Hashemite University
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Scientific Team
الفريق العلمي

PATHOLOGY

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Reference: ROBBINS BASIC PATHOLOGY, By Kumar et al. 9th Ed. 2013: CNS In 133 W + 95 F = 230 PPP @ 9-3-2020: Lectures prepared by Associated Professor Dr. Mohammad Kamel Alwiswasi, MBChB, PhD, FRC Path

The Nervous System

PATTERNS OF INJURY IN THE NERVOUS SYSTM

MARKERS of Neuronal Injury

Nervous system cells respond in different ways to various injuries & the changes can be observed in neurons & their processes (dendrites & axons).

◘ Within 12 hours of an irreversible **hypoxic/ischemic** insult, ***acute neuronal injury*** becomes evident even on routine H & E staining called ***"red neurons"*** (F23-1A) , which include:

☠ **Shrinkage of the cell body + pyknosis & angulation of the nucleus + disappearance of the nucleolus + loss of Nissl substance + with intense eosinophilia of the cytoplasm**

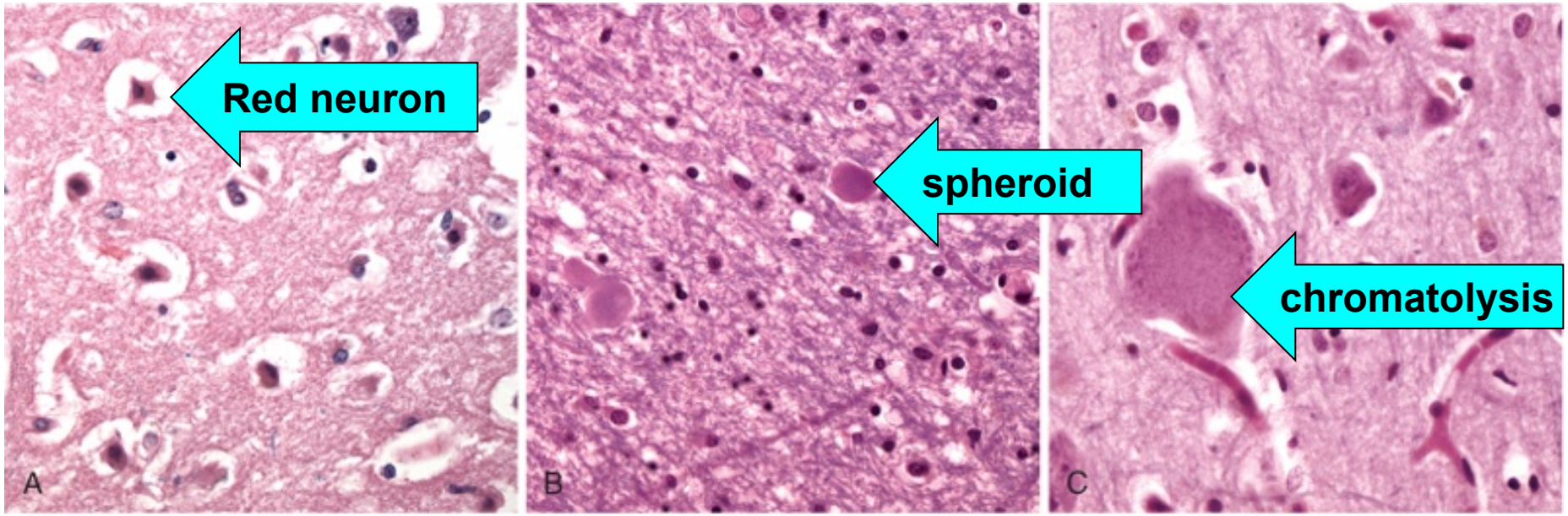
هذا ← ميت neuron

F 23-1: **Patterns of neuronal injury.**

A, Acute hypoxic/ischemic injury in cerebral cortex. The necrotic neuronal cell bodies & their nuclei are shrunken & are prominently eosinophilic, so-called **"red neurons".**

B, Axonal **spheroids** are visible as bulbous swelling at points of **disruption or altered axonal transport**.

C, With **axonal injury,** there is swelling of the cell body & peripheral dispersal of the Nissl substance i.e., **chromatolysis.**



- Injured axons show disruption of axonal transport, & (1) undergo swelling, the swellings (***spheroids***) can be recognized on H & E stains (F23-1B) & can be highlighted by ***silver staining*** or immunohistochemistry for *axonally transported proteins such as amyloid precursor protein (APP)*.

(2) Axonal injury also leads to cell body enlargement & rounding, peripheral displacement of the nucleus, enlargement of the nucleolus, & dispersion of Nissl substance from the cell center to the periphery (***central chromatolysis***). (F23-1C).

- Many neurodegenerative diseases are associated with specific intracellular **inclusions** that help in their diagnosis (e.g., **Lewy bodies** in Parkinson disease & **tangles** in Alzheimer disease). In some neurodegenerative diseases, neuronal processes also become thickened & tortuous; these can be seen as ***dystrophic neurites (e.g.,*** Alzheimer disease).
- **Viral infections can form inclusions** in neurons.
- **With age**, neurons also accumulate complex lipids in their cytoplasm & lysosomes (***lipofuscin***).

نتيجة تكاثر ال viruses

Astrocytes in Injury & Repair

★ The main cells responsible for **Repair & scar** formation in the brain are the astrocytes; the process termed ***gliosis***. not scar formation.

★ In response to injury, **astrocytes undergo both hypertrophy & hyperplasia**. The nucleus enlarges & becomes eccentric, vesicular & with prominent nucleolus. The scant cytoplasm expands to a bright pink from which emerge numerous stout, ramifying processes (***gemistocytic astrocyte*****).** There is minimal ECM deposition.

★ Unlike the repair after injury elsewhere in the body, the **fibroblasts** participate in healing after brain injury ***only*** to a ***limited extent*** (usually after (1) **penetrating** brain trauma or (2) around **abscesses**). ↖ الـfibroblast ما الها دور بال healing ما عدا هالحالتين

★ In long-standing gliosis, astrocytes have less distinct cytoplasm & appear more fibrillar ***(fibrillary astrocytes).***

★ ***Rosenthal fibers*** are thick, elongated, brightly eosinophilic protein aggregates that can be found in astrocytic processes in chronic gliosis & in some low-grade gliomas.

↳ The most common tumor in the brain.

✱ ***Corpora amylacea*** are round, 5 to 50 μm in ∅, faintly basophilic, PAS positive, concentrically lamellated aggregates of polyglucosans, **located** wherever there are **astrocytic end processes**, especially in the subpial & perivascular zones.
☼ They represent a degenerative change in astrocytes & occur in ↑ numbers with **advancing age**.

Oligodendrocytes, → Dendrites ال خلية

★ **Produce myelin**; their pathologic changes include:
(I) damage to myelin, as in multiple sclerosis (**MS**), or
(II) cell death. In progressive multifocal leukoencephalopathy, viral **inclusions** can be seen as a smudgy, homogeneous-enlarged nucleus.

Ependymal cells

★ **line the ventricular system**,& are located in the region of the obliterated central canal of the spinal cord. Their disruption is often associated with a local proliferation of *subependymal astrocytes* to produce small irregularities on the ventricular surfaces termed ***ependymal granulations***. Certain infectious agents, particularly CMV, can produce extensive ependymal injury & **viral inclusions** may be seen in them.

Choroid plexus

★ **Secret CSF**. It is in continuity with the ependyma, extending into the ventricular cavities. It has a specialized epithelial covering with a fibrovascular stroma that may contain meningothelial cells.

Microglias → for removal of dead tissue/Myelin

★ Are **bone marrow-derived phagocytes of the CNS**.

★When activated after tissue injury /infection/or trauma, they **proliferate** & become more evident.

- They may be recognizable as "**activated macrophages"** in areas of **organizing infarct, hemorrhage & demyelination.**

- or they develop elongated nuclei (***rod cells***) in neurosyphilis or other infections.

- Rod cells aggregates (1) at sites of tissue injury, are termed ***microglial nodules*** *&*
(2) if they surround portions of dying neurons, are termed ***neuronophagia***. → will swallow dead tissue. (Remove)

EDEMA, HERNIATION, & HYDROCEPHALUS

☺ The brain & spinal cord exist within a rigid compartment defined by the skull & spinal canal, & lined by dura. Nerves & blood vessels pass through this structure via specific foramina, but the brain is confined to the cranial vault.

☺ The **protective** advantage of housing the delicate CNS within such environment is obvious, yet

☹ these rigid confines provide **little room** for **expansion** of brain parenchymal in disease states, including:
(1) **generalized cerebral edema,** (2) **hydrocephalus, &**
(3) **focally expanding intracranial mass lesions,** → abcess, tumor, or hemorrhage
any of which may result in ⇧ intracranial pressure (ICP).

Cerebral Edema

★Cerebral edema is the accumulation of **excess fluid within the brain parenchyma.** There are 2 underlying mechanisms for the development of cerebral edema that often **occur together particularly when there is generalized injury.**

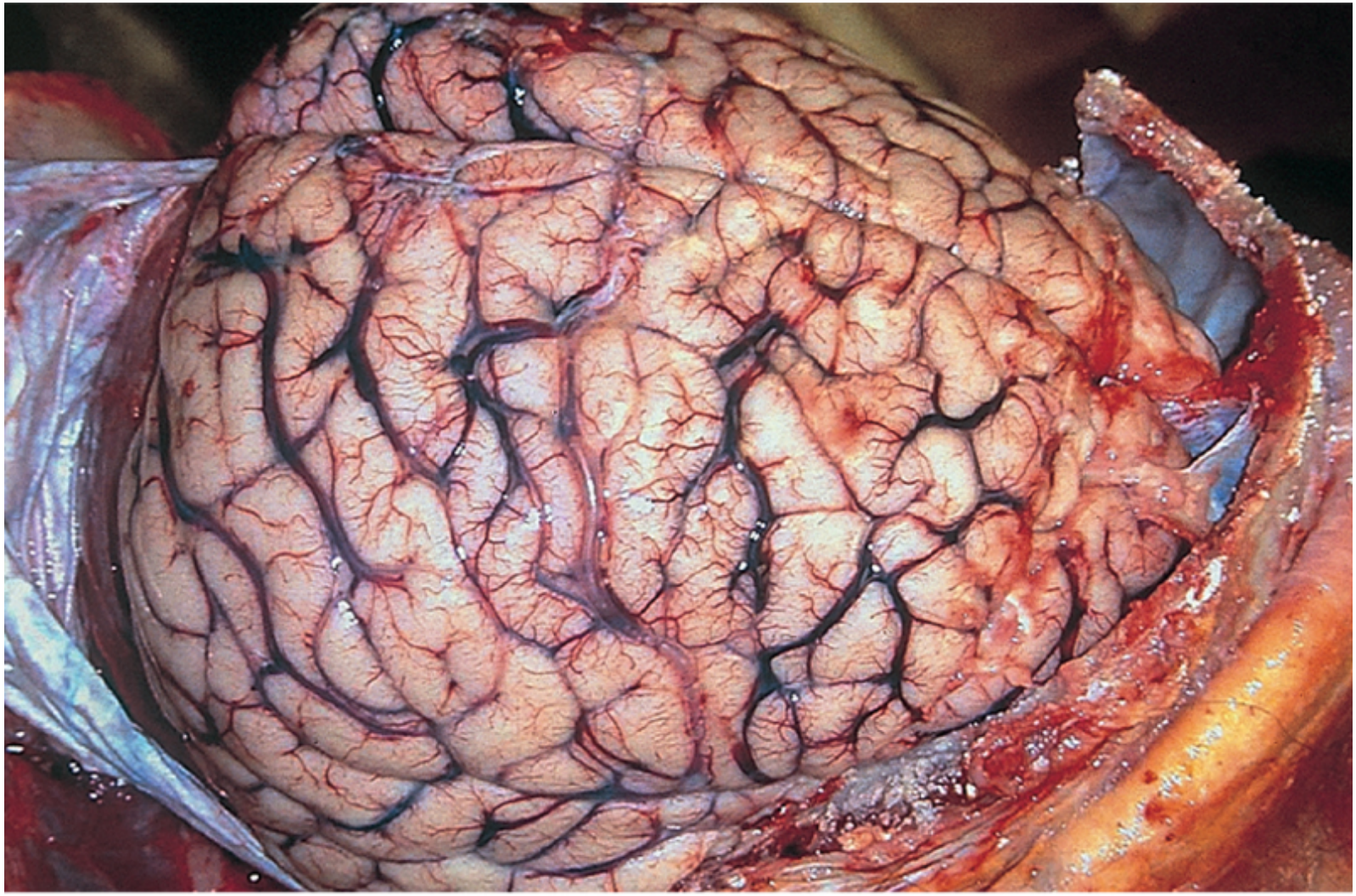
►**(I) Vasogenic edema** occurs when the integrity of the normal blood-brain barrier is disrupted. With ↑ **vascular permeability, fluid shifts from the vascular compartment into the intercellular spaces of the brain (like edema in other body tissues).** Vasogenic edema can be either:

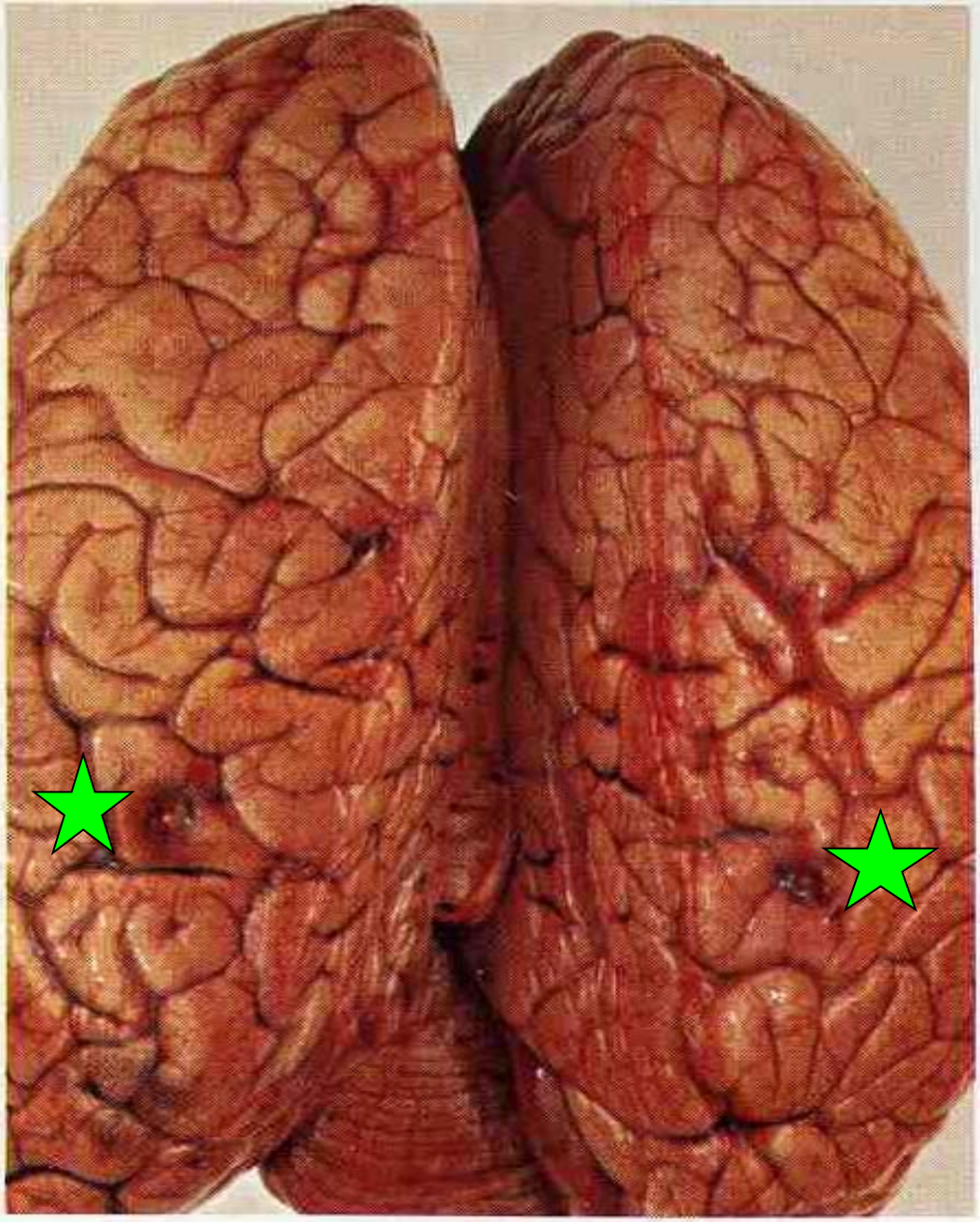
(A) localized; because of abnormal ⇧ permeability of BV adjacent to inflammation or tumors, or (B) generalized.

► **(II) Cytotoxic edema** implies an **increase in intracellular fluid** secondary to neuronal, glial, or endothelial cell membrane injury, e.g., in an individual with a generalized **hypoxic/ischemic** insult, or with exposure to some **toxins.**

►**GROSSLY,** ➔ the edematous brain is **swollen** & **softer than normal**, & **generalized edema causes:** flattening of the **gyri/** narrowing of the intervening **sulci/** compression of the **ventricular cavities** .(F23-2 & 9-81).

F 23-2: **Cerebral edema**. The surfaces of the **gyri are flattened** as a result of compression of the expanding brain by the dura matter & inner surface of the skull, These changes cause ⇧ intracranial pressure (**ICP**) & death.





9.81 Swelling and oedema: brain

شاملة الدماغ كامل.

F 9-81: Brain edema: Symmetrical cerebral swelling & edema, with marked flattening of the convolutions (gyri) & compression of the groves (sulci).

★ 2 parasagittal needle holes are present.

☠ **Cause:** subependymal astrocytoma obstructing CSF flow, resulting in hydrocephalous & cerebral edema, leading ⇧ **ICP & ☠ death.**

عملناها حتى نخفف الضغط على الـ brain

حتى لو استعملنا الـ holes ولكن لم تكن كافية.

Hydrocephalus (F 23-3 & 9-17)

➔ ☼ The CSF, **produce** by the choroid plexus within the ventricles, circulates through the ventricular system & exits through the foramina of Luschka & Magendie. CSF fills the subarachnoid space around the brain & spinal cord, & help in cushioning of the CNS within its bony confines. يحمي الدماغ من الصدمات العظمية

➔ The CSF is **resorb** by the arachnoid granulations of the dural venous sinuses back to the blood. → in sagital venous sinus.

☺The **balance** between CSF generation & resorption keeps the CSF volume stable.

very rare ← 1- Excessive production
2- Obstruction → most common

☹ ***Hydrocephalus*** refers to the **accumulation of excessive CSF within the ventricular system.**

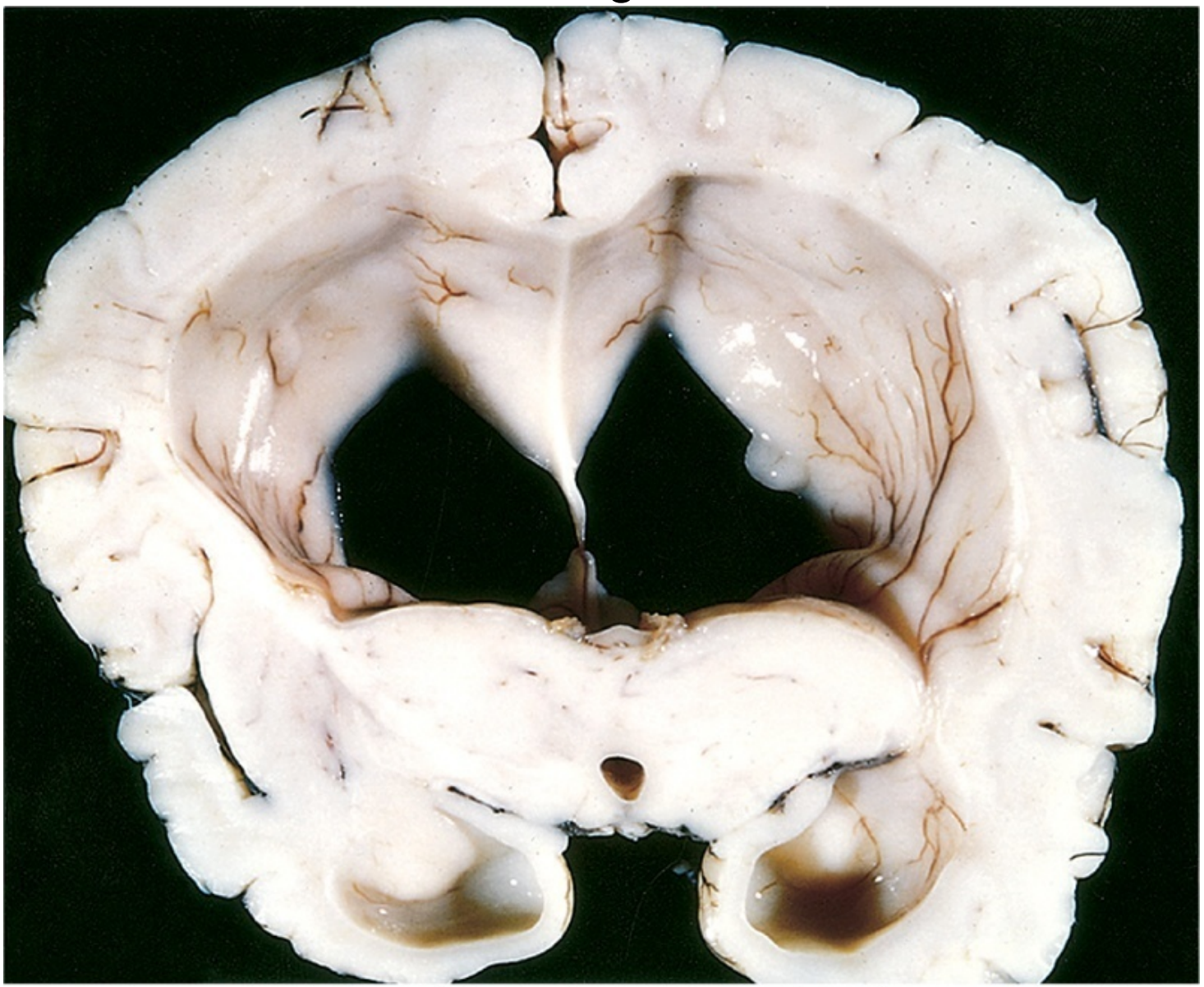
★ Most cases occur as a result of **impaired flow (obstruction)** or **impaired resorption of CSF**; while …

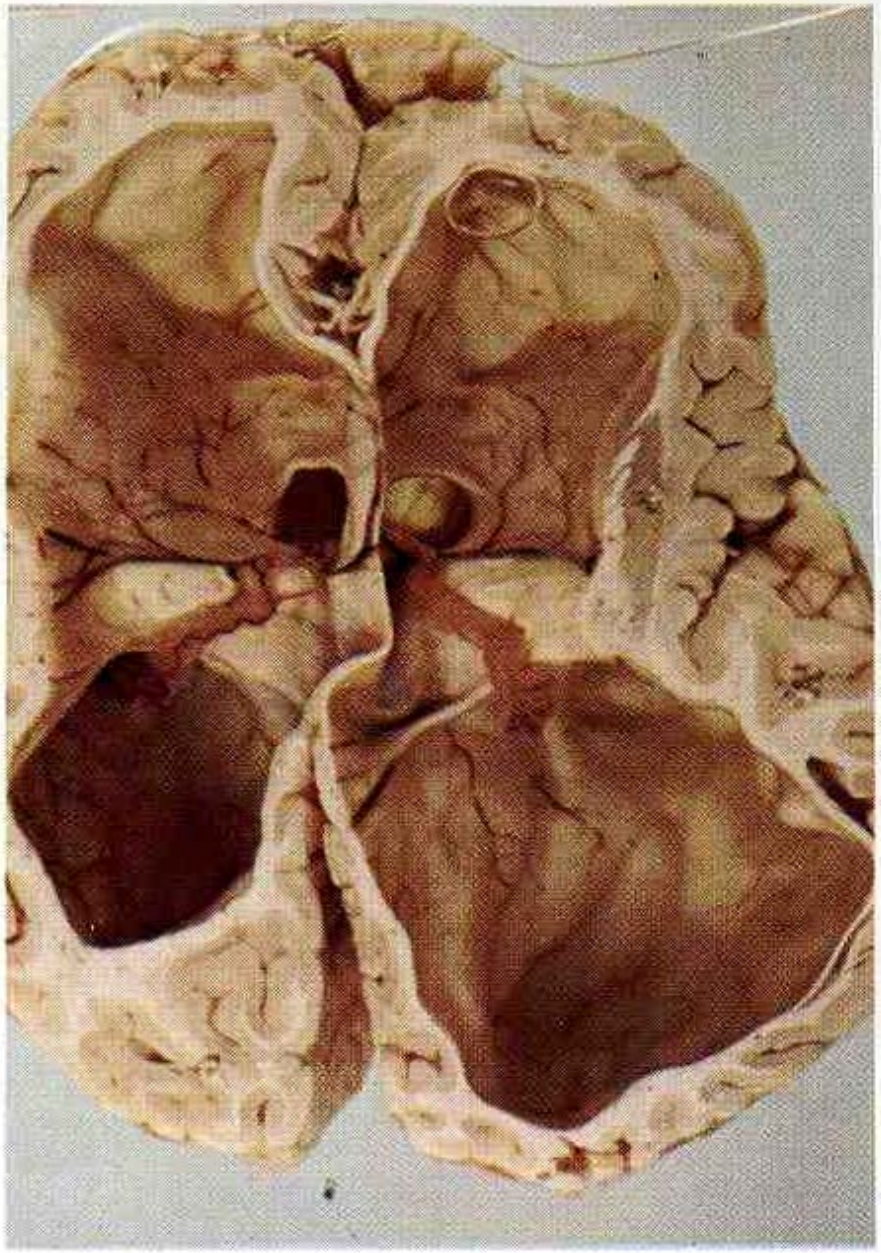
★ in **rare** instances (e.g., tumors of the choroid plexus), **overproduction of CSF** may be responsible.

★ When hydrocephalus develops **in infancy** → only. before closure of the cranial sutures, **there is enlargement of the head**.

في مجال لل skull انها تتوسع.

F 23-3: **Hydrocephalus.** Dilated lateral ventricles seen in a coronal section through the mid-thalamus.





9.17 Hydrocephalus: brain

F 9-17: **Hydrocephalus: brain.**

very thin and atrophic brain tissue.

Noncommunicating, with marked symmetrical dilatation of the lateral ventricles & interventricular foramina, with subsequent thinning of the periventricular white matter.

★ In contrast, hydrocephalus developing **after fusion of the sutures** is associated with expansion of the ventricles & ↑ ICP, without a change in head circumference. لأنه الـ sutures اتحدت في infant. فما عكس الـ

★ If there is an obstruction to CSF flow **within the ventricular system,** then the portion of the ventricles proximal to the obstruction enlarges, while the remainder does not; this pattern is referred to as

★ ***Noncommunicating hydrocephalus*** (F9-17) commonly seen with masses at the formamen of Monro or aqueduct of Sylvius, & the ***CSF dose not reach the subarachnoid space.*** معوجة

★ In ***communicating hydrocephalus,*** *the obstruction is in the subarachnoid space (e.g., healed meningitis with fibrosis),* leading to enlargement of all of the ventricular system. Here the cause is most often reduced resorption of CSF. معوجة

★ **Loss or atrophy of brain parenchyma** (as may occur after **infarcts** or with a **degenerative disease)** is usually associated with dilation of the ventricular system and a compensatory ↑ in CSF, this condition is called ***hydrocephalus ex vacuo.*** ← dementia or Alzheimer أو أي أسباب

بتوقع السبب هو انه المادة الدماغية انضمرت وبالتالي الـ cavities تتكبر.

Herniation

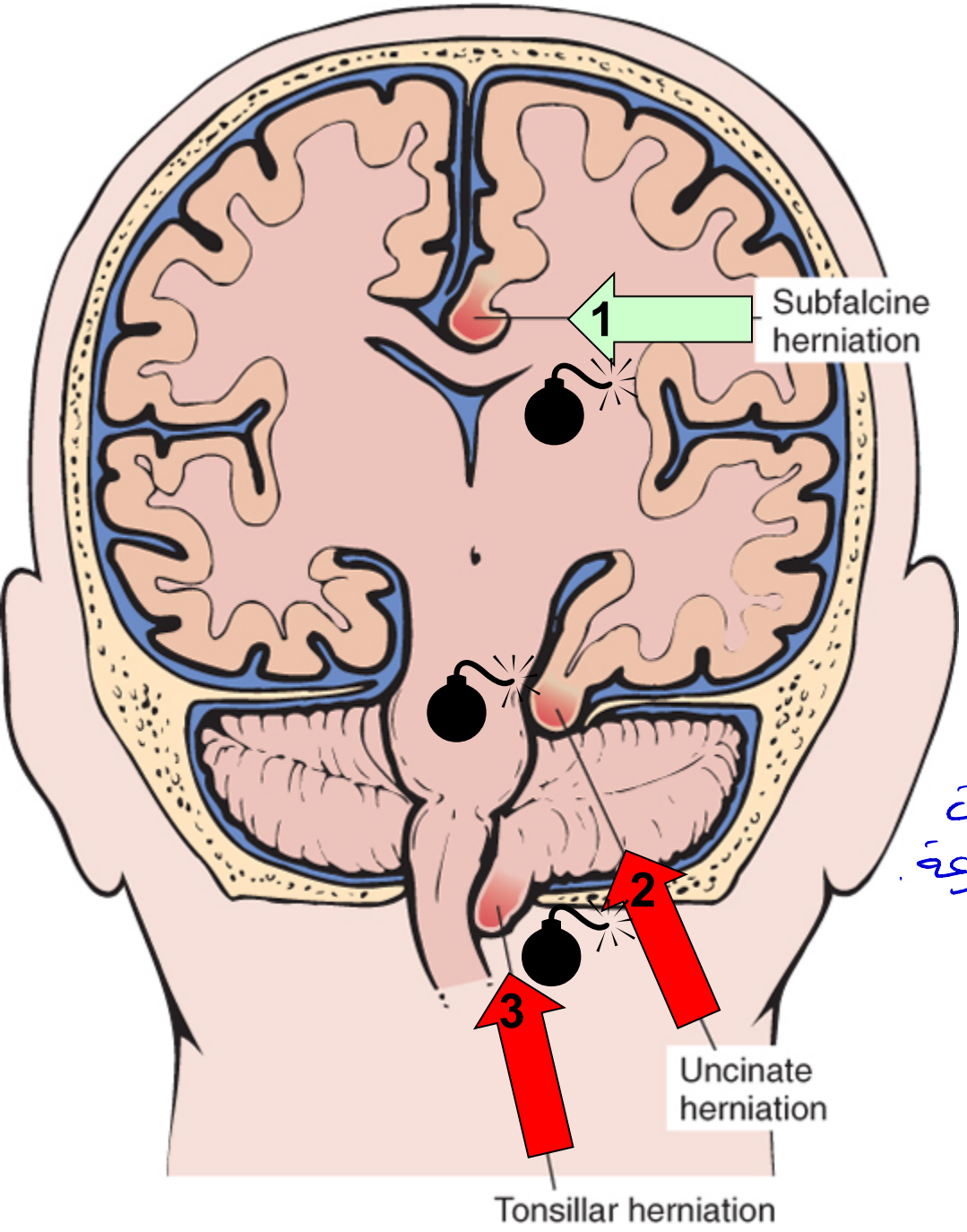
☹ When the volume of brain tissue ↑ beyond the limit permitted by compression of veins & displacement of CSF, the ICP ⇧. Because the cranial vault is subdivided by rigid dural folds (falx & tentorium), a focal expansion of the brain causes it to be: (1) **displaced** in relation to these partitions, & if the expansion is sufficiently severe, (2) **herniation** will occur (F23-4).

★Herniations are **named** by either the displaced part of the brain (1+3) or the structure across which it moves (2).

☹ The usual consequence of herniation is **compression of the blood supply to the "pushed" tissue, resulting in infarction**. This often leads to further swelling & herniation (vicious circle).

(I) ***Subfalcine (cingulate) herniation*** is displacement of the cingulate gyrus under the lower free edge of falx cerebri, due to unilateral expansion of a cerebral hemisphere.

☹ This may be associated with compression of branches of the **anterior** cerebral artery.



F23-4: Patterns of brain herniation:

(1) subfalcine (**cingulate**),

(2) **transtentorial** (uncinate, mesial temporal), &

(3) **tonsillar**.

(II) ***Transtentorial (uncinate) herniation*** is compression & herniation of the medial aspect of the temporal lobe against the free margin of the tentorium causing:

(1) **3rd cranial nerve** compression, resulting in pupillary dilation & **ipsilateral** {on the side of the lesion} impairment of ocular movements **("blown pupil")**.

(2) **Posterior cerebral artery compression** (F9-47), resulting in ischemia in it's territory, including the primary visual cortex.

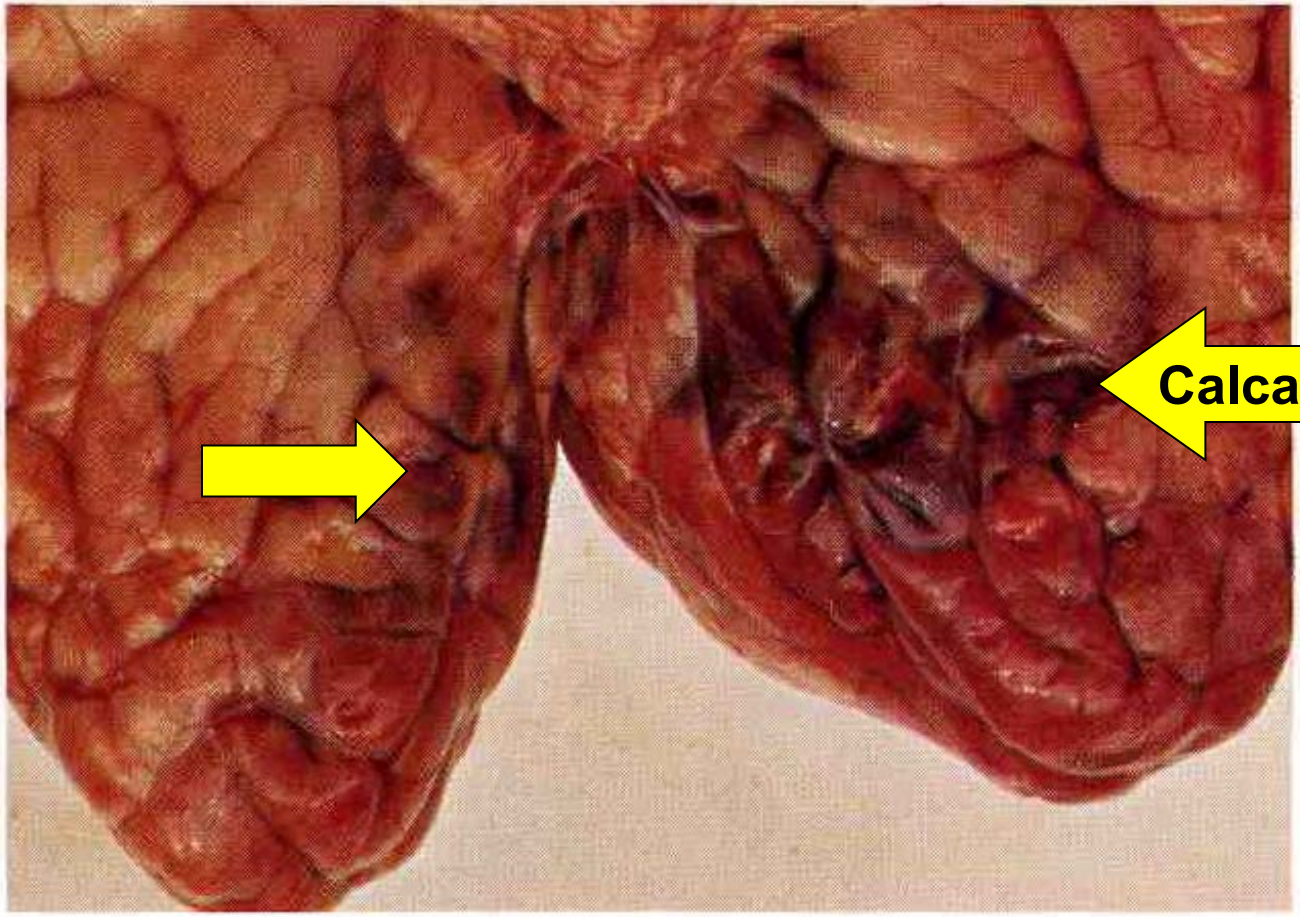
(3) When the herniation is large enough the **contralateral cerebral peduncle** may be compressed {lesion known as **Kernohan's notch**} resulting in **ipsilateral hemiparesis to the side of the herniation**.

(4) ☠ Progression of transtentorial herniation is often accompanied by **hemorrhage in the pons & midbrain, termed *Duret hemorrhages*** (F 23-5), occuring in the midline & paramedian regions, & are due to tearing of penetrating veins & arteries supplying the upper brain stem.

☠ **Duret hemorrhages is usually fatal** ☠.

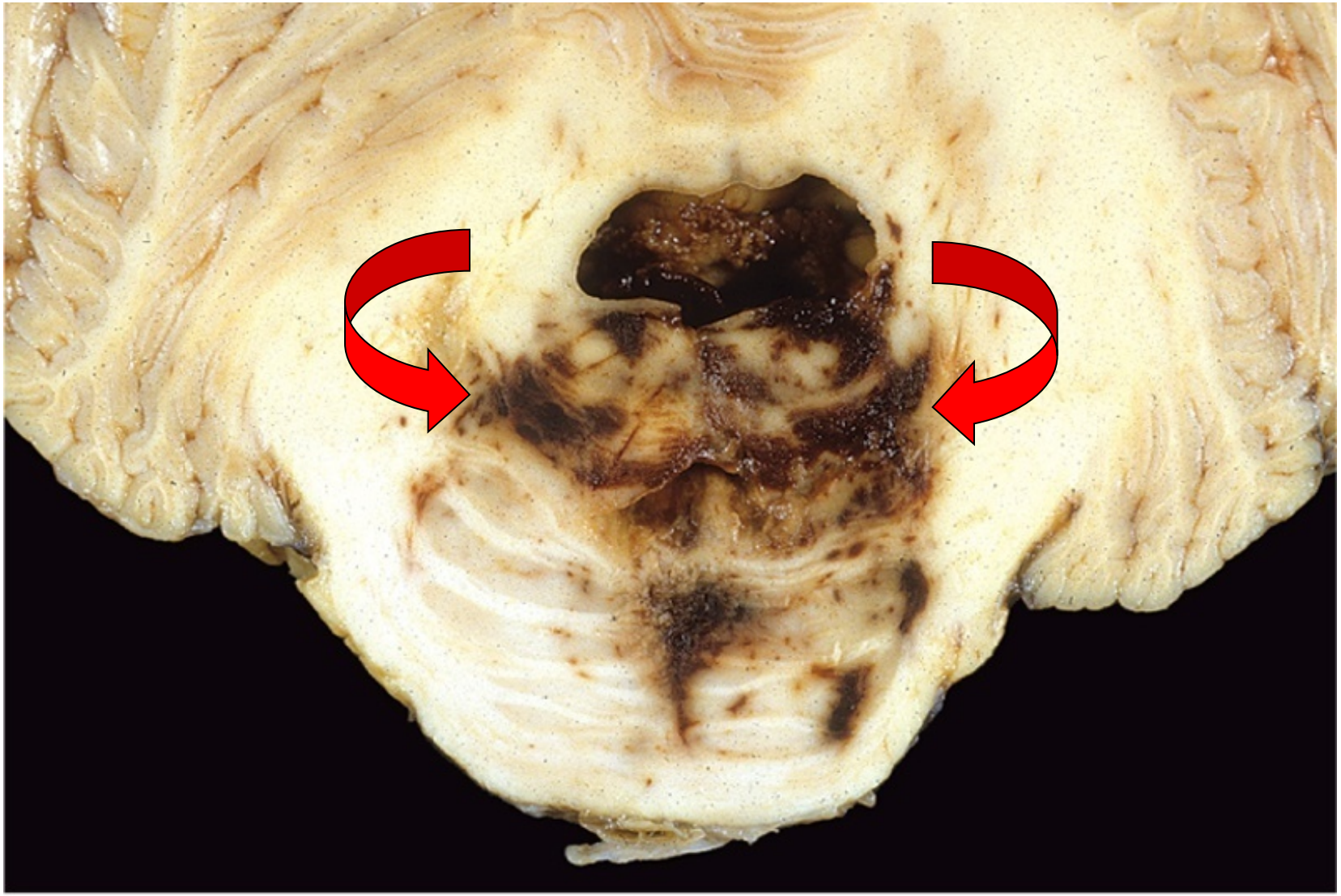
30 cm² hemorrhage in mid brain is sufficient to be fatal.

F 9.47: Infarction: Brain. ☠The patient had transtentorial herniation obstructing the posterior cerebral arteries, resulting in **recent hemorrhagic infarction** of the infero-medial aspects of both occipital lobes, especially affecting the calcarine area.



9.47 Infarction: brain

F23-5:**Duret (Pontine) hemorrhage**. As mass effect displaces the brain downwards, there is disruption of the penetrating BV that enter the pons along the midline leading to ☠ **fatal hemorrhage**.



(III) Tonsillar herniation (F9-82) is displacement of the cerebellar tonsils through the foramen magnum.

☠ This herniation is **life-threatening & usually ☠ fatal**, because it causes brain stem compression & compromises vital respiratory & cardiac centers in the medulla.

CEREBROVASCULAR DISEASES ("Stroke")

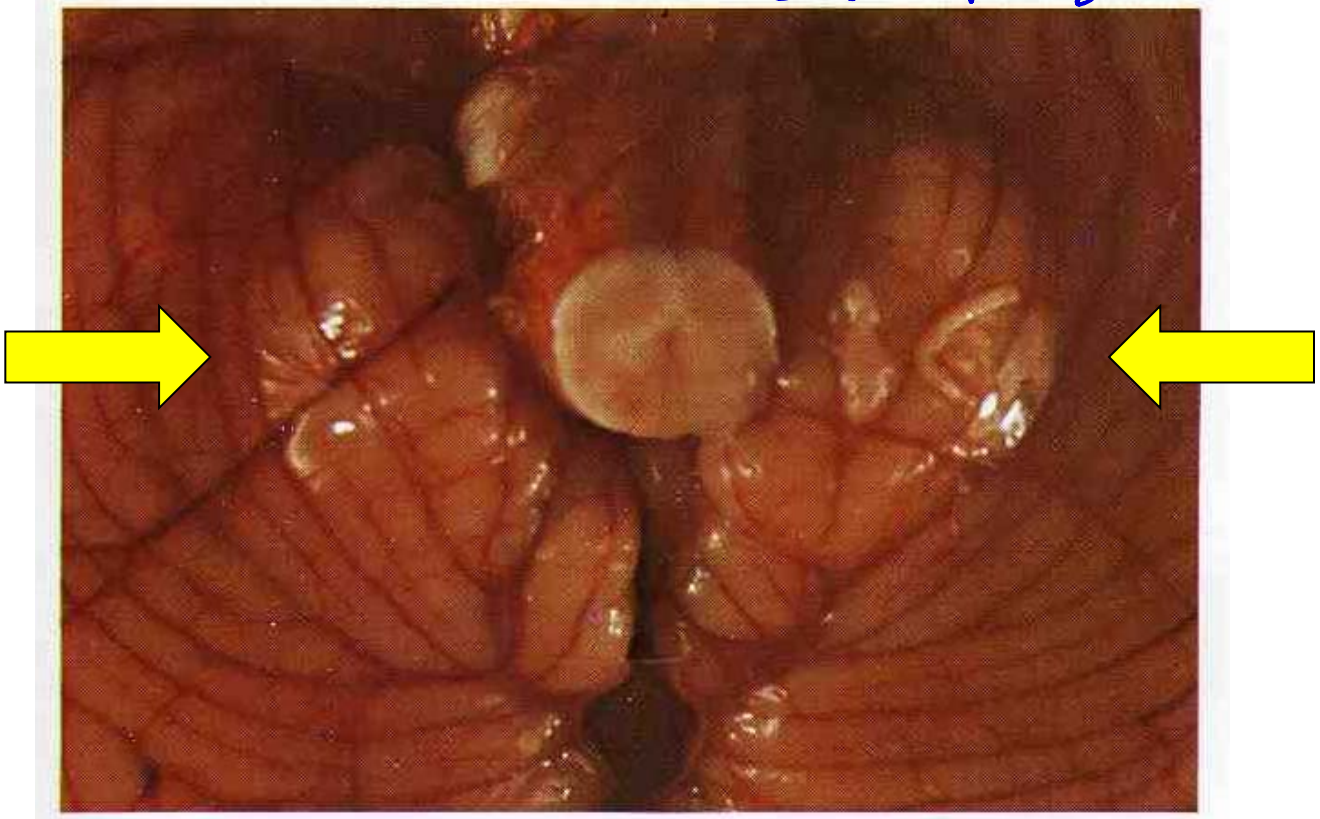
▲ Cerebrovascular disease is the 3rd (after IHD & cancer) common cause of death in US; & it is also, the most prevalent neurologic disorder in terms of both morbidity & mortality.

★ *Cerebrovascular disease* means **{any abnormality of the brain caused by blood vessel (BV) pathologic process}.**

☹ The 3 basic processes are occlusion of BV by (1) **Thrombus** or (2) **Embolus; or** (3) **BV rupture**, causing **Hemorrhage**

★ The first 2 share many characteristics, because their effect on the brain is the same ➔ the loss of oxygen & metabolic substrates, resulting in **ischemic injury ➔ brain infarction** of specific regions of the brain **(regional effect),** depending on the BV involved.

F9-82: **Tonsillar herniation ("pressure cone"): cerebellum.** The cerebellum is deeply grooved, forming a well- marked **'pressure cone' (arrows),** caused by the margins of the foramen magnum pressing on the cerebellar tonsils, which are displaced downwards through the foramen, compressing the medulla & causing ☠ death **(Why?)** → when they press upper part of spinal cord (Respiratory and cardiac centers).



9.82 Tonsillar herniation ('pressure cone'): cerebellum