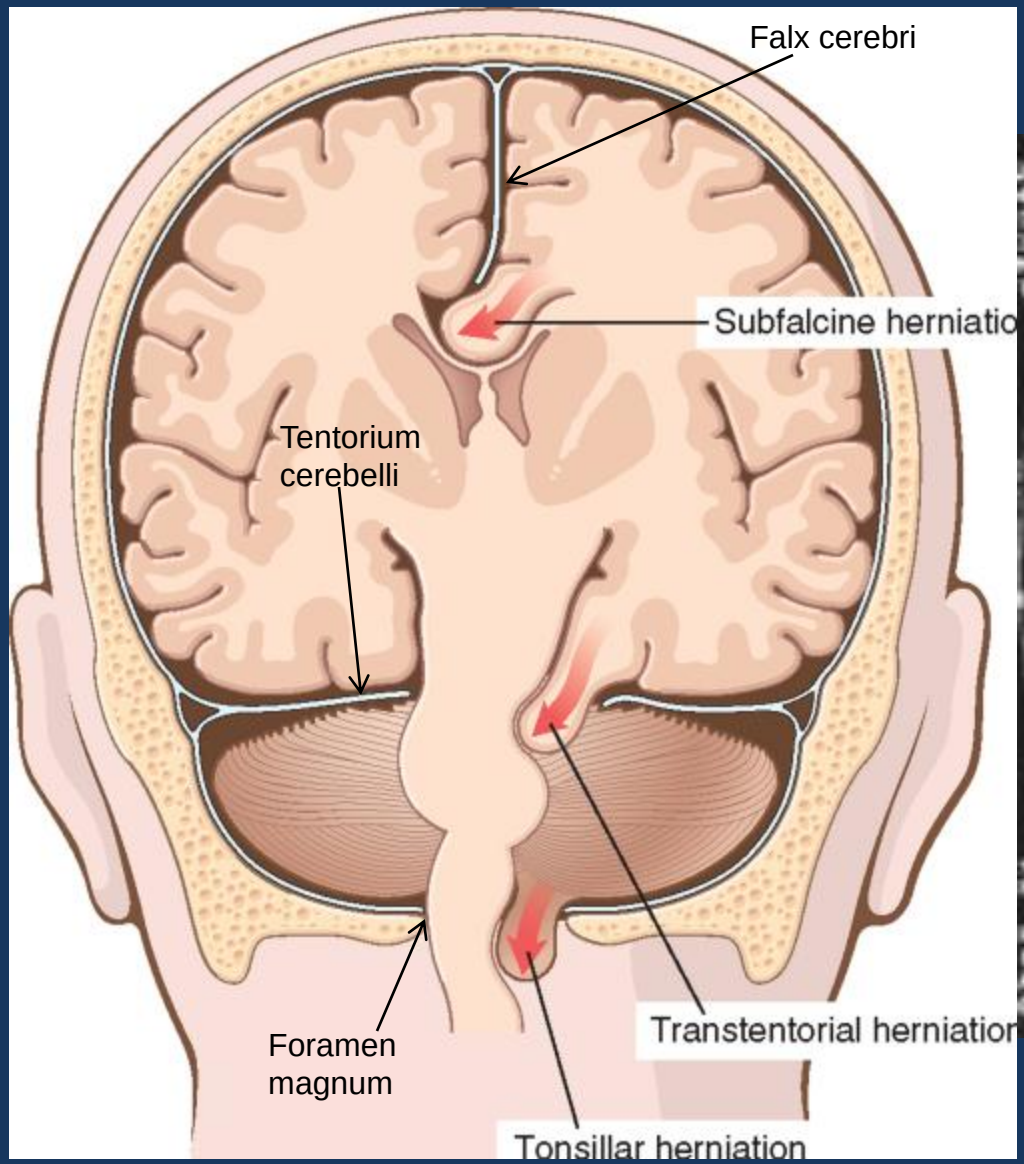
Raised intracranial pressure due to:
- Cerebral edema
- Pressure hydrocephalus
- Tumor
- Hemorrhage
- Abscess

Initial signs and symptoms of increased intracranial pressure:

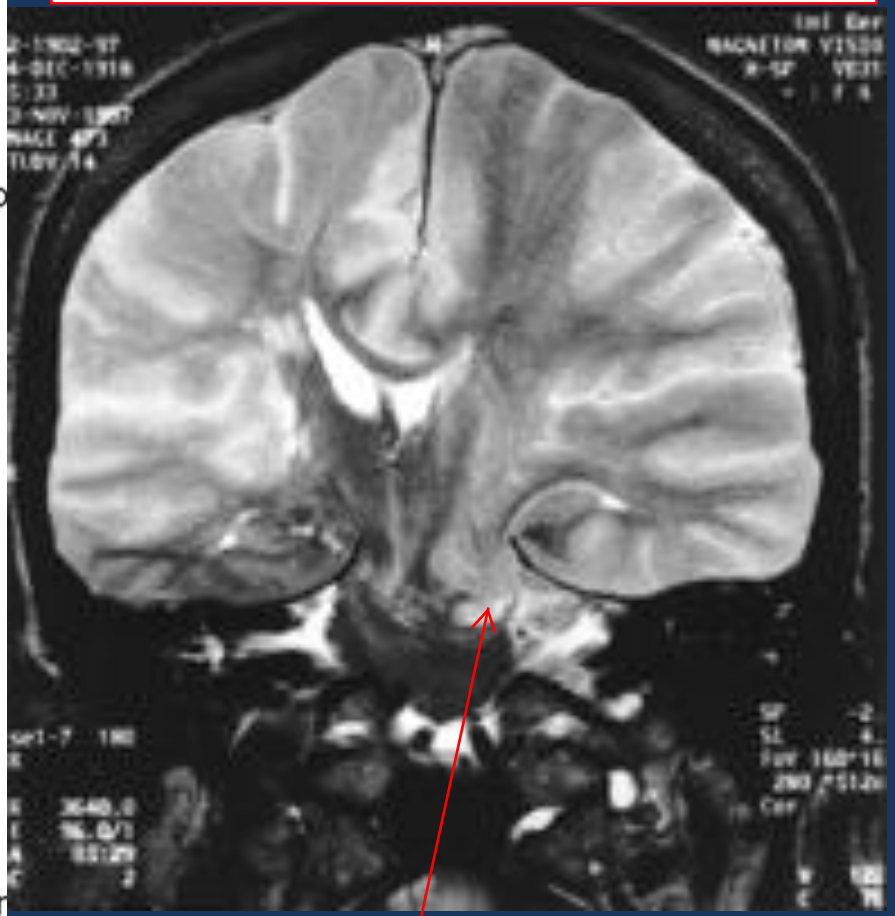
Increased pressure starts by shifting the brain tissues, then compression of vasculature, then flattening of sulci and gyri and serious damage.

- **headache**
- **vomiting**
- **altered mental status**
- **papilledema (engorgement of the optic disk)**

Endpoint of severe IIP: Herniation



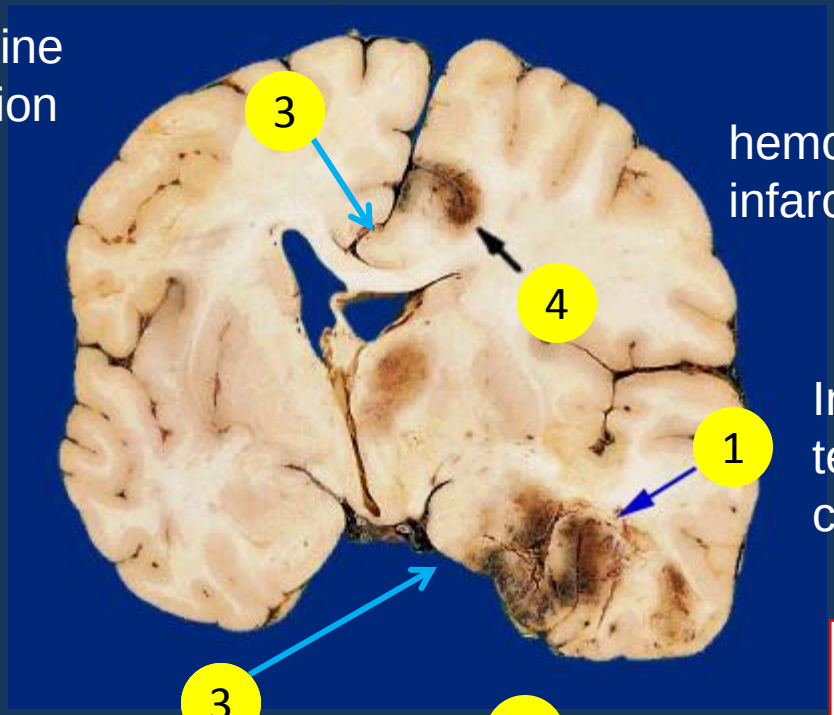
If increased pressure persists, brain squeezes out like jello. It will go wherever it can - around dural flaps, down spinal cord, etc.



Tonsillar herniation

stroke.ahajournals.org

Example: herniation following trauma



subfalcine herniation

hemorrhagic infarction

Inferior temporal lobe contusion

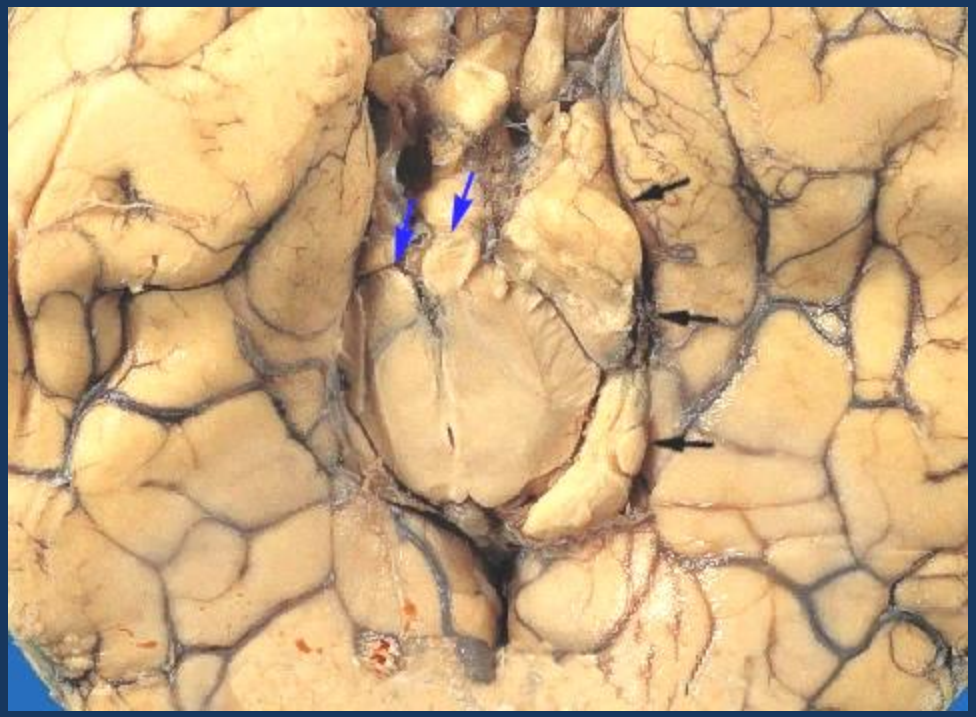
uncal (transtentorial) herniation

diffuse hemispheric vasogenic edema with midline shift

Contusion leads to edema, leads to diffuse swelling and shifting of midline to the left. This causes herniations around falx cerebri and the tentorium cerebelli. This falcine herniation gets trapped and bleeds, leading to hemorrhagic infarction.

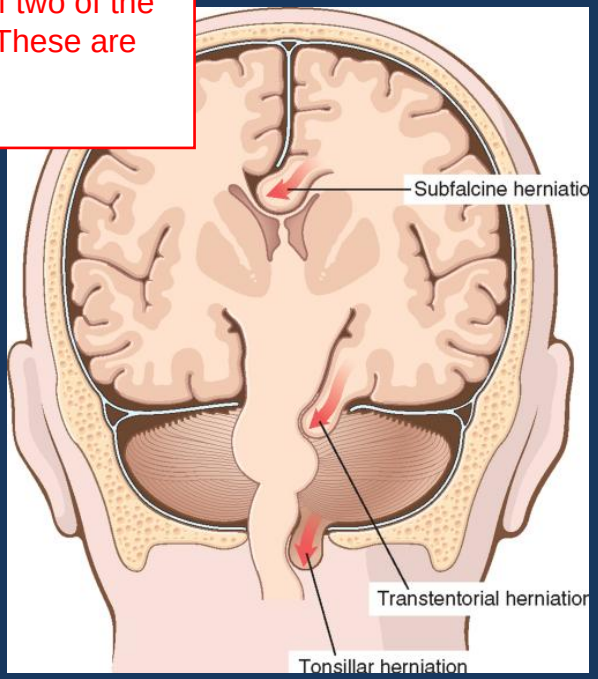
Neuropathology (1998) Ellison,Love et al

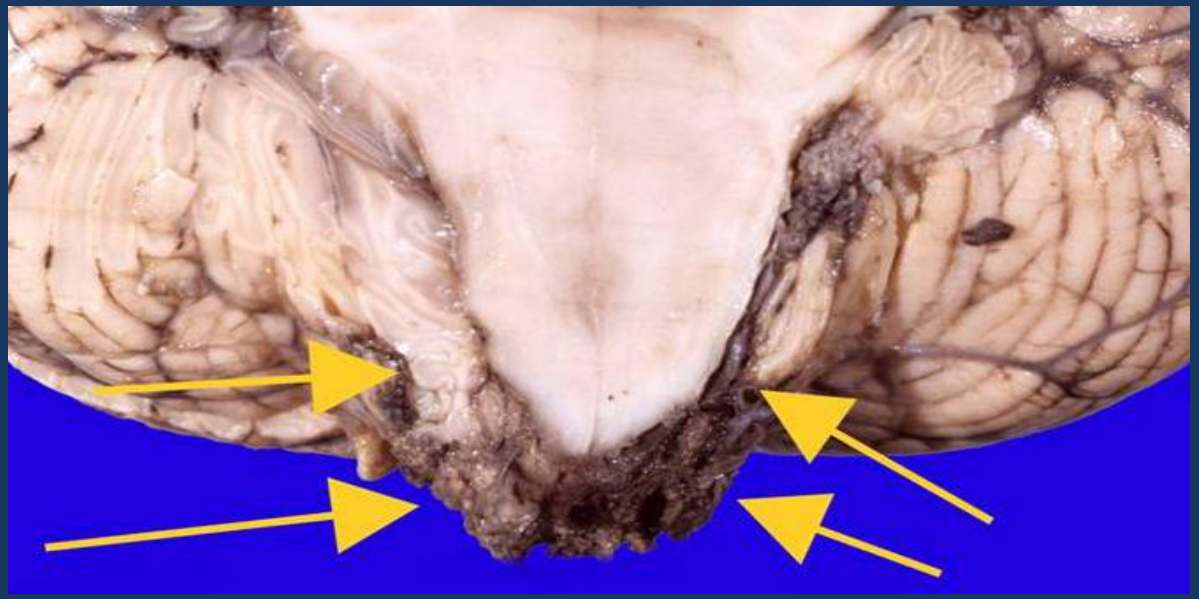
Uncal (transtentorial) herniation



Neuropathology (1998) Ellison,Love et al

Illustrations of two of the herniations. These are real bad.





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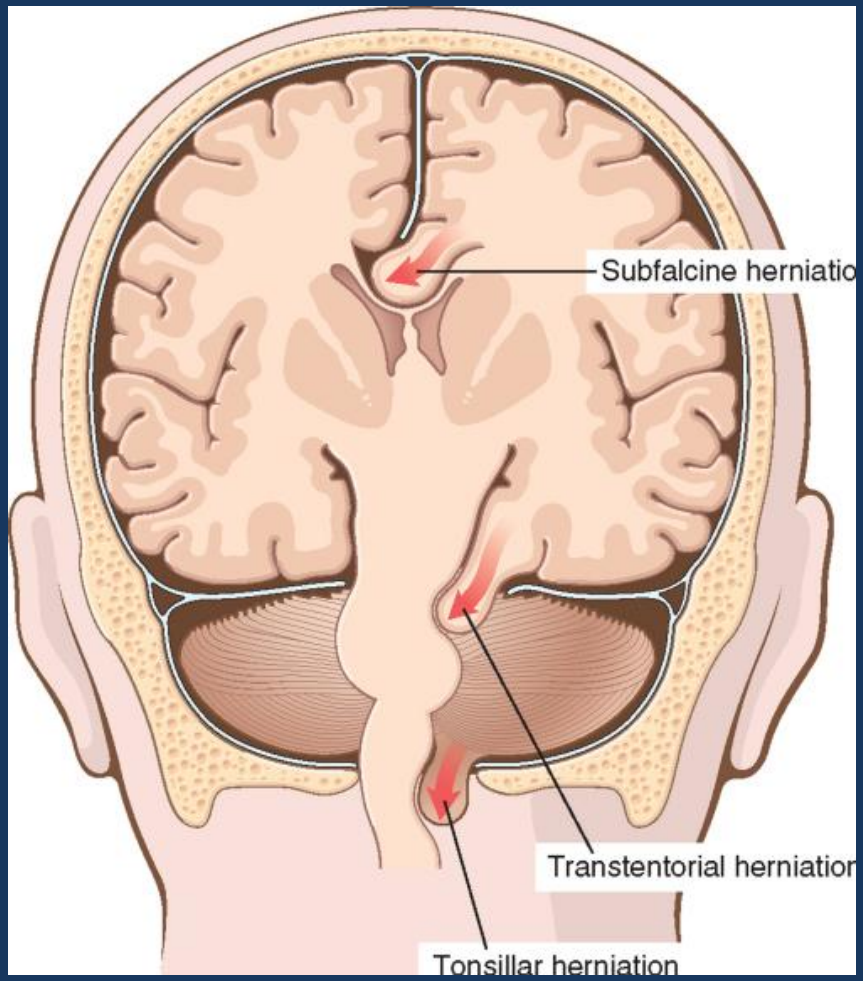
Tonsillar herniation

Site-specific consequences of herniation

Symptoms of these three herniations are different, as shown below.



- can be clinically silent
- ACA compression

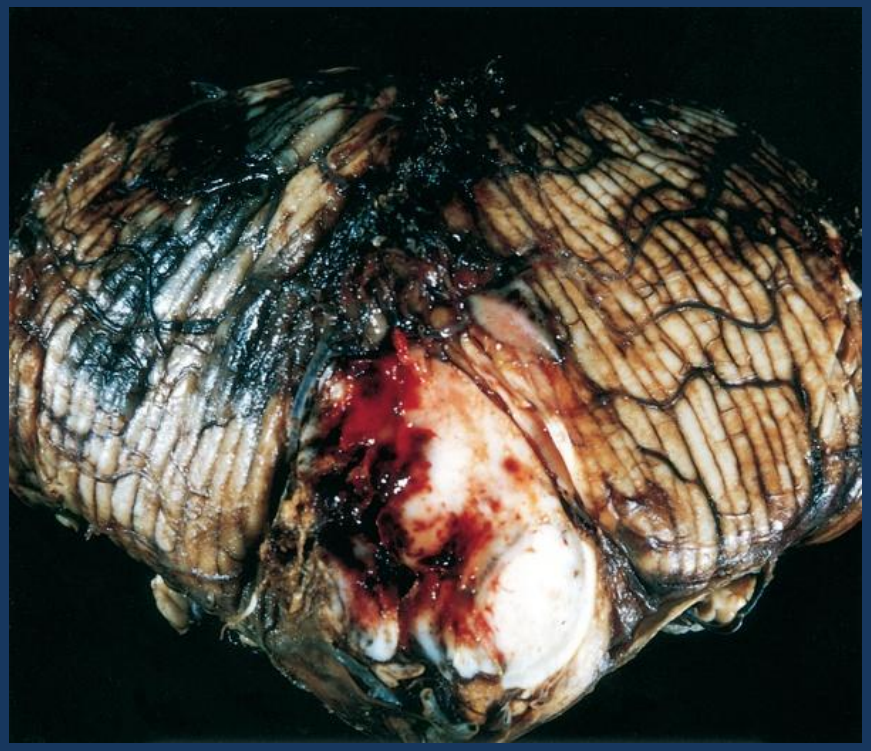
- PCA compression (visual field defect)
- CNIII compression (blown pupil)
- Cerebral peduncle compression (paresis)
- Sylvian aqueduct occlusion (hydrocephalus)
- Duret hemorrhages

- compression of the medulla (cardiorespiratory arrest)

Read this slide

Duret (secondary brainstem) hemorrhages

- Sequela of transtentorial (uncal) herniation
- Caused by stretching of the penetrating branches of the basilar artery as the midbrain descends



Neuropathology (1998) Ellison,Love et al

R&C Chapter 28: The CNS

- Cellular Responses to Injury
- Cerebral Edema, Hydrocephalus, Raised Intracranial Pressure & Herniation
- **Perinatal Brain Injury**
- Trauma

Childrens brains in perinatal period are still developing, have different kinds of injury.

Perinatal brain injury

Sites of injury

Only in developing brain, has stem cells

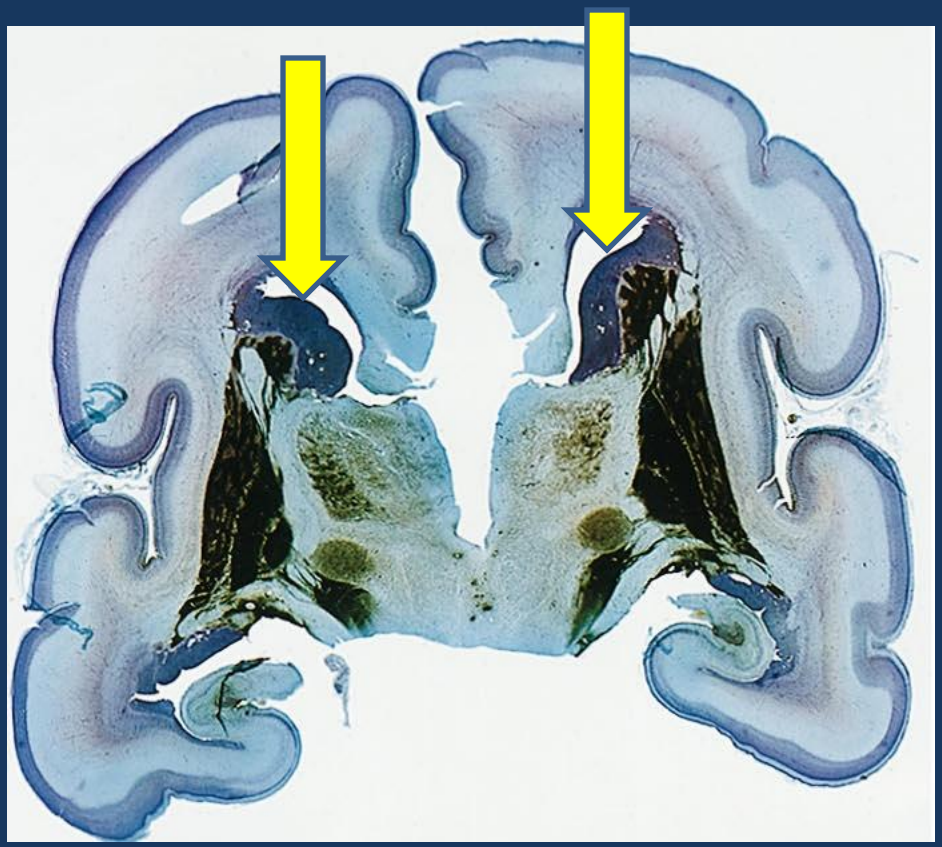
- Germinal matrix
- Periventricular white matter
- Cortex and underlying white matter
- Deep nuclei

Sequelae

non-progressive

- Static motor deficits (cerebral palsy): spasticity, dystonia, ataxia/athetosis, and paresis
- Cognitive deficits

Germinal matrix



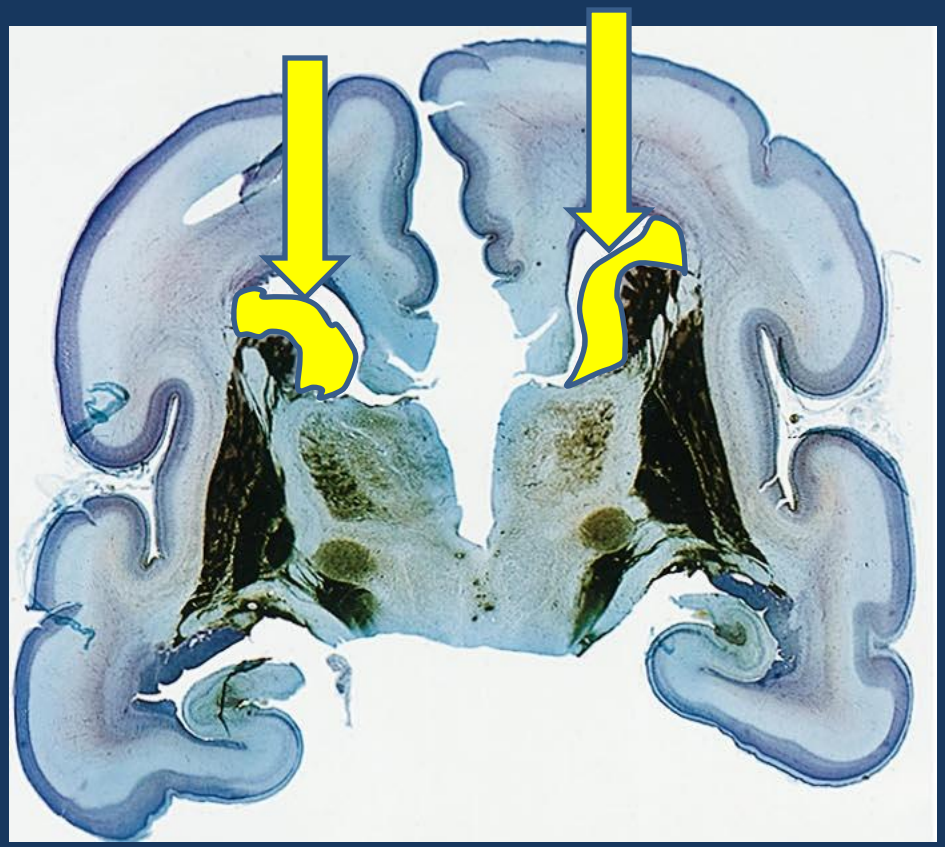
Ghazi-Birry et al (1997) *Am J Neuroradiol* 18:219

24-week-postconception neonate
(alkaline phosphatase and cresyl violet)

Stem or progenitor cells in this region that are active in the developing brain. This region does not exist in the adult brain. This region is very sensitive, especially in premature babies. These neurons are not myelinated, they are easily damaged.

Germinal matrix bleeds are especially common when pressing on the head during rescussitation, this can lead to serious brain damage or may be subclinical.

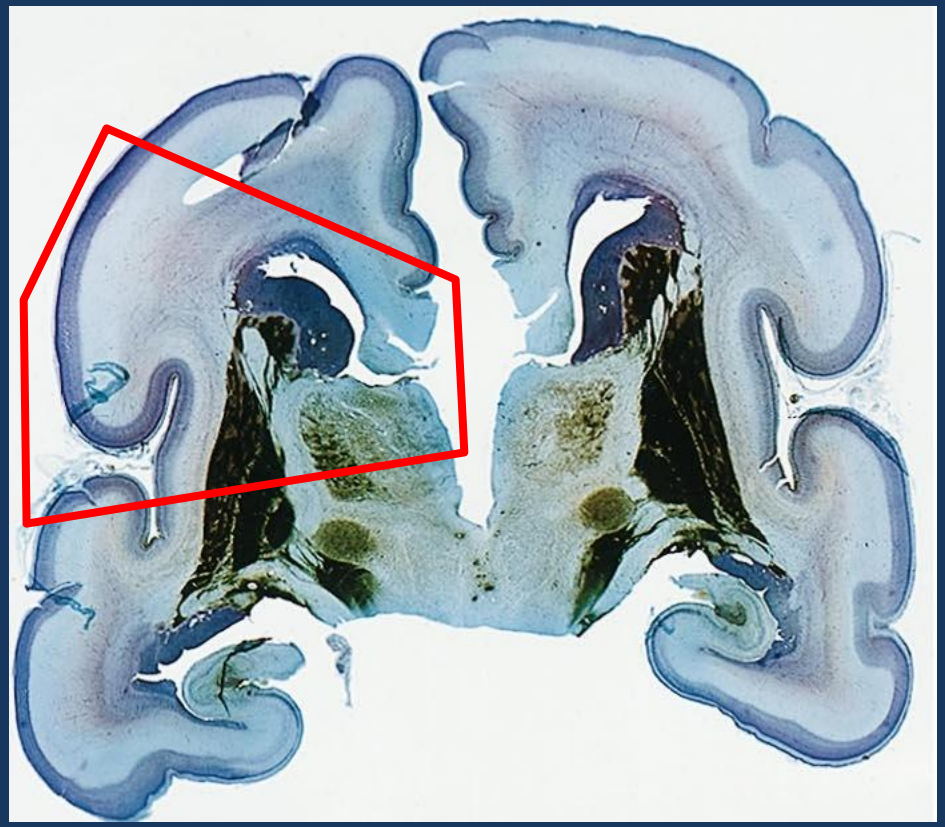
Germinal matrix



Ghazi-Birry et al (1997) *Am J Neuroradiol* 18:219

24-week-postconception neonate
(alkaline phosphatase and cresyl violet)

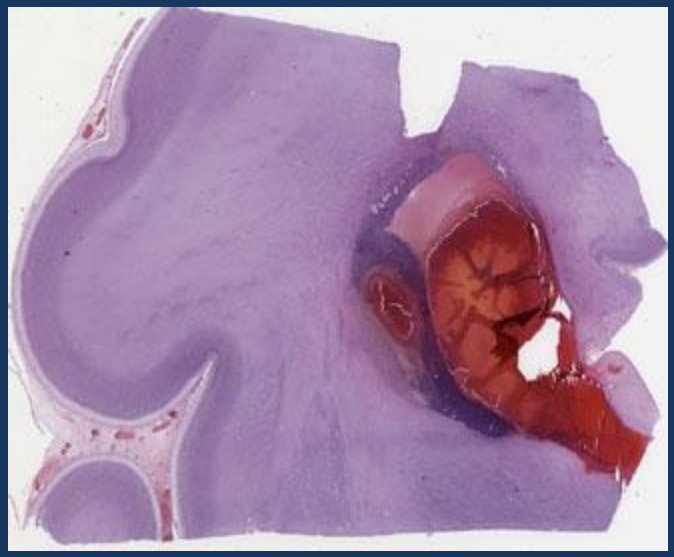
Germinal matrix



Ghazi-Birry (1997) AJNR Am J Neuroradiol 18:219

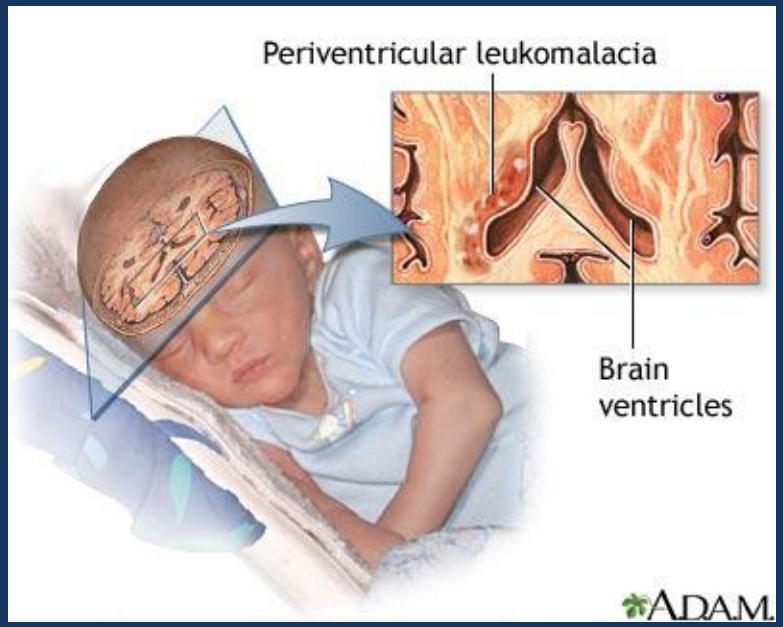
24-week-postconception neonate
(alkaline phosphatase and cresyl violet)

Germinal matrix bleed



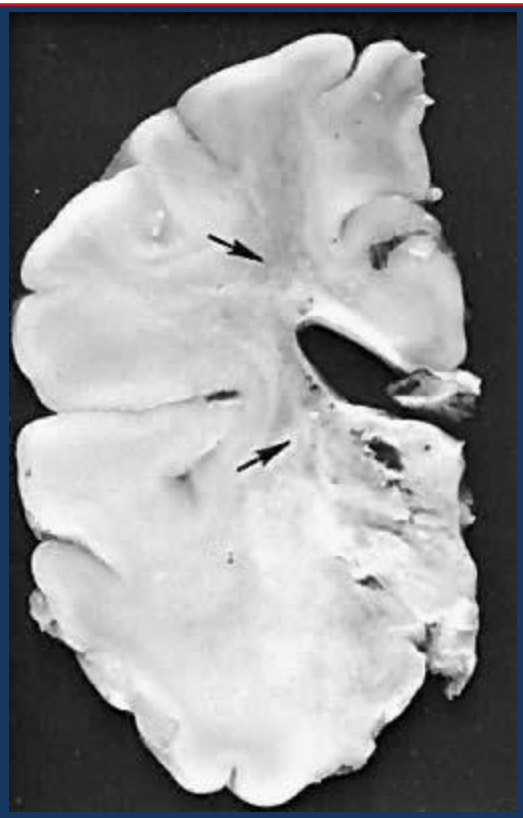
dartmed.dartmouth.edu

Periventricular leukomalacia (from white matter damage)

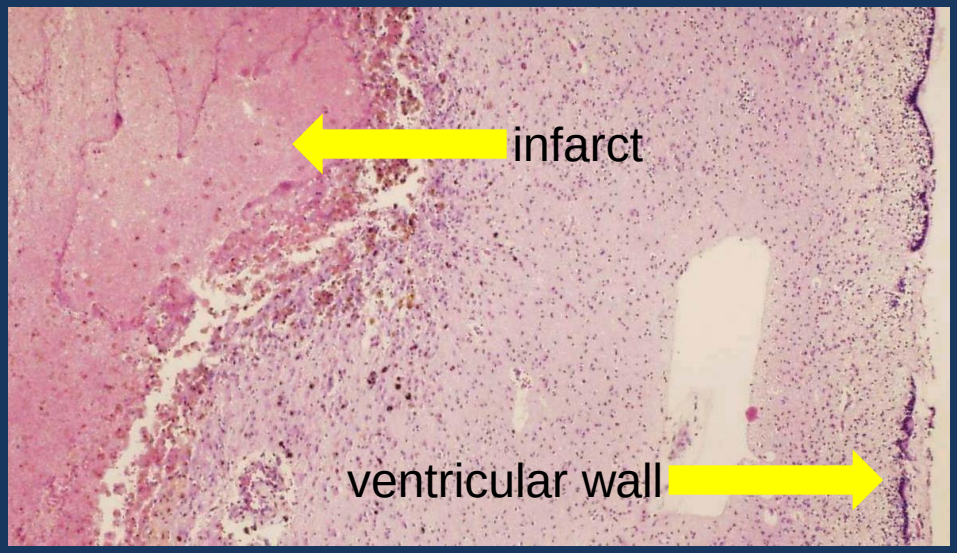


nim.nih.gov

Hypoxia or infection of white matter around the ventricles will lead to hydrocephalus.

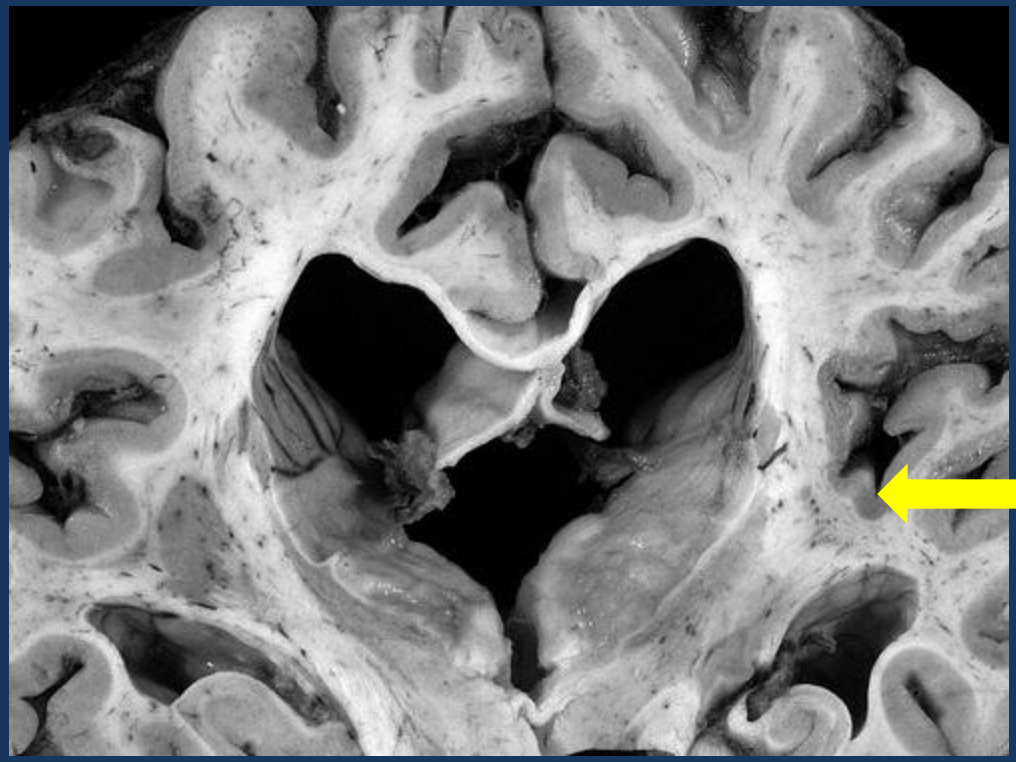


glowm.com



emedicine.medscape.com

Ulegyria
(from cortical hypoxia/ischemia)

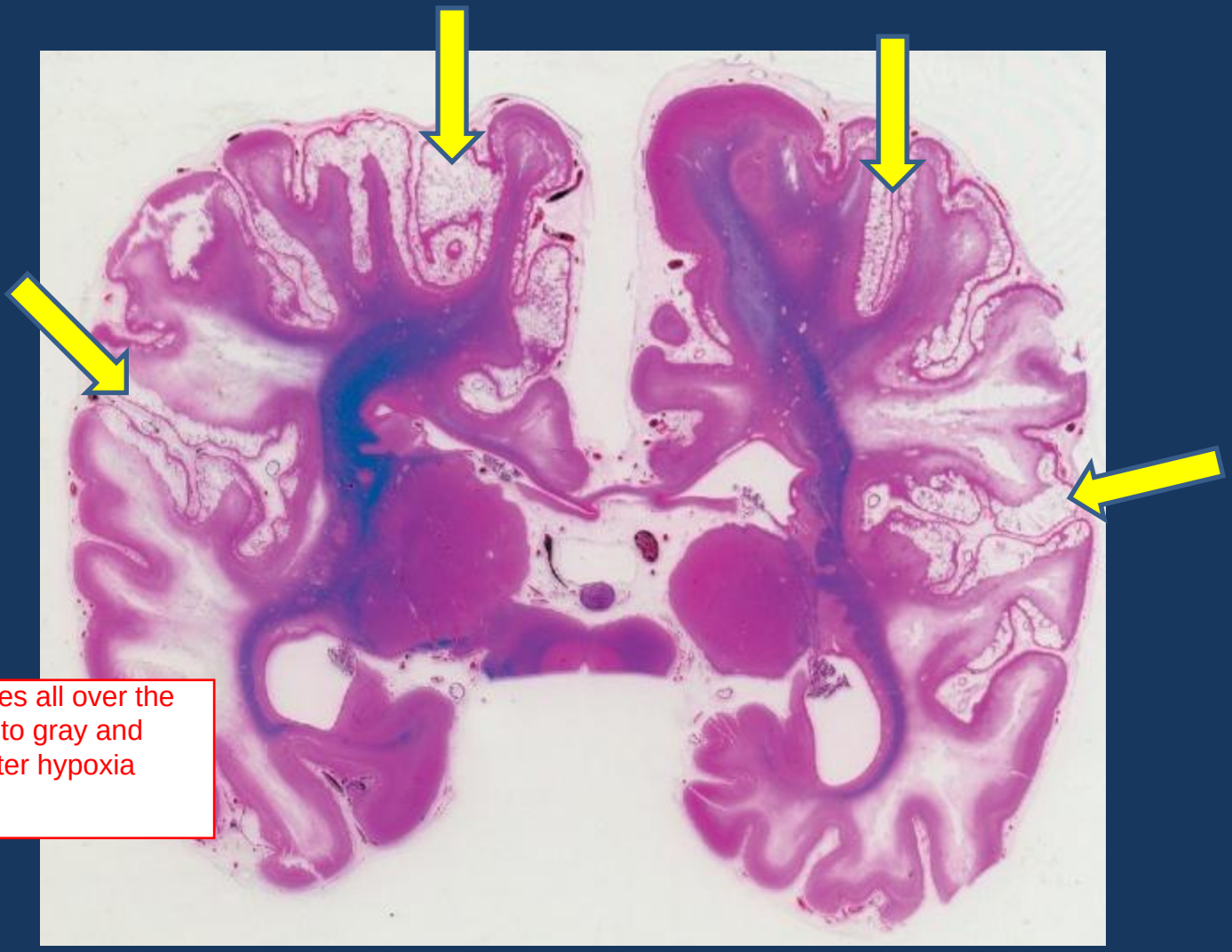


Thinned, gliotic gyri

gliageek@flikr.com

Gray matter ribbon has different widths in different places. Due to cortical hypoxia or ischemia.

Multicystic encephalopathy
(from gray and white matter hypoxia/ischemia)

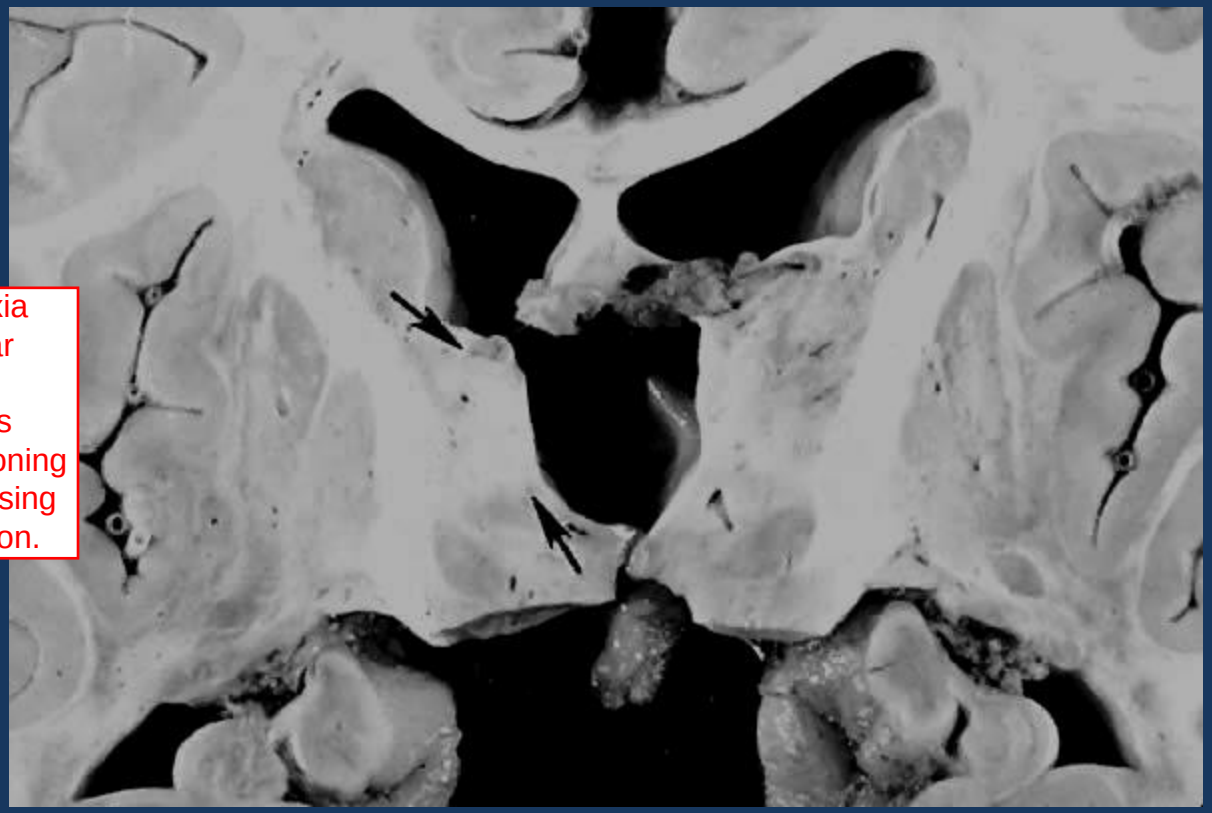


Cystic holes all over the brain due to gray and white matter hypoxia

Status marmoratus

(from hypoxia/ischemia of deep nuclei)

Deep nuclei hypoxia leads to a glial scar and improper myelinization. This leads to malfunctioning basal ganglia, causing inappropriate motion.



glowm.com

Glial “scar” and aberrant myelinization in basal ganglia

Clinical sequelae include choreoathetosis and related movement disorders

R&C Chapter 28: The CNS

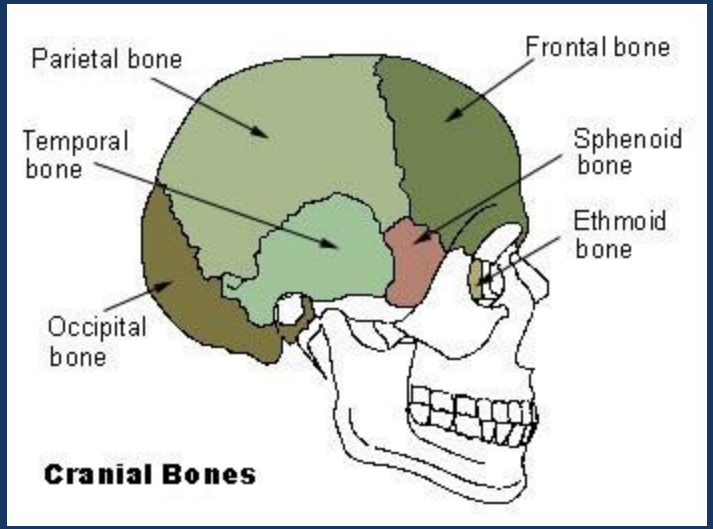
- Cellular Responses to Injury
- Cerebral Edema, Hydrocephalus, Raised Intracranial Pressure & Herniation
- Perinatal Brain Injury
- **Trauma**

Trauma

- **Skull fractures**
- **Parenchymal injury** Direct injury to the brain
- **Vascular injury**

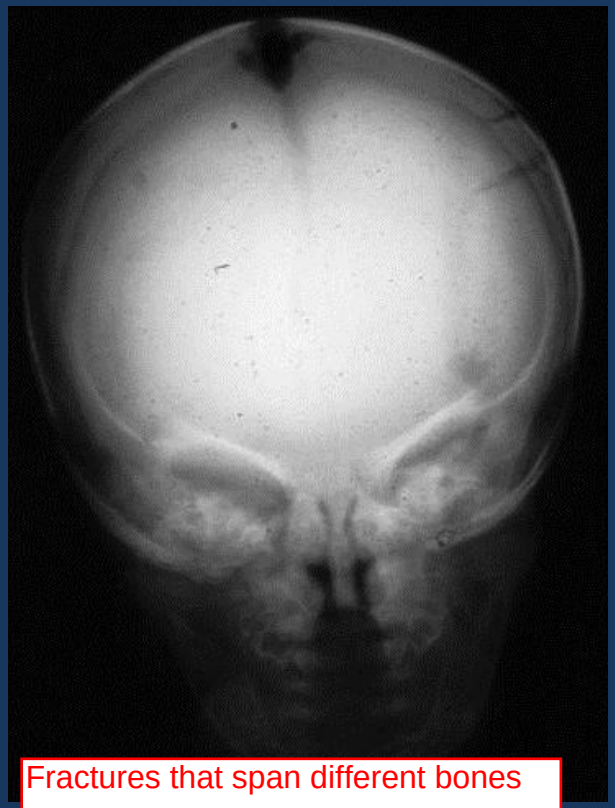
Trauma: Skull fractures

Different signs on face depending on what bone is fractured

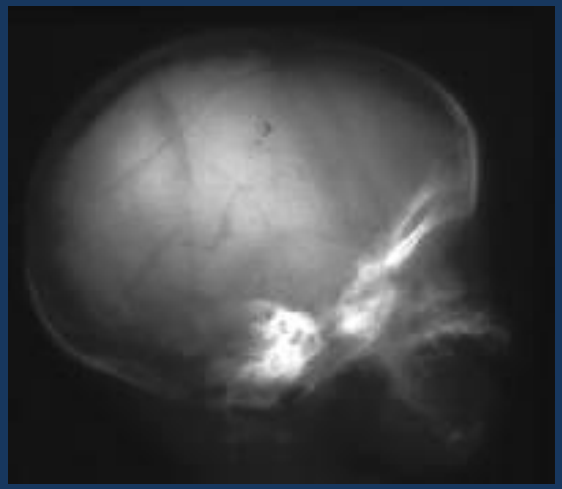


wikipedia.org

Diastatic fractures

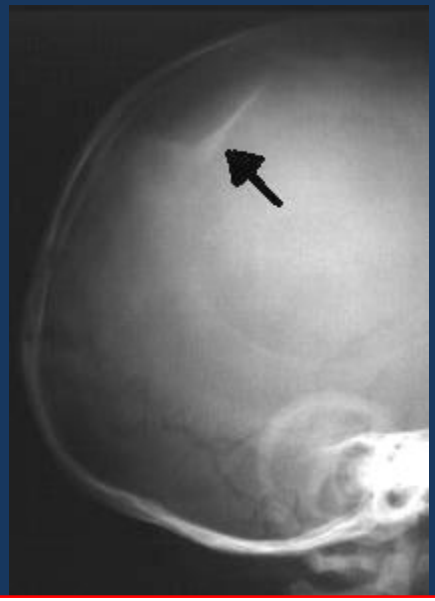


Fractures that span different bones



Emedicine.medscape.com

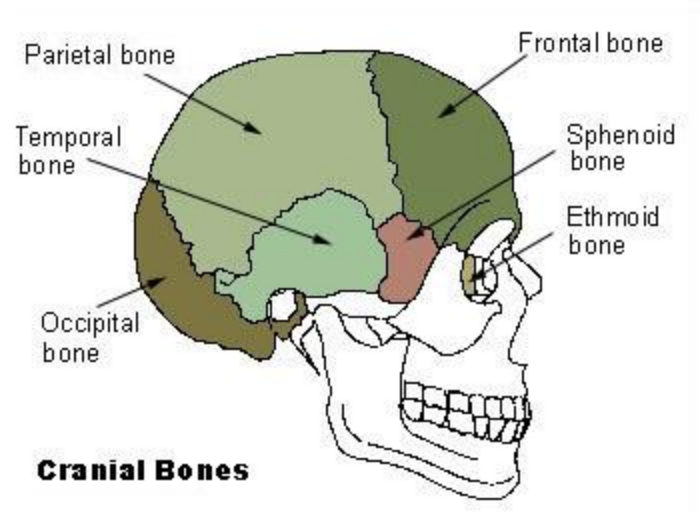
Displaced fracture



wikipedia.org

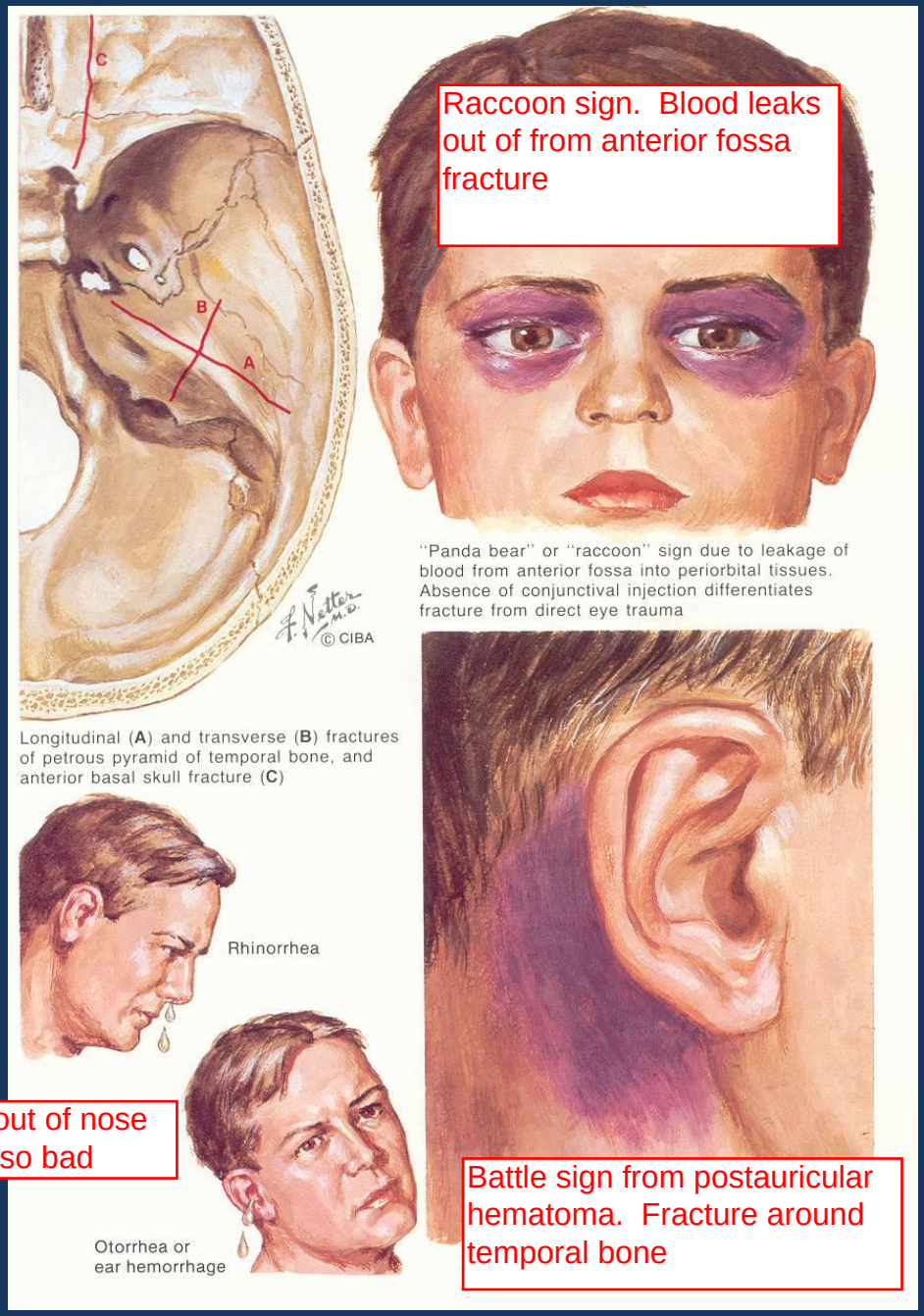
Chunk of bone dives into the brain

Trauma:
Skull fractures



wikipedia.org

Basal skull fractures



Raccoon sign. Blood leaks out of from anterior fossa fracture

"Panda bear" or "raccoon" sign due to leakage of blood from anterior fossa into periorbital tissues. Absence of conjunctival injection differentiates fracture from direct eye trauma

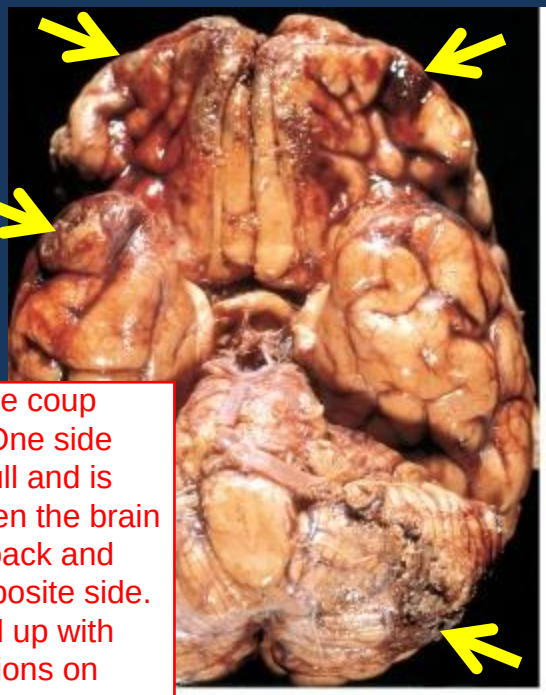
CSF leaking out of nose and ears is also bad

Battle sign from postauricular hematoma. Fracture around temporal bone

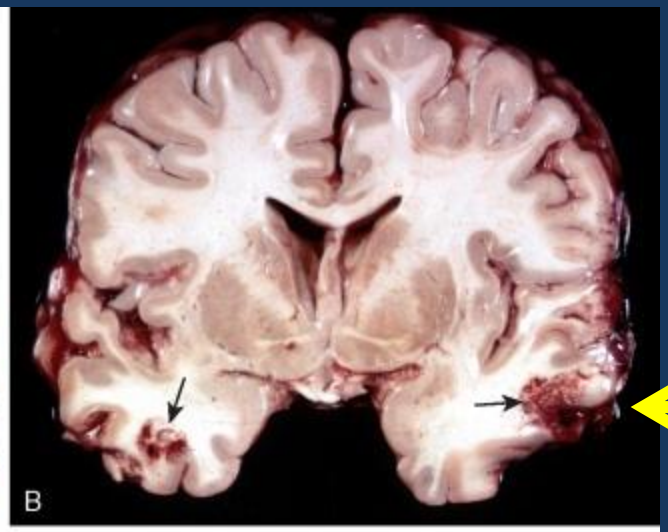
The CIBA collection Vol 1 Nervous System Part 2 1996

Trauma: Parenchymal injury

- lacerations
- contusions
- diffuse axonal injury

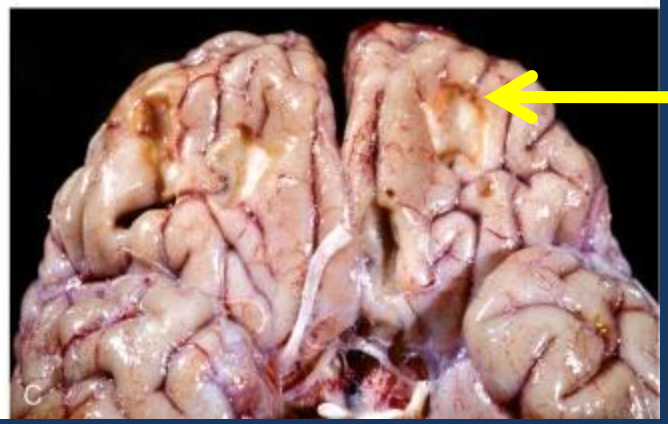


Coup-contre coup damage. One side hits the skull and is bruised, then the brain rebounds back and hits the opposite side. So you end up with two contusions on opposite sides.



acute

contusion



remote

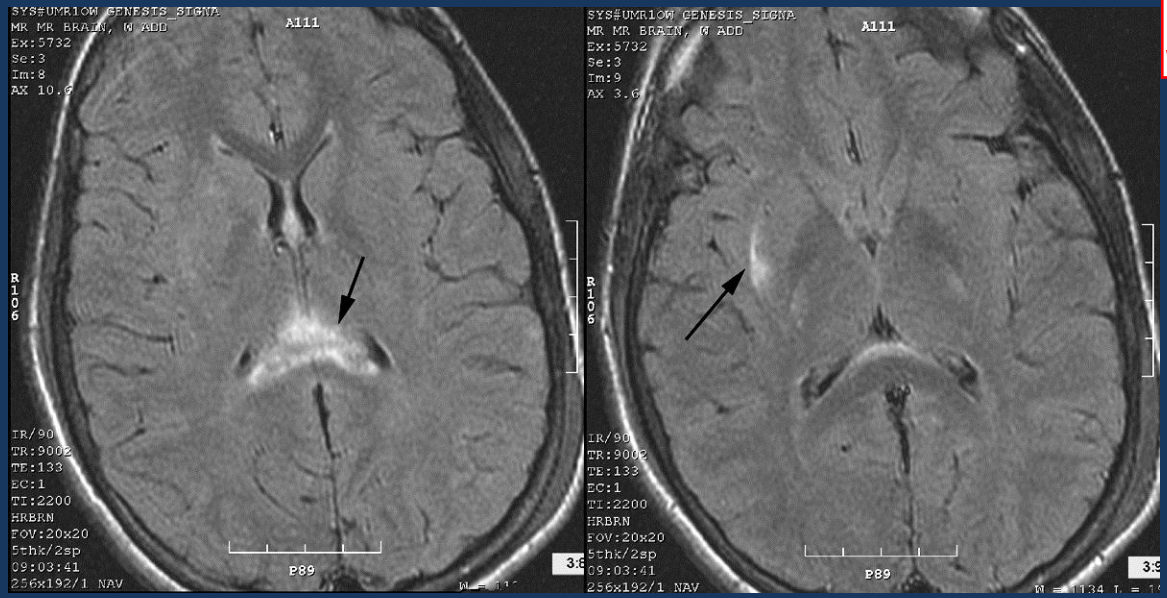
yellowish plaque is an old insult that has become a glial scar

Contusions

Diffuse axonal injury

(traumatic rotation, deep white matter stretching)

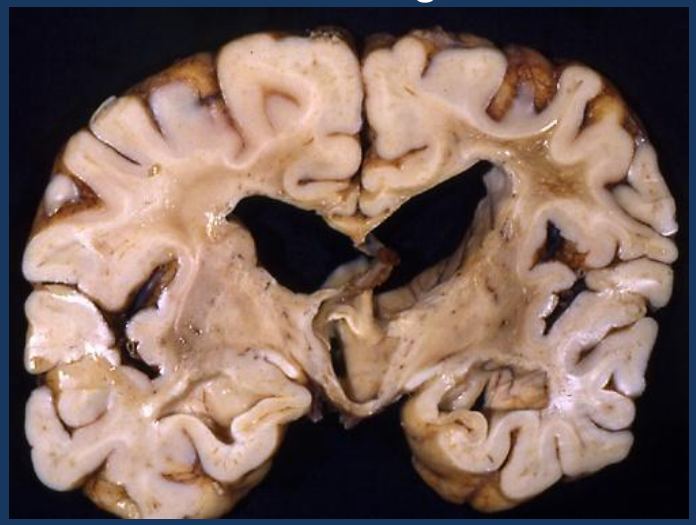
High torque on the brain causes stretching of axons, which can lead to damage - tearing, swelling, etc. This can easily be seen on MRI and in histology. Eventually this leads to white matter degeneration.



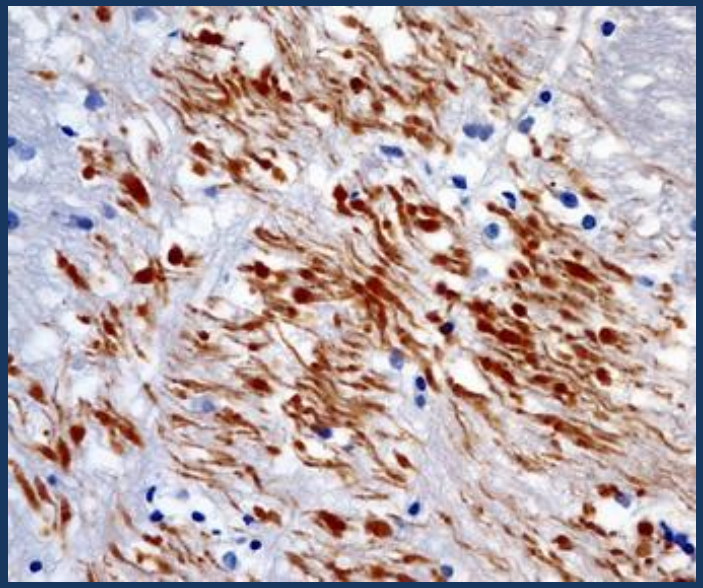
img.medscape.com

MRI: hyperintense signal in the corpus callosum, septum pellucidum, and external capsule

White matter degeneration



neuropathology.neoucom.edu



Beta amyloid precursor protein (BAPP) stain

Axonal swelling

Trauma: Vascular injury

Intra-axial: parenchymal hemorrhage

Inside the brain tissue

Extra-axial: subarachnoid hemorrhage

Outside the brain

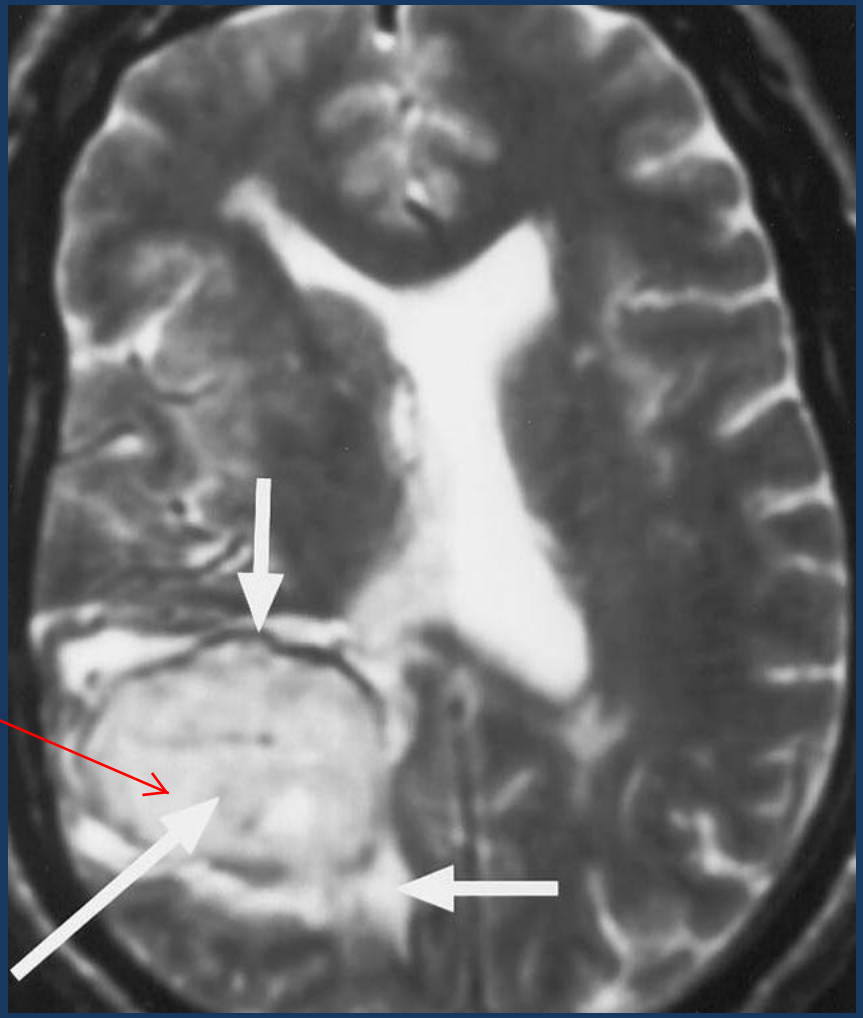
subdural hemorrhage

epidural hemorrhage

Parenchymal hemorrhage

-hypertension, vascular malformations, tumors, drugs, amyloid angiopathy

Due to small vessels inside the brain tissue leaking or bursting.



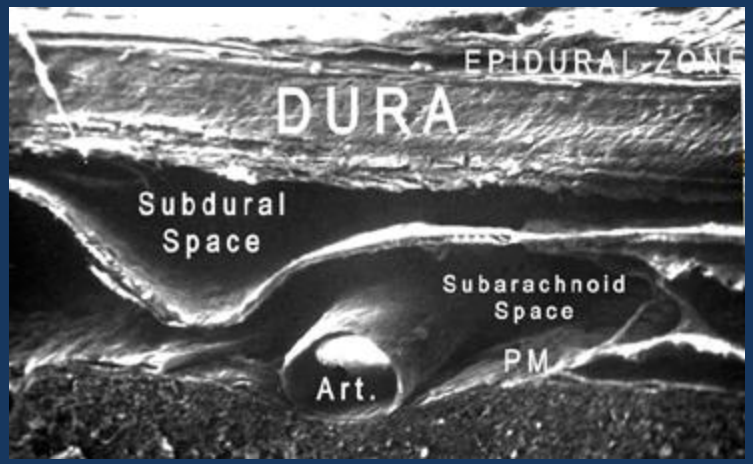
MRI: acute hemorrhage with associated edema

Hemorrhage with edema surrounding it, causing intracranial swelling.X

Atlas &Thulborne (1998) *AJNR Am J Neuroradiol 19:1471*

Subarachnoid hemorrhage

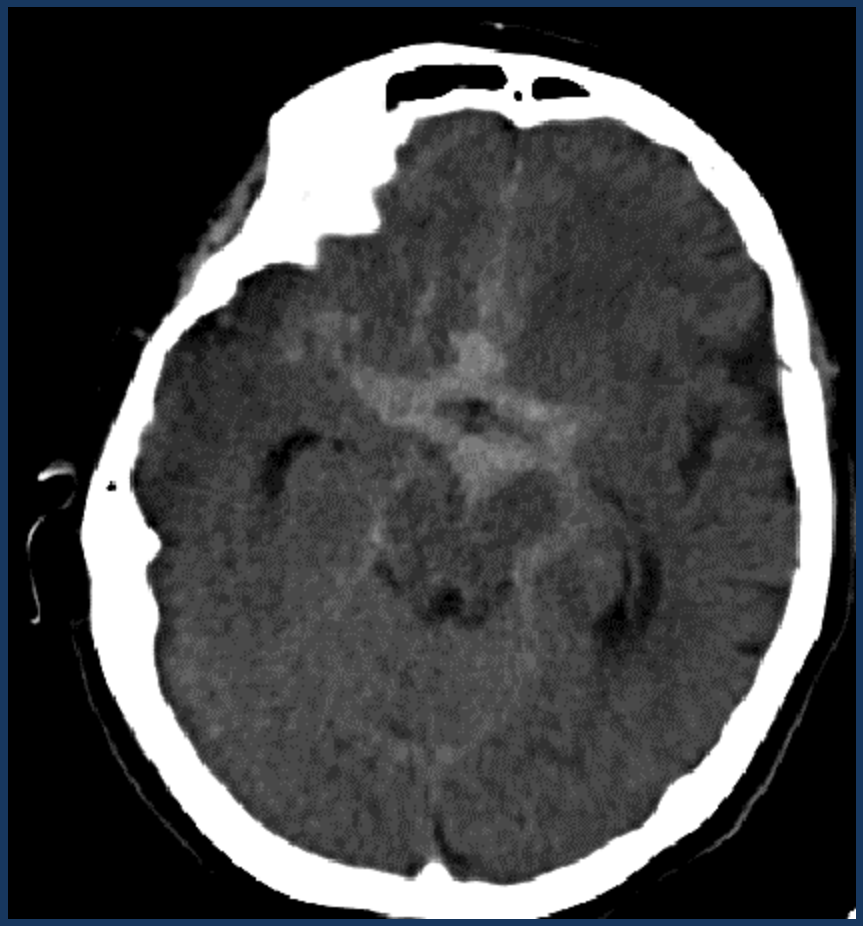
-bleeding from corticomenigeal arteries into the CSF space
-rupture of a cerebral aneurysm in most cases
-sudden onset (“thunderclap headache”)
-poor prognosis (up to 50% death rate)



VandenBerg/missinglink.ucsf.edu

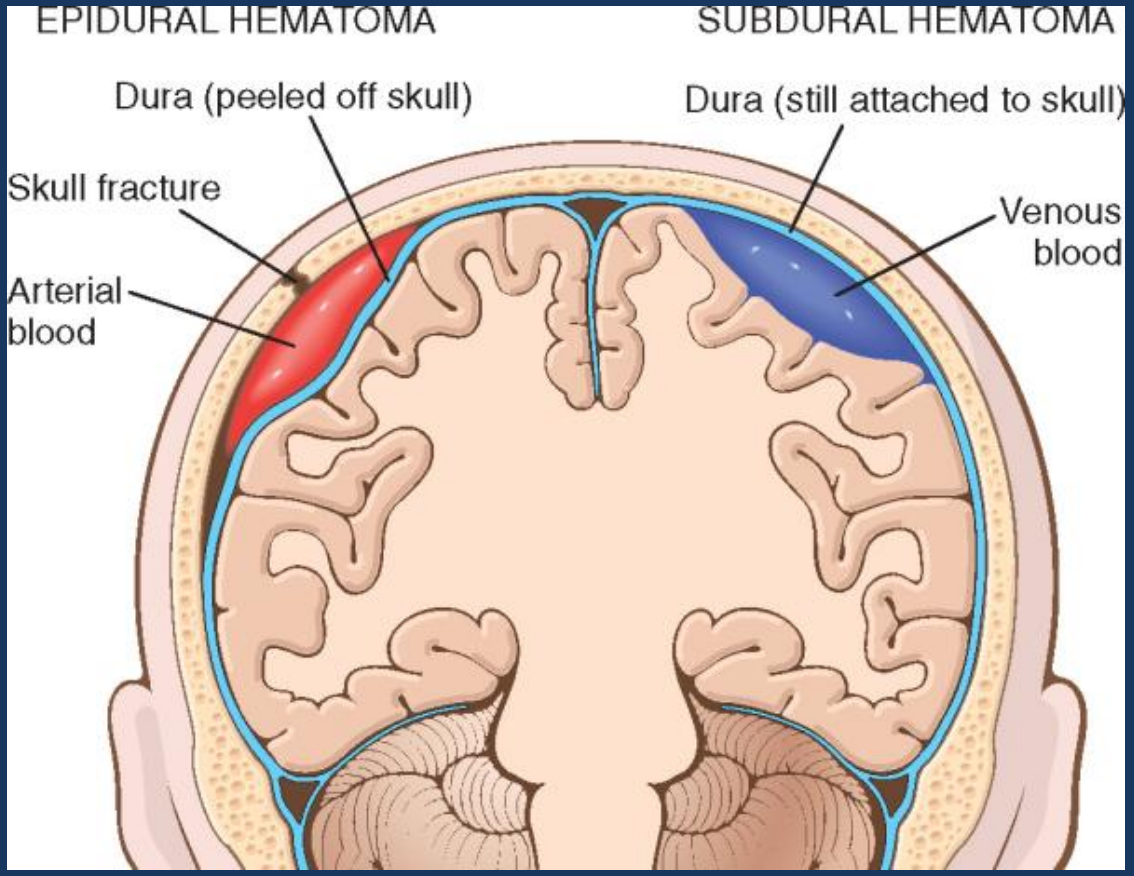
Arteries on the outside of the brain run in subarachnoid space. Rupture of vessels leads to bleeding into this space. High pressure bleed, so expands very quickly. Usually caused by ruptured aneurysm around the circle of willis. Not usually from traumatic injury like the epidural and subdural hemorrhages.

CT scan of SAH

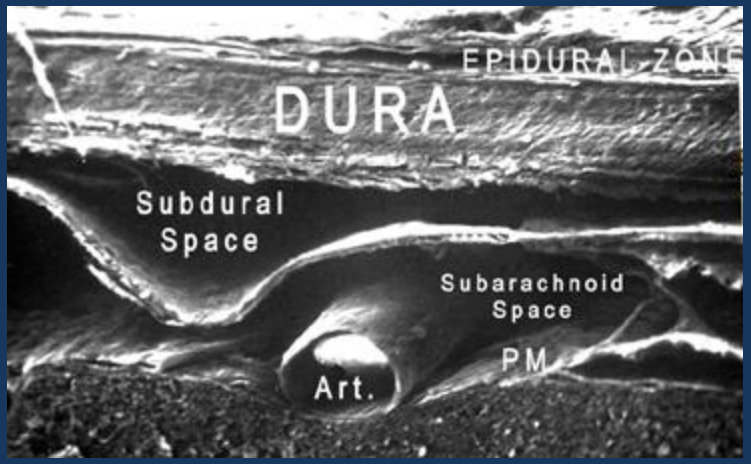


emedicine.medscape.com

Epidural versus subdural hemorrhage



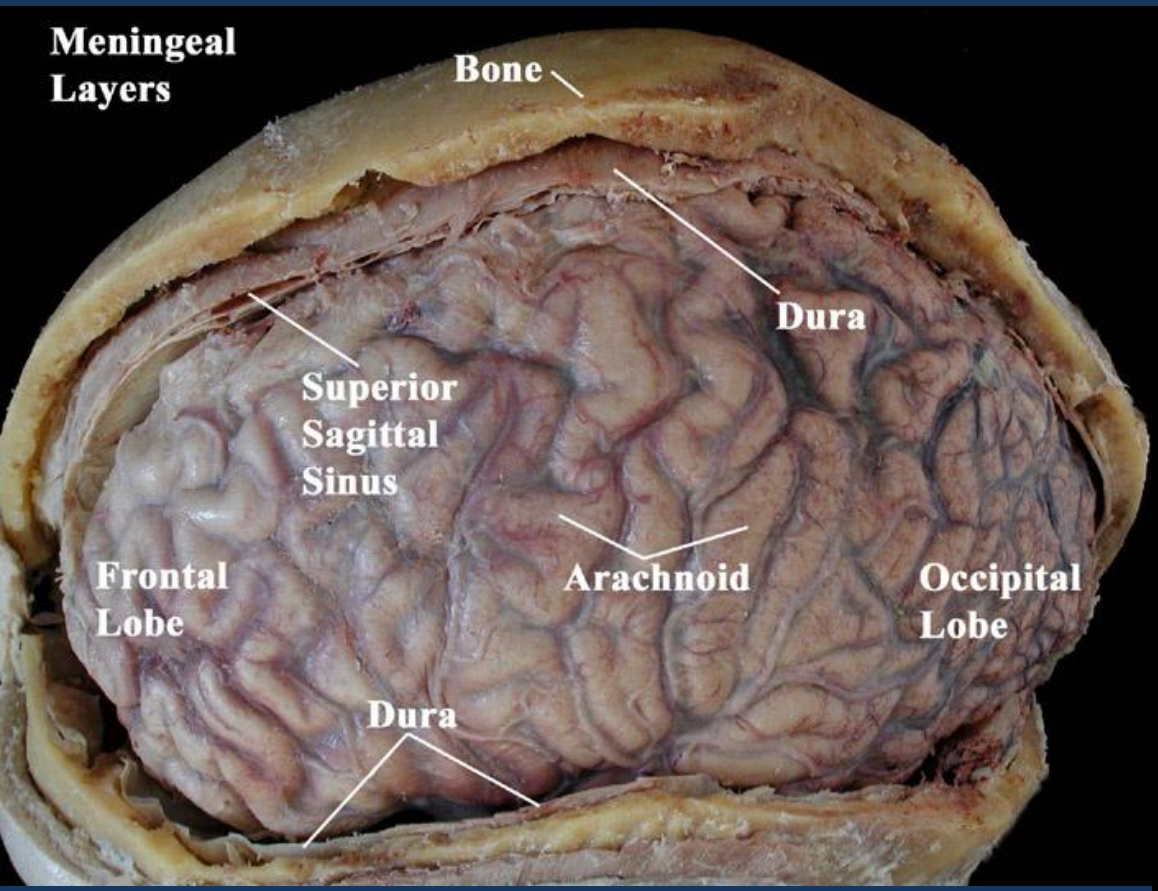
Epidural bleeds are arterial. Dura is very tightly connected to skull, so it takes a lot of pressure to fill this space.

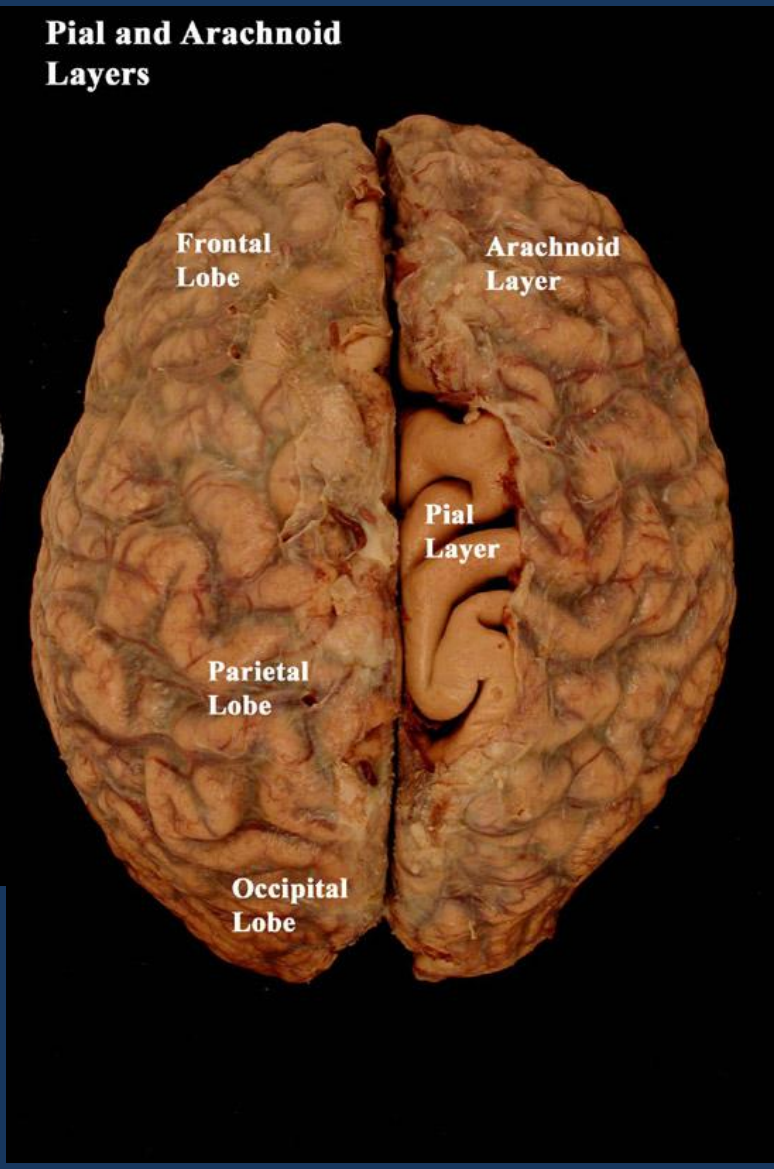


VandenBerg/missinglink.ucsf.edu

Subdural space can be filled with venous blood with vein tears. This is a low pressure bleed, so it expands very slowly. Much less deadly.

Review of Meningeal Layers

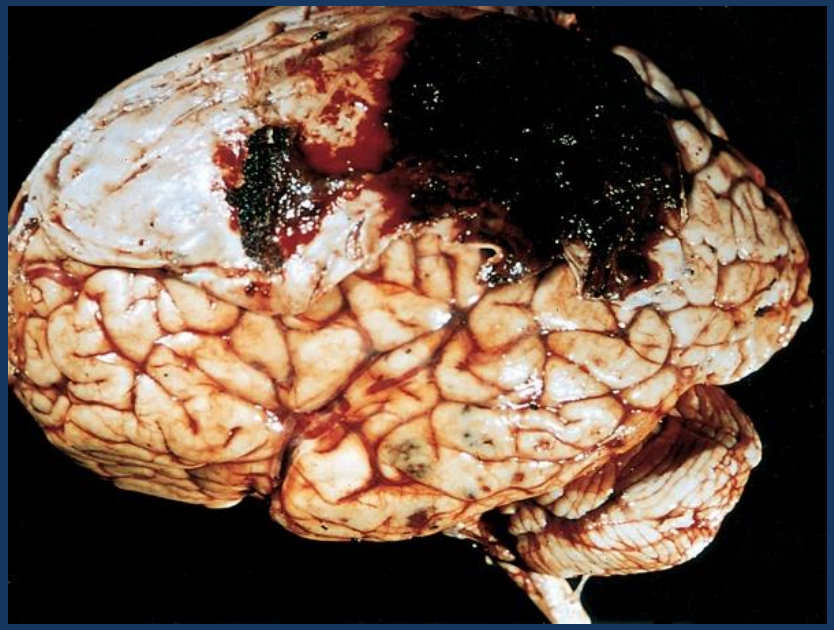


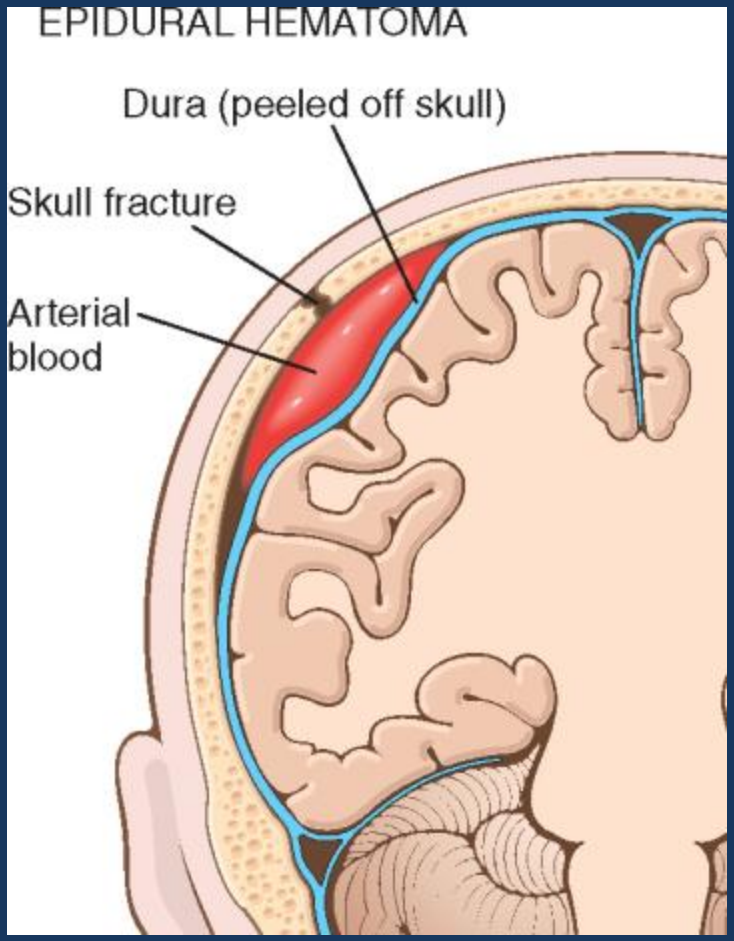


http://www.profelis.org

Epidural hematoma

-ruptured dural/meningeal artery
-often associated with intoxication
-period of lucidity following trauma
-mortality rate up to 50% (varies with level of consciousness at surgery)

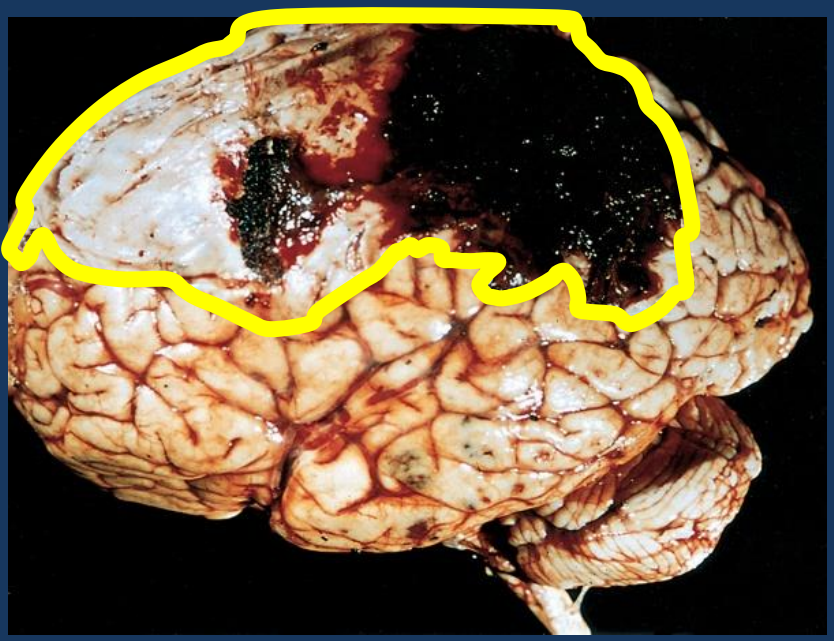


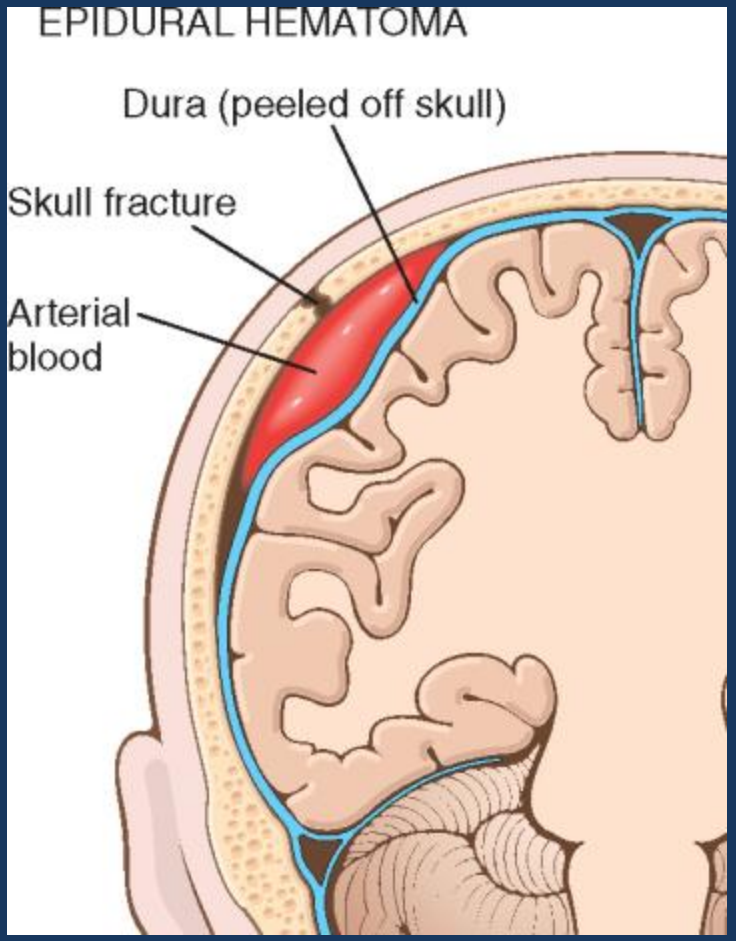


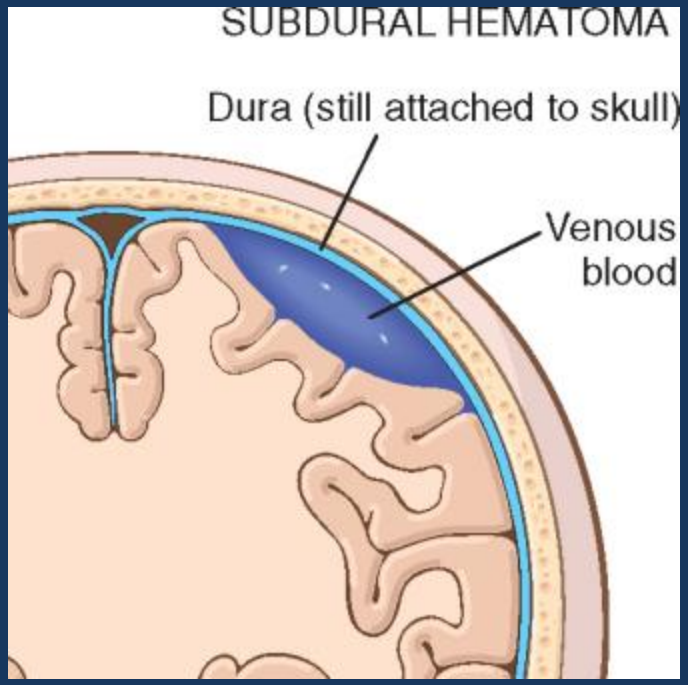
Often occurs when someone falls down and hits their head. Due to rupture of dural or meningeal artery. Develops quickly. Bleeding is on top of the dura.

Epidural hematoma

-ruptured dural/meningeal artery
-rare in infants and elderly (intracranial)
-often associated with intoxication
-period of lucidity following trauma
-mortality rate up to 50% (varies with level of conciousness at surgery)

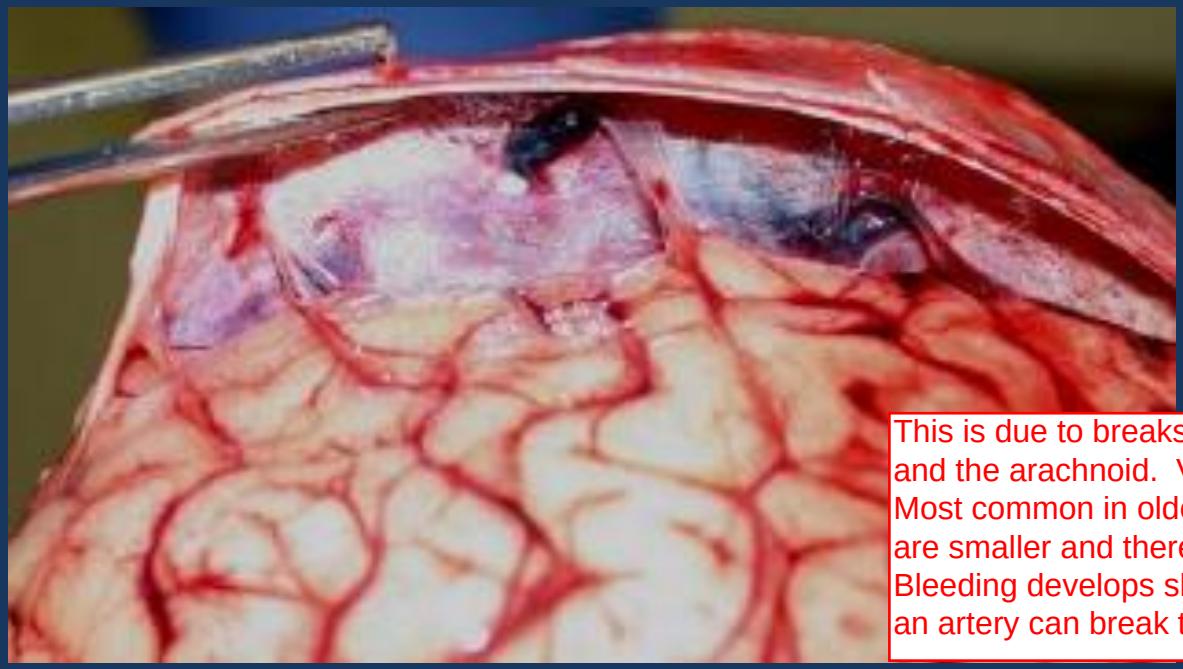


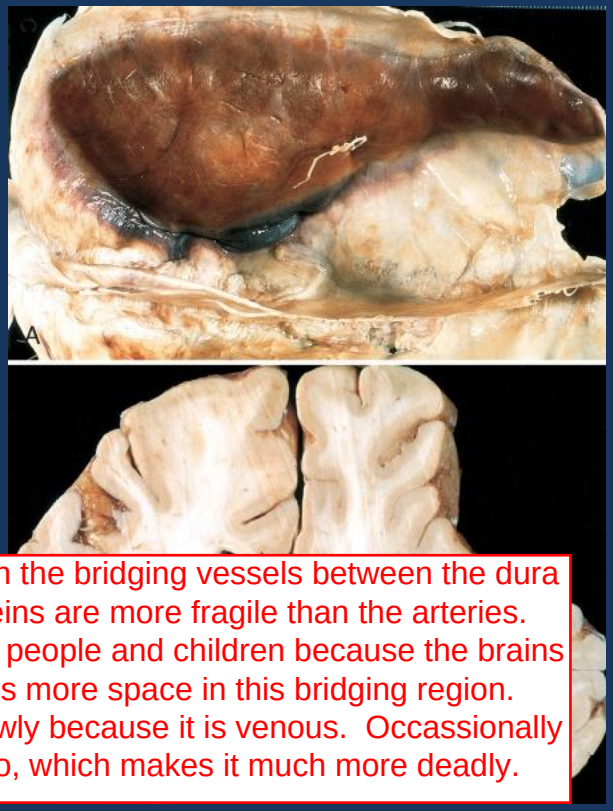




Subdural hemorrhage

-bleeding from bridging veins (and accompanying arteries)
-elderly (atrophy) and infants (thin vessel walls and larger space)
-may be subclinical; more rapid development of symptoms if with arteries





This is due to breaks in the bridging vessels between the dura and the arachnoid. Veins are more fragile than the arteries. Most common in older people and children because the brains are smaller and there is more space in this bridging region. Bleeding develops slowly because it is venous. Occassionally an artery can break too, which makes it much more deadly.

Stein et al *Forensic Science International*, Volume 163, Issue 1

R&C Chapter 28: The CNS

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