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:

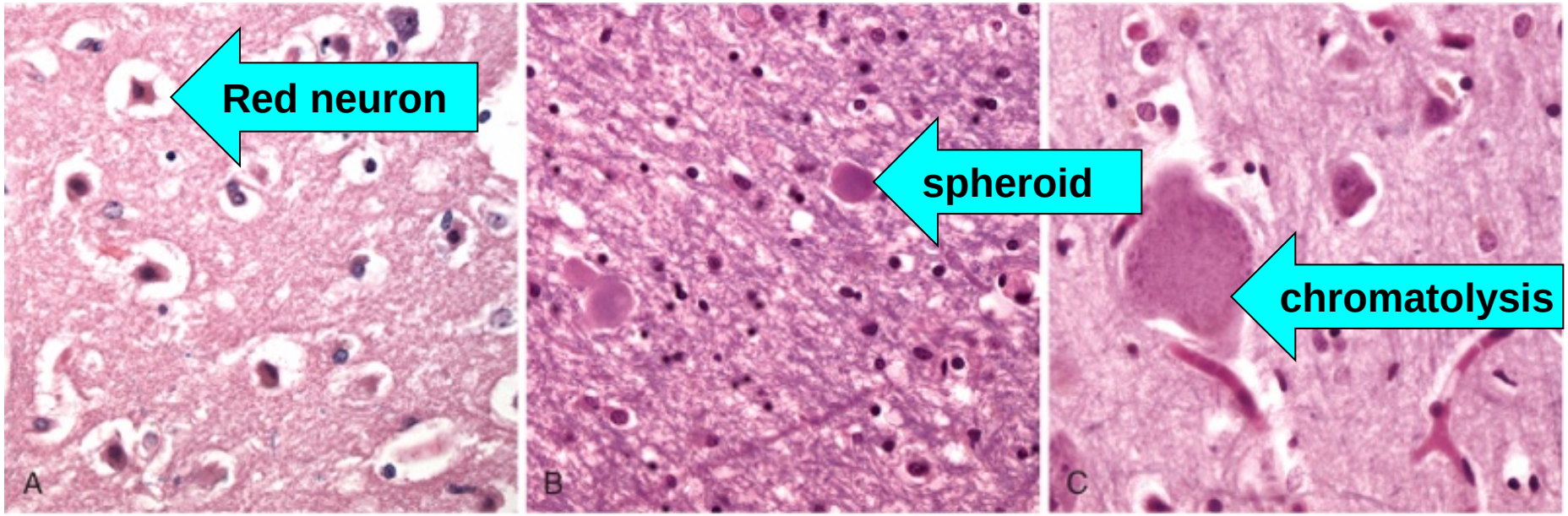
☠ **Shrinkage of the cell body + pyknosis & angulation of the nucleus + disappearance of the nucleolus + loss of Nissl substance + with intense eosinophilia of the cytoplasm**

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*).**

Astrocytes in Injury & Repair

★ The main cells responsible for **Repair & scar** formation in the brain are the astrocytes; the process termed ***gliosis***.

★ 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**).

★ 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.

✱***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,

★ **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

★ 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***.

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,
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.**

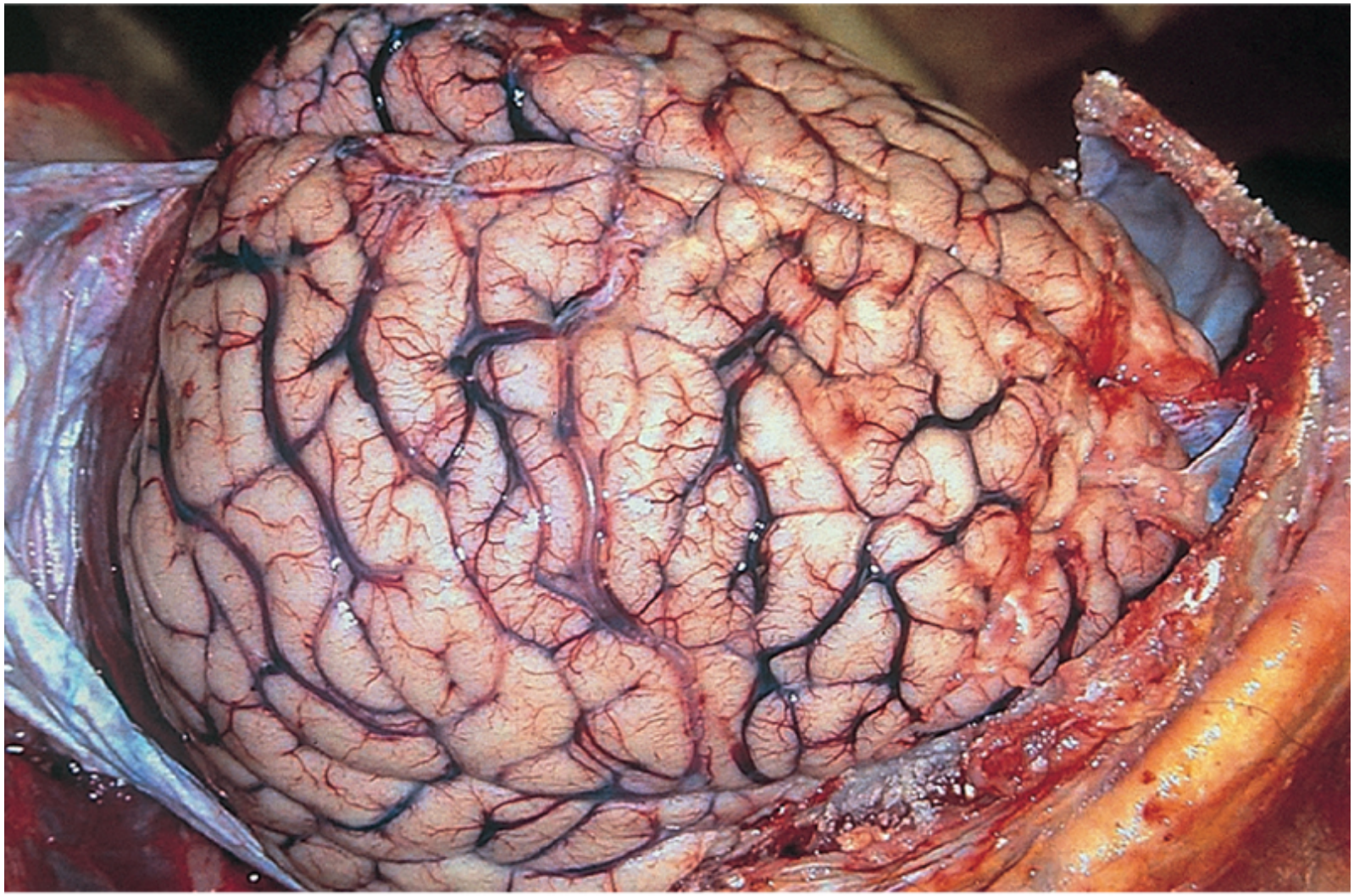
►**(I) Vasogenic edema** occurs when the integrity of the normal blood-brain barrier is disrupted. With ↑ **vascular permeability, fluid shifts from the vascular compartment into the intercellular spaces of the brain (like edema in other body tissues).** Vasogenic edema can be either:

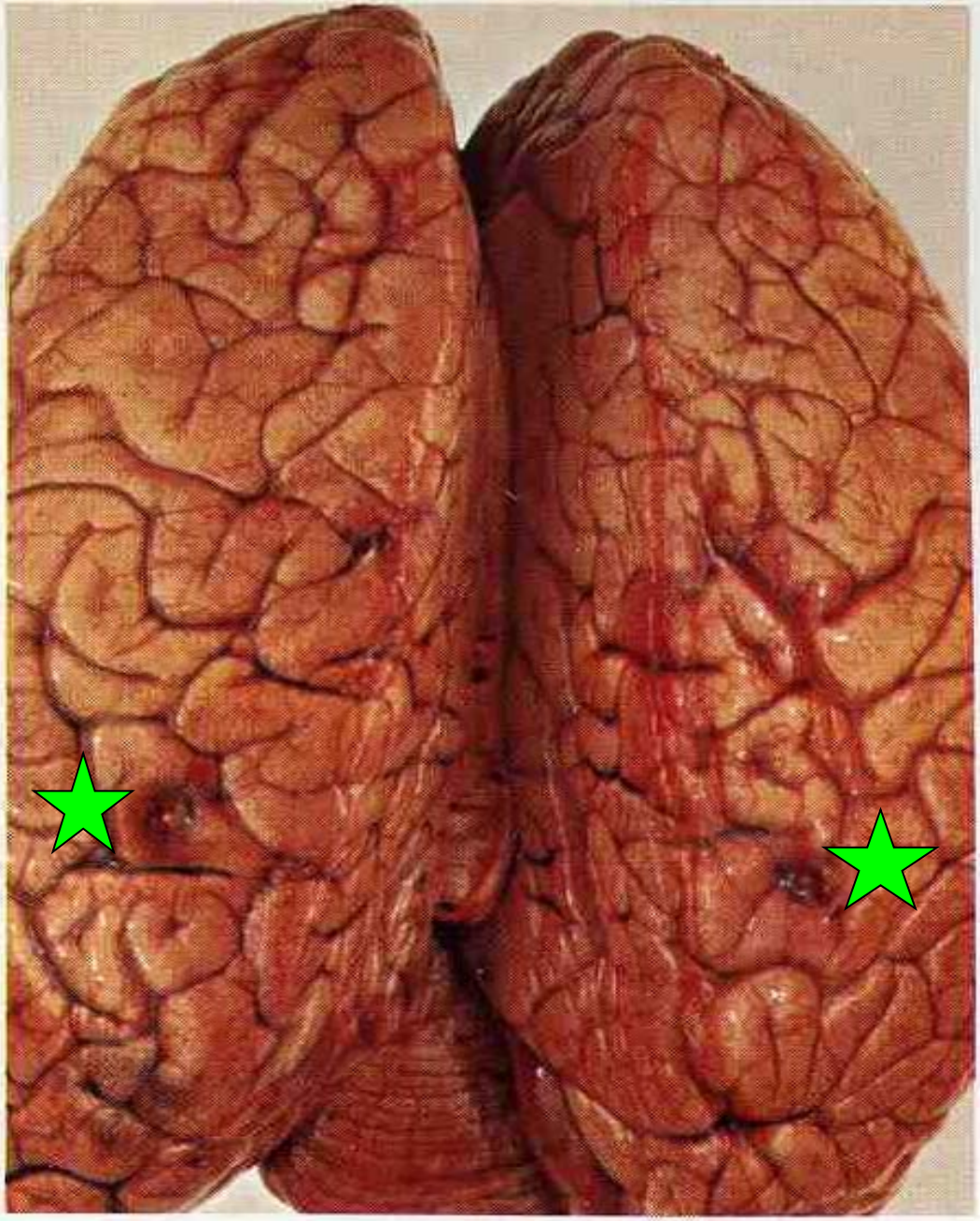
(A) localized; because of abnormal ⇧ permeability of BV adjacent to inflammation or tumors, or (B) generalized.

► **(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

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.**

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.

➔ The CSF is **resorb** by the arachnoid granulations of the dural venous sinuses back to the blood.
☺The **balance** between CSF generation & resorption keeps the CSF volume stable.

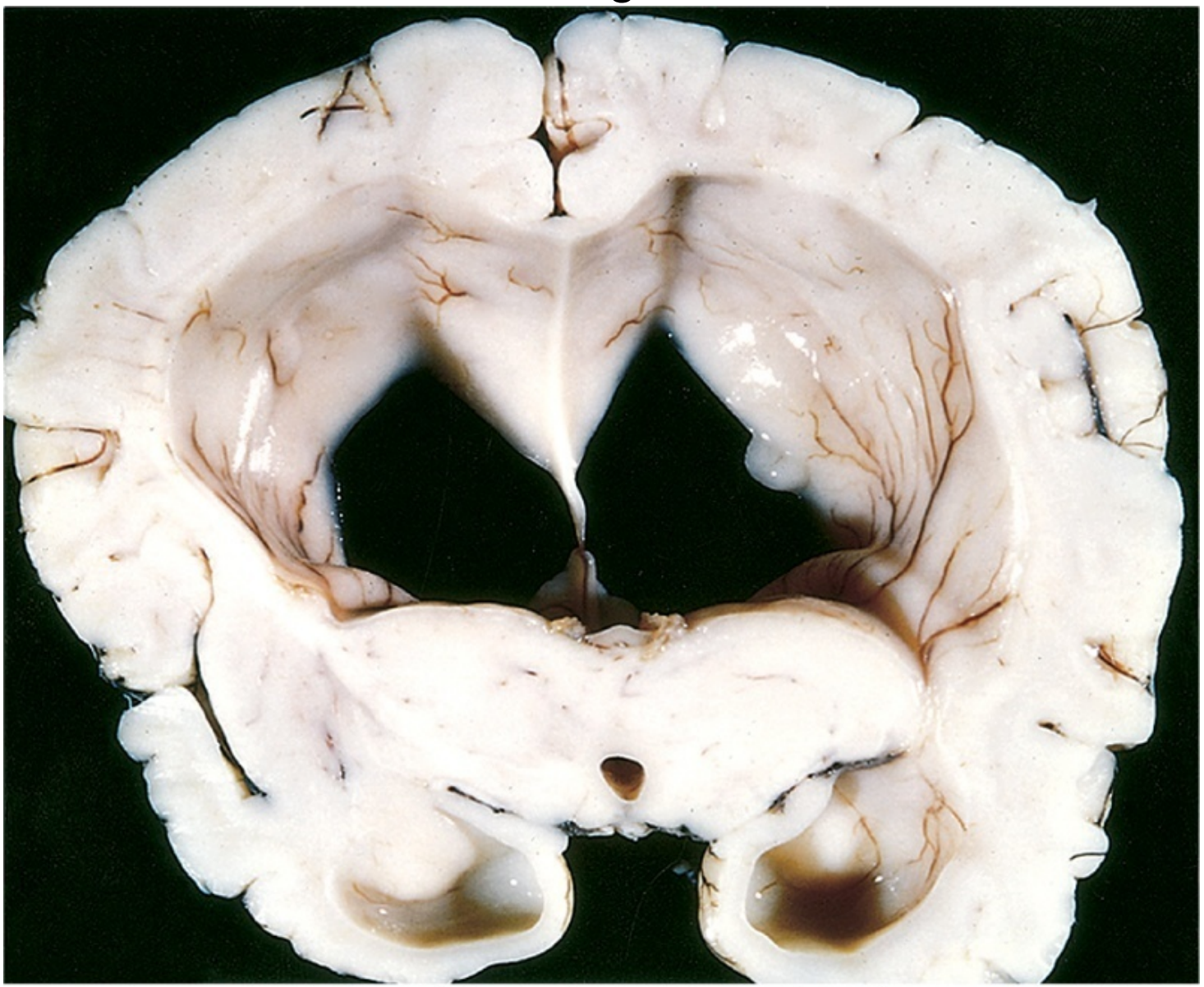
☹ *Hydrocephalus* refers to the **accumulation of excessive CSF within the ventricular system.**

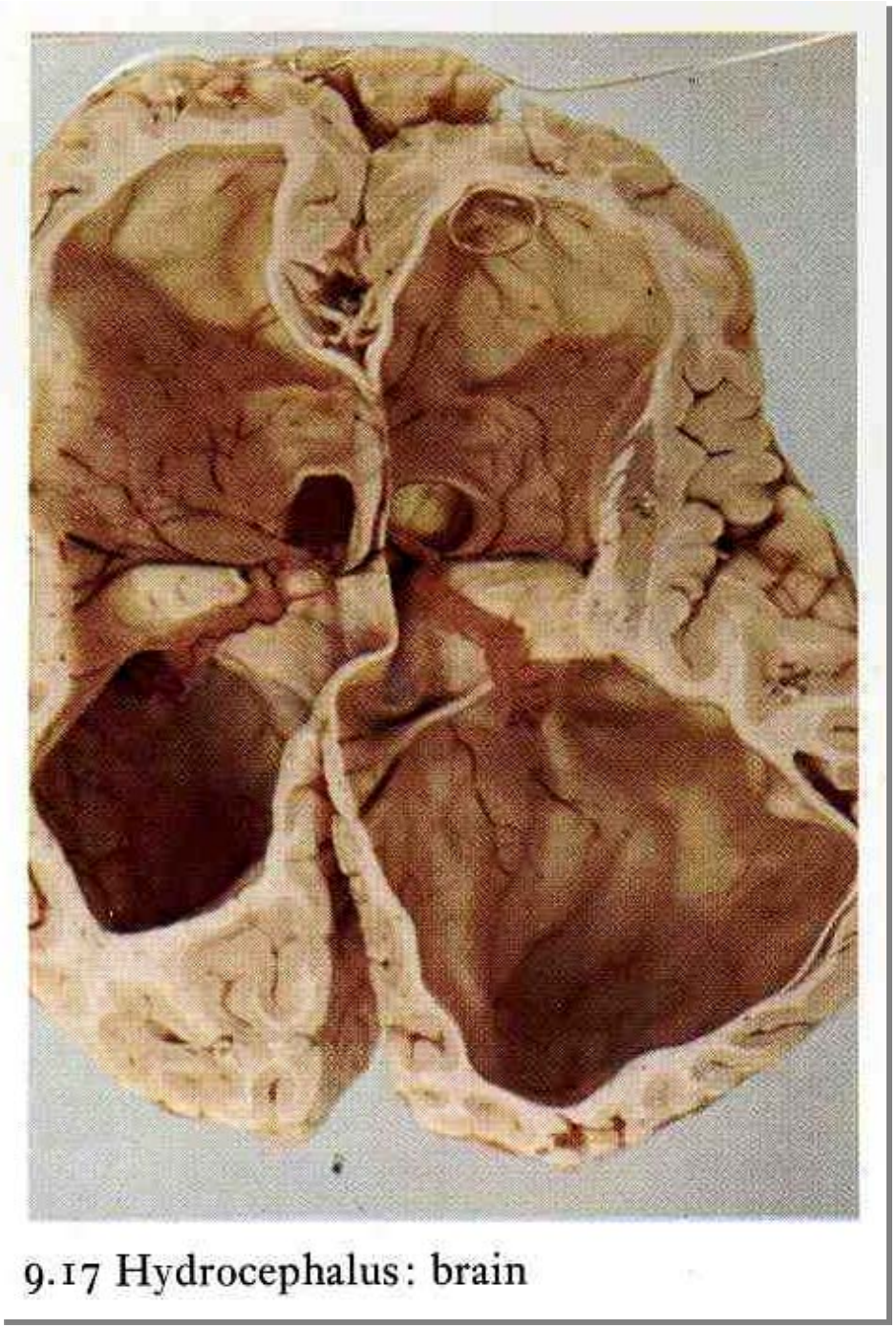
★ Most cases occur as a result of **impaired flow (obstruction)** or **impaired resorption of CSF**; while …

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

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

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.**

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

★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***.

★ 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.

★**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.***

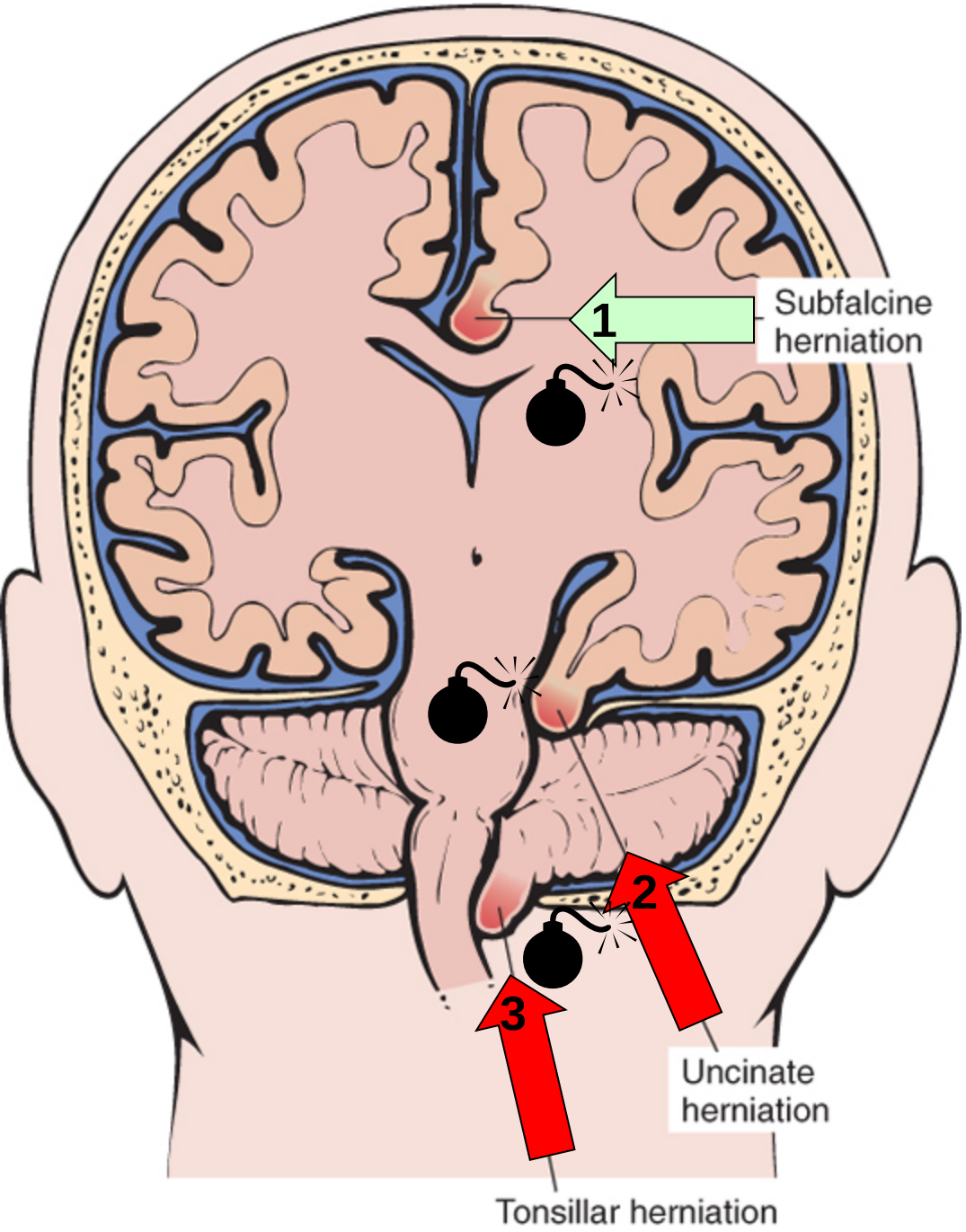
Herniation

☹ 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").**

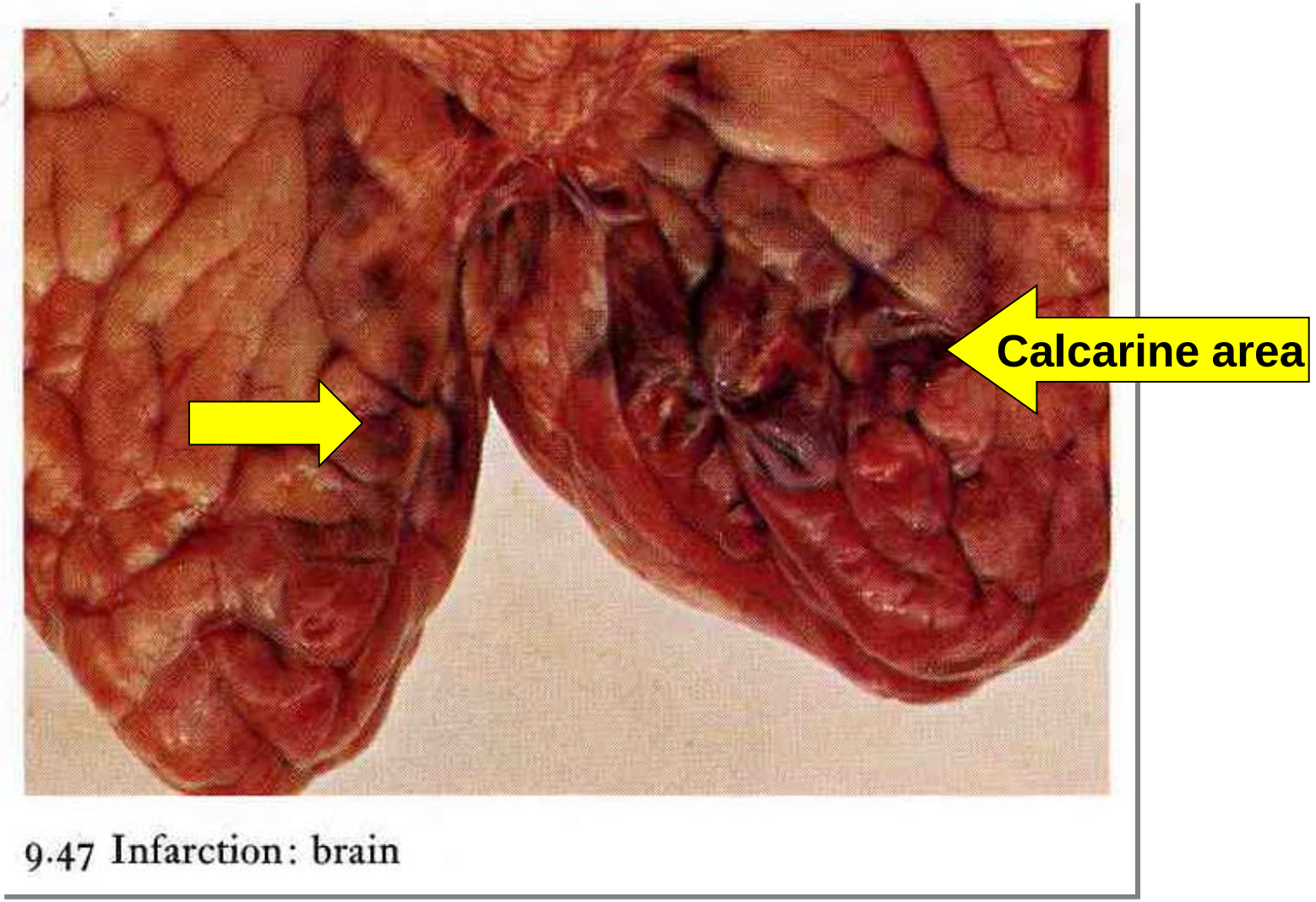
(2) **Posterior cerebral artery compression** (F9-47), resulting in ischemia in it's territory, including the primary visual cortex.

(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.

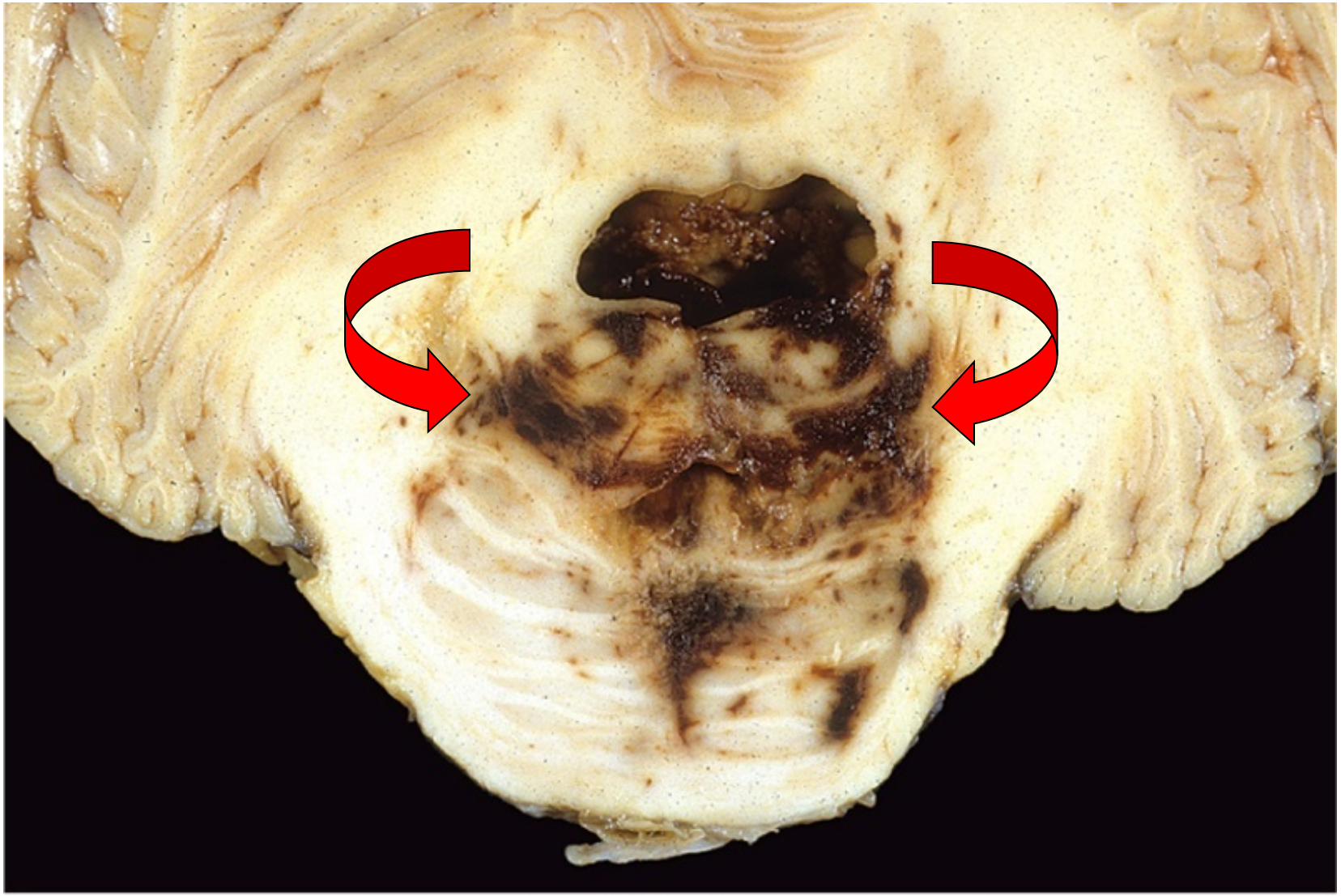
☠ Duret hemorrhages is usually fatal ☠.

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")

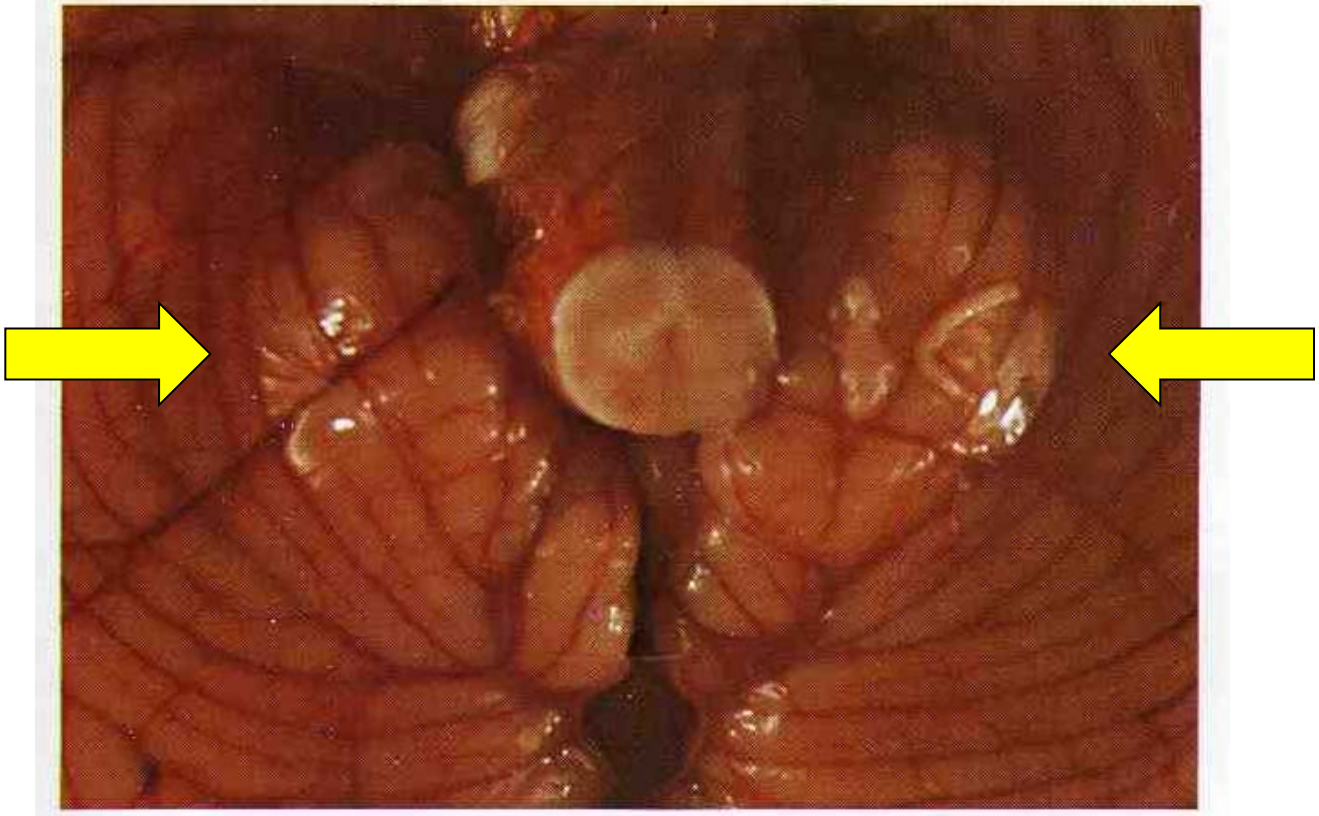
▲ Cerebrovascular disease is the 3rd (after IHD & cancer) common cause of death in US; & it is also, the most prevalent neurologic disorder in terms of both morbidity & mortality.

★ *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?)**



9.82 Tonsillar herniation ('pressure cone'): cerebellum

★A similar pattern of **ischemic injury** may occur **diffusely** when there is complete loss of perfusion (**Global ischemia**).

★**Rupture of BV results in hemorrhage,** leads to direct tissue damage + as well as secondary ischemic injury.

►**"Stroke“ (i.e., Hit or Blow)** is the clinical designation that applies to all these conditions, particularly when symptoms begin **acutely**.

Hypoxia, Ischemia, & Infarction

☺ The brain requires a constant delivery of glucose& oxygen from the blood. Although the **brain** accounts for only **1% to 2%** of **body weight**, it receives **15% of the resting cardiac output** & accounts for **20% of the total body oxygen consumption**.

☺ Cerebral blood flow remains constant over a wide range of blood pressure & intracranial pressure because of autoregulation of vascular resistance (What are these?)

☹ The **brain is a highly aerobic tissue, & can be deprived** of oxygen by one of several mechanisms:

{A} ***Functional hypoxia*** in a setting of a low partial pressure of oxygen (PO2); impaired oxygen-carrying capacity; inhibition of oxygen use by tissue; or

{B} Interruption or ↓ of the normal blood flow **with the resulting** ***Ischemia****, (transient* or *permanent),* due to either:

(1) Reduction in perfusion pressure, as in hypotension, or (2) Secondary to vascular obstruction, or (3) Both.

Global Cerebral Ischemia

►When the **systolic BP decease to less than 50mm Hg** due to **(1) cardiac arrest, (2) shock, or (3) severe hypotension,** it causes generalized reduction of cerebral perfusion, **resulting** in widespread cerebral ischemic/hypoxic injury.

▲The clinical outcome varies with the severity of the insult.
☺ When **mild**, there may be only a **transient post ischemic confusional** state, with eventual complete recovery.
☹ **Irreversible** damage of CNS tissue does occur in some individuals who suffer mild or transient global ischemic insults.

☹ **Neurons** are much more sensitive to hypoxia than are **glial** cells. There is also variability in the susceptibility of different populations of neurons in different regions of the CNS;

☹ **Pyramidal cells of the Sommer sector** (CA1) of the hippocampus, **Purkinje cells of the cerebellum, & pyramidal neurons in the neocortex** are the *most susceptible* to ischemia of short duration**.**

▼In **severe** global cerebral ischemia, **widespread** neuronal death, irrespective of regional vulnerability, occurs. Individuals who survive in this state often remain severely impaired neurologically, & deeply comatose **(persistent vegetative state).**

☠ Other patients are in **"brain death,"** state with cortical injury **(isoelectric or flat electroencephalogram, EEG)** & brain stem damage, including absent reflexes & respiratory drive.

☠ When patients with this severe form of injury are maintained on mechanical ventilation, the **brain** gradually undergoes an **autolytic** process, resulting in the so-called **"respirator brain."**

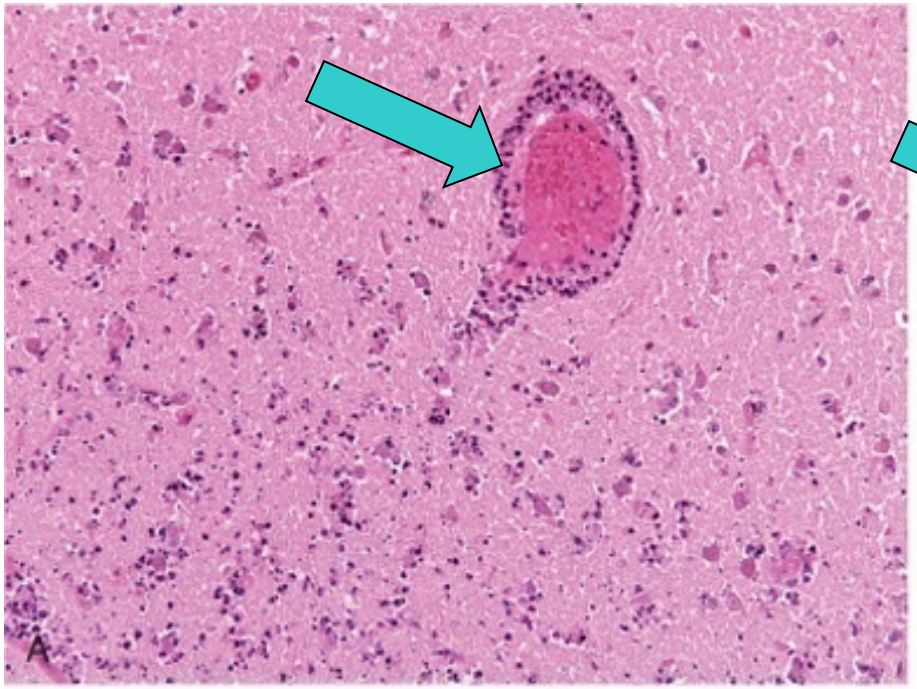
►**GROSSLY,** in **global ischemia**, the brain is **swollen**, with **wide gyri & narrowed sulci, C/S** shows **poor demarcation between gray & white matter.**

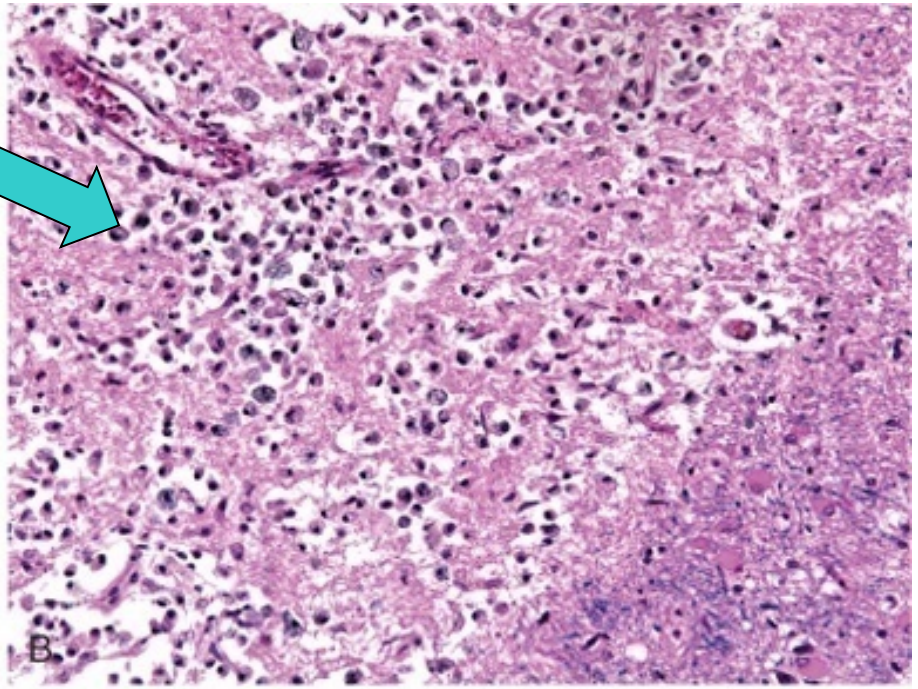
◘ H, the changes of infarction is grouped into 3 categories:

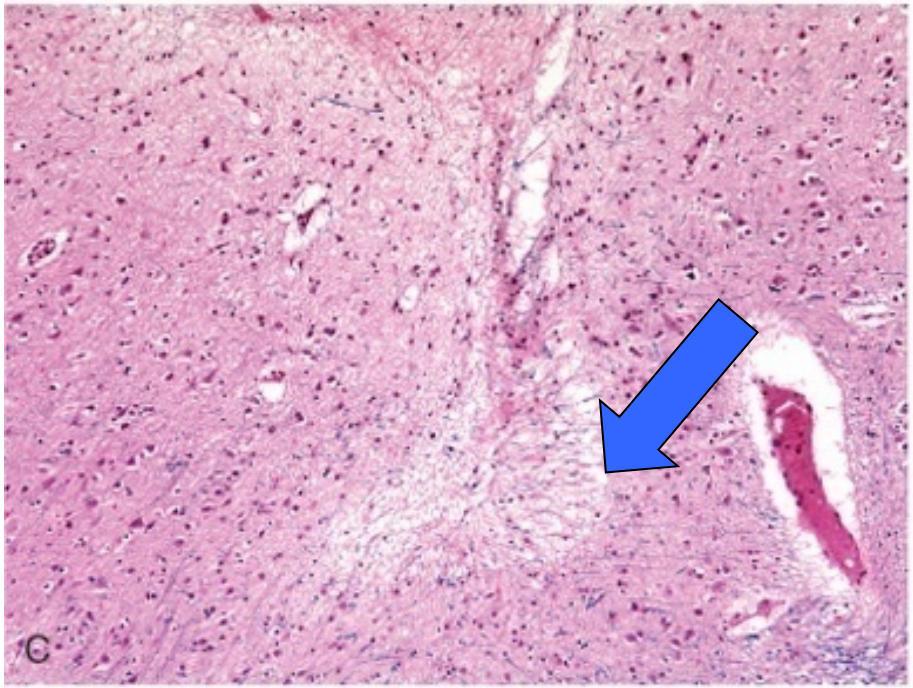
(1) **Early changes,** occurring 12 to 24 hours after the insult, include acute **neuronal cell change** (red neurons; F23-1A) characterized → initially by microvacuolization, → followed by cytoplasmic eosinophilia, & → later nuclear pyknosis & karyorrhexis **(necrosis).** Similar changes occur somewhat later in **astrocytes & oligodendroglia**. After this, the **reaction** to tissue damage begins with infiltration by neutrophils (F23-6A).

(2) **Subacute changes,** occurring at 24 hours to 2 weeks, include necrosis of tissue, influx of macrophages, vascular proliferation, & reactive gliosis (F23-6B).

(3) **Repair,** seen after 2 weeks, is characterized by **removal** of all necrotic tissue, **gliosis & loss of organized CNS structure,** (F23-6C & ◘ 4.4). In the cerebral cortex the neuronal loss & gliosis produce an uneven destruction of the neocortex, with preservation of some layers & involvement of others - a pattern termed **pseudo laminar necrosis.**

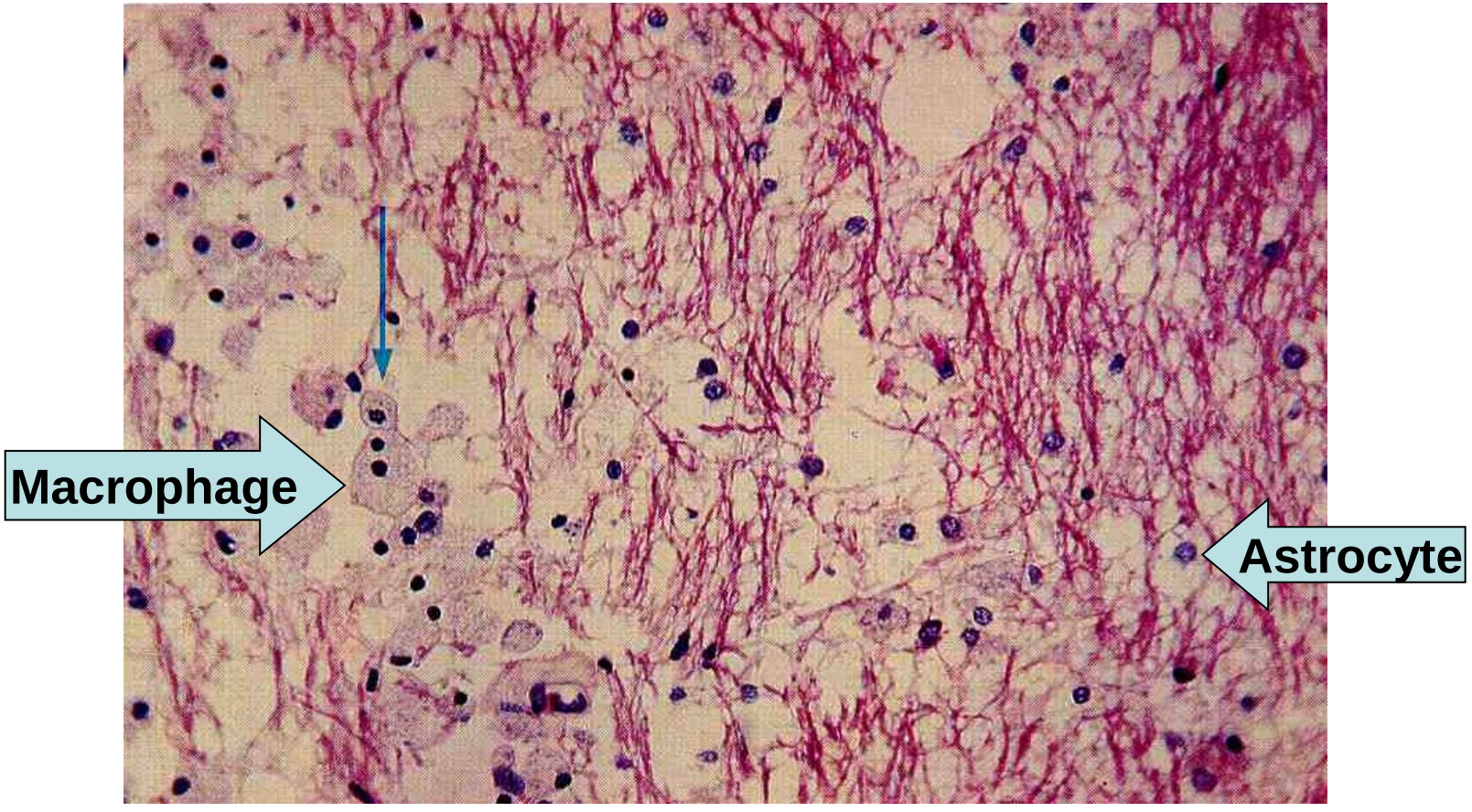






F 23-6: Cerebral infarction **(CI)** .
A, Recent CI **infiltrated** by neutrophils, begins at the edges of the lesion from intact BV.
B, After 10 days, the CI is infiltrated by macrophages & surrounded by reactive gliosis.
C, Old small intracortical CI seen as areas of tissue loss with a small amount of residual gliosis.

◘4.4; **Brain infarction** of 6 weeks duration X335. White matter (I) Most **myelinated fibers** undergone ischemic necrosis & **disappeared.** (II) large round **Macrophages** with foamy cytoplasm **(**from phagocytosed lipoproteins of the necrotic tissue), lying in the spaces between the surviving fibers. (III) **Astrocytes** with small round basophilic nuclei & ill-defined cytoplasmic boundaries.



★**Border zone ("watershed") infarcts {**usually seen **after hypotensive episodes}** are wedge-shaped areas of infarction that occur in those regions of the brain & spinal cord that **lie at the most distal fields of arterial perfusion**.

★In the cerebral hemispheres, the border zone between the anterior & the middle cerebral artery distributions is at **greatest risk**. Damage to this region produces a band of necrosis over the cerebral convexity, a few cm lateral to the interhemispheric fissure.

Focal Cerebral Ischemia

Cerebral arterial **occlusion** leads to → **focal ischemia & -if sustained- to ➔ infarction** of CNS tissue in the distribution of the occluded BV.

★ The site, size, & shape of the resulting infarct are determined by many factors, the most important of which is the adequacy of **collateral flow**.

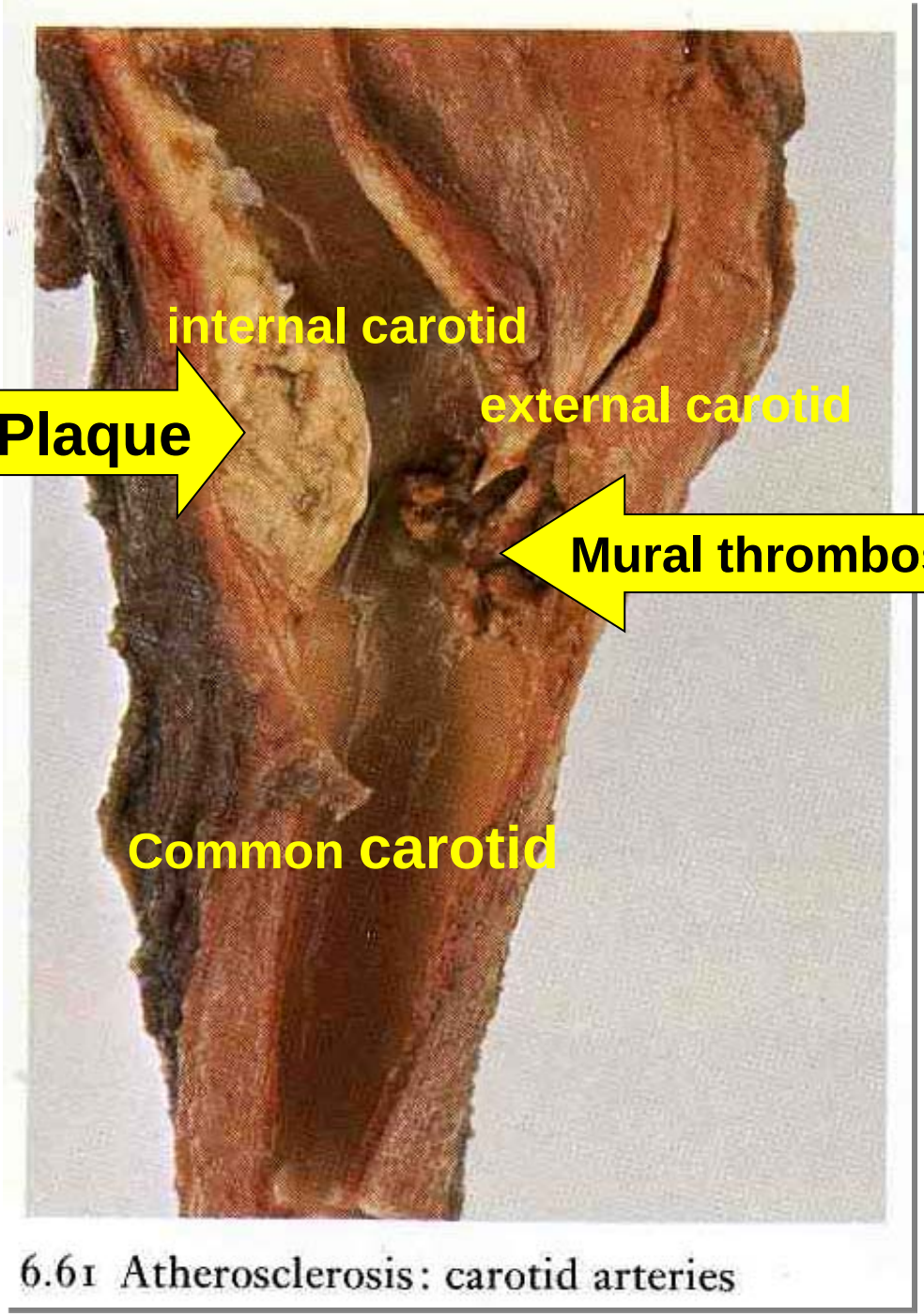
☺ The **major** source of collateral flow is the **circle of Willis.**
☺ Partial collateralization is also provided over the surface of the brain through **cortical-leptomeningeal anastomoses**.

☹ **In contrast**, there is little, if any, collateral flow for the deep penetrating vessels supplying structures such as the **thalamus**, **basal ganglia, & deep white matter**.
☹ Arterial occlusion leading to cerebral infarction is due to:

(1) Most commonly, ***Embolization*** from a distant source, Or
(2) Less commonly, ***In situ thrombosis.***

➔ (1) Overall, **embolic** infarctions are **more common**.
★**Cardiac mural thrombi** are a frequent source, including:
• atrial fibrillation • valvular disease, & • MI;
★ *Thromboemboli* arising most often from atheromatous plaques within the carotid **arteries** (F6-61).
★ **Other** sources are • **paradoxical** emboli, particularly in children with cardiac anomalies; • emboli associated with **cardiac surgery**; & • other rare **tumor, fat, or air** emboli.

☹The **territory** of distribution of the **middle cerebral artery(**the direct extension of the internal carotid artery) is **most** frequently affected by embolic infarction; **emboli tend to lodge** where vessels **branch** or in areas of preexisting luminal **stenosis.**



6.61 Atherosclerosis: carotid arteries

F6.61: Yellow-white ☹ **calcified atheromatous plaque** at the origin of the Rt internal carotid artery (top left), causing marked luminal stenosis. Opposite the plaque, at the origin of the Rt. external carotid artery, there is an irregular small brown mass of ☹ **mural thrombosis**.

➔ (2) Most of ***in situ*** primary ***thrombotic occlusions*** causing cerebral infarctions are due to ***atherosclerosis;*** **the most common sites** of which are the:

(1) **carotid bifurcation** (F6.61), the

(2) **origin of the middle cerebral artery**, &

(3) at either end of the **basilar artery**.

➔ **Thrombosis,** superimposed on atherosclerotic stenoses, can be accompanied by anterograde (forwards) extension, fragmentation, & ➔ **distal embolization!**

►Based on their macroscopic & corresponding radiologic appearance, infarcts (F23-7) can be divided into 2 groups:

(A) ***Nonhemorrhagic infarcts*** can be treated, ☺ if identified **shortly** after presentation with thrombolytic = thrombolysis = dissolution of thrombus therapies, by **streptokinase** or tissue plasminogen activator, **(t-PA**),

Thrombolytic therapies approach for the ***Nonhemorrhagic infarcts*** is **contraindicated** when lesions are of the second group, the…

- (B) ***Hemorrhagic infarcts*** (F23-7A & B), in which, multiple confluent petechial hemorrhages occurs secondary to **Reperfusion** of ischemic tissue, either through
  (1) **collaterals** or,
  (2) after **dissolution** of intravascular occlusions.

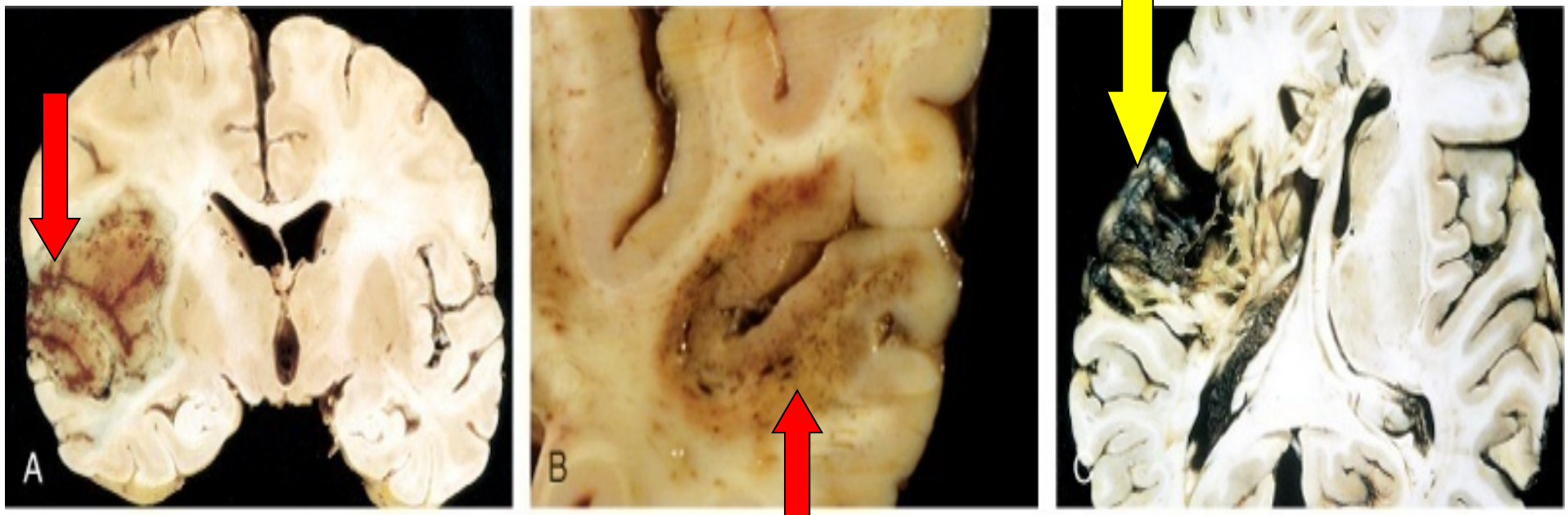
Reperfusion injury

😐 is **mediated** by oxygen free radicals (**FR**) generated by the ↑ number of infiltrating WBC facilitated by reperfusion;

☹ it can incite *greater* local damage than might have otherwise occurred without **rapid** restoration of blood flow!

Reperfusion-induced microvascular injury, causes **hemorrhage.**

F23-7: **Cerebral infarction.** Brain sections showing:
A, Large red hemorrhagic infarct in the distribution of the left middle cerebral artery.
B, Temporal lobe red infarct, with punctate hemorrhages, due to **ischemia-reperfusion injury**,
C, Old cystic infarct, shows destruction of cortex & surrounding gliosis.



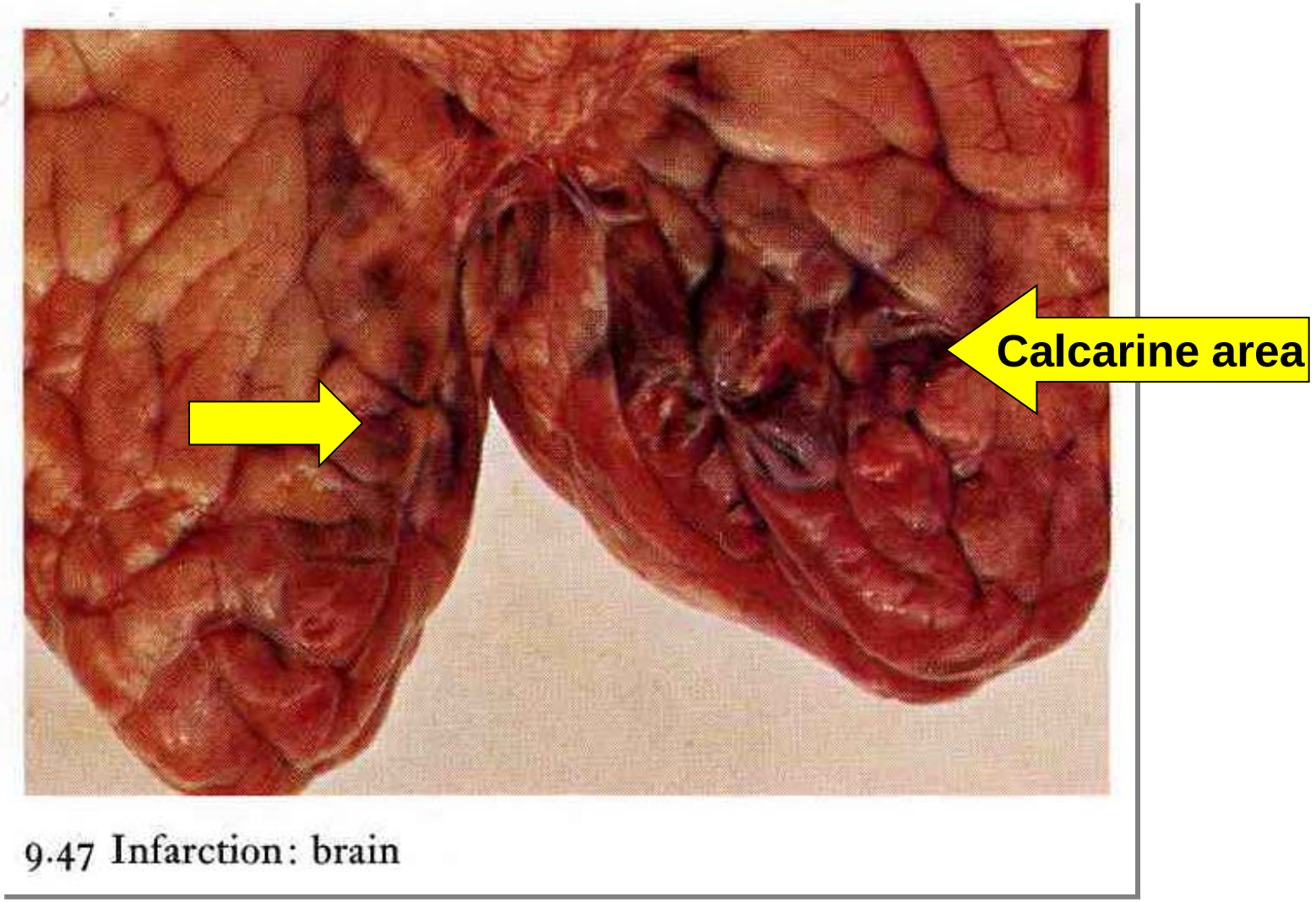
►Grossly, the **nonhemorrhagic infarct** changes in time.

- In the first **6 hours** of irreversible injury, **little** can be seen.
- By **48 hours**, the infarct becomes **pale, soft, & swollen, &** the corticomedullary junction becomes **indistinct.**
- From **2 to 10 days** the infarct becomes **gelatinous & friable**, & the previously ill-defined boundary between normal & abnormal tissue becomes **more distinct** as edema resolves in the adjacent tissue that has survived (F9-47).
- From **10 days to 3 weeks**, the necrotic tissue **liquefies (Liquefaction necrosis)**, eventually leaving **a fluid-filled cavity (**F1-11) **lined by dark gray tissue**, which gradually expands as dead tissue is removed (F23-7C & 9-46).

◙ H, the tissue reaction follows a characteristic sequence:

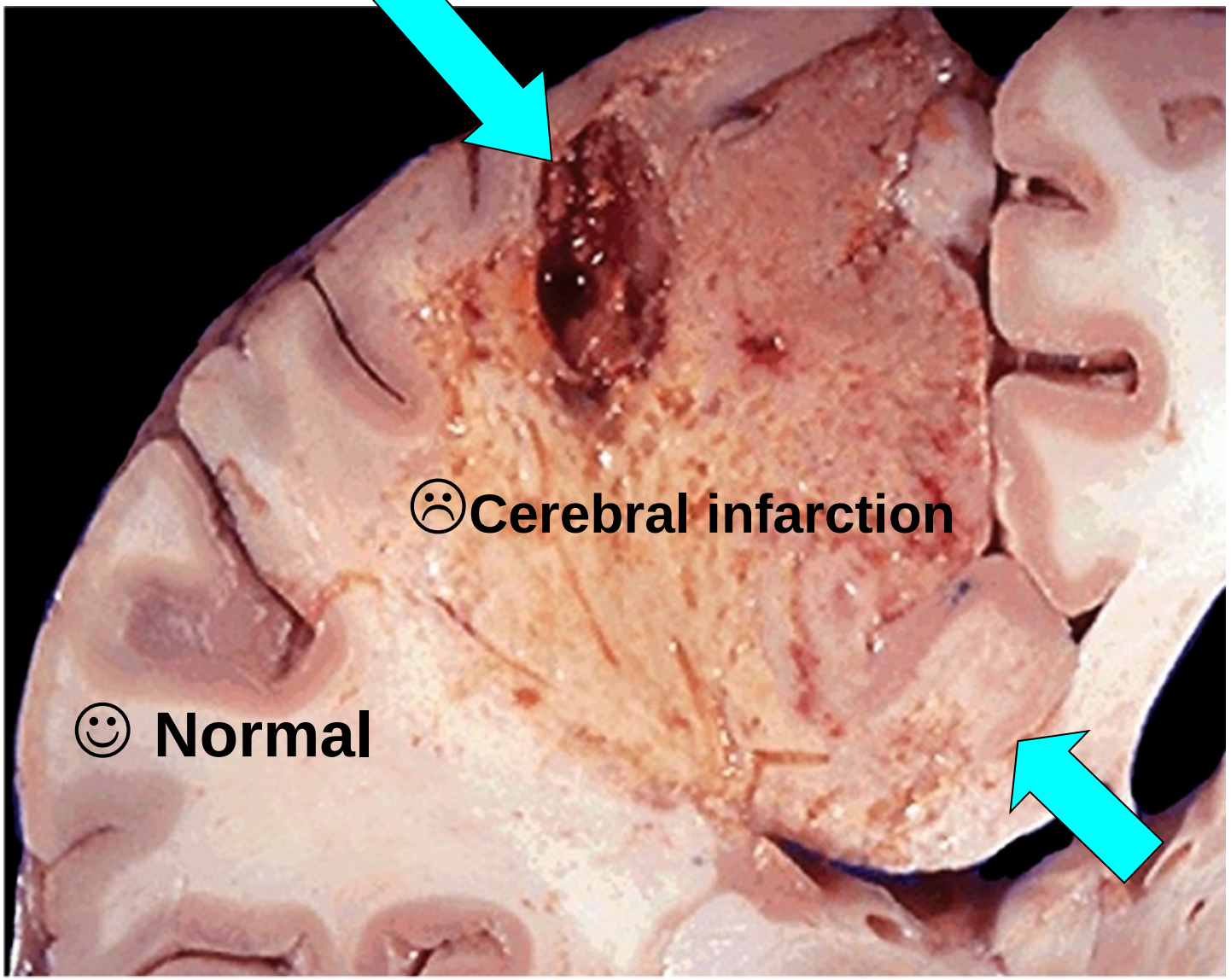
★**After the first 12 hours** ischemic **neuronal necrosis (red neurons,** F23-6A) & **edema** (both cytotoxic & vasogenic) predominate. There is loss of the usual tinctorial characteristics of white & gray matter structures. EC & glial cells (mainly astrocytes) swell, & myelinated fibers begin to disintegrate.

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.



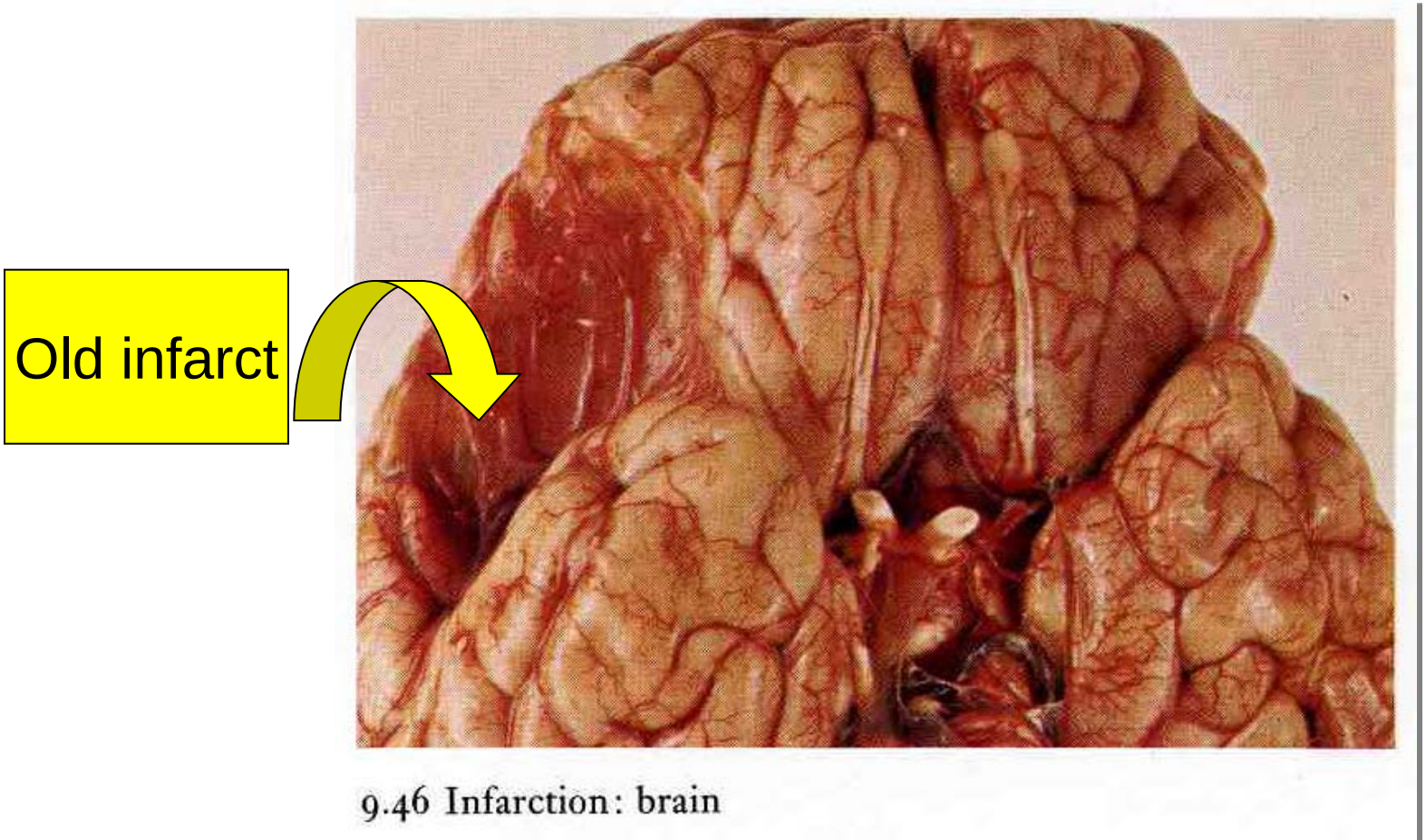
9.47 Infarction: brain

F1-11: **Brain:** Cerebral infarct, 10 to 21 days after stroke, liquefactive necrosis of the brain tissue, eventually leaving **a fluid-filled cavity.**



Normal Cerebral grey & white matter.

F 9.46: Infarction: Brain. The patient had chronic RHD with left **atrial thrombus** ⇨ **embolization** of which in the ⇨ Rt. middle cerebral artery causes large **infarction** of the ⇨ inferior aspect of the right fronto-temporal region. The **<u>old infarct</u>** appears as a large **'cavity',** covered by a thin, brown membrane, which is either filled with clear fluid or, appears collapsed (as here).



9.46 Infarction: brain

★**Up to 48 hours,** there is **neutrophilic** emigration followed by **mononuclear** phagocytic cells in the following **2 to 3 weeks. Macrophages containing myelin breakdown products or blood** may persist in the lesion for months to years.

As the process of phagocytosis & liquefaction proceeds, **astrocytes** at the edges of the lesion progressively enlarge, divide, & develop a prominent network of protoplasmic extensions.

★ **After several months** the striking astrocytic nuclear & cytoplasmic enlargement recedes.

• In the **wall** of the cavity, astrocyte processes form a dense **gliosis** (network of **glial fibers admixed with new capillaries)** & a few perivascular connective tissue fibers.

In the cerebral cortex, the cavity is delimited (separated) from the meninges & subarachnoid space by a **gliotic layer of tissue**, derived from the molecular layer of cortex.

😐 **The pia & arachnoid are not affected & do not contribute to the healing process**.

(B)◘ The H & evolution of **hemorrhagic** infarction **parallel ischemic** infarction, with the **addition of blood extravasation & resorption**.

☹ In persons receiving anticoagulant treatment, hemorrhagic infarcts may be associated with extensive intracerebral hematomas.

Intracranial Hemorrhage (H)

➔**H** within the skull can occur in many locations, & each one is associated with a set of underlying causes:

★ **Intraparenchymal H** = **H** within the brain itself :
(1) Most commonly occur secondary to **hypertension,** or
(2) other forms of vascular wall injury, or specific lesion like an arteriovenous **(AVM)** or cavernous malformation, or / an intraparenchymal tumor.

★ **Subarachnoid H most commonly** result from (1) rupture of **Berry aneurysms,** (2) less commonly from rupture of other vascular malformations.

★**Dural (epidural or subdural) H** are usually **traumatic.**

Primary Brain Parenchymal Hemorrhage (H)

►**Spontaneous (nontraumatic)** intraparenchymal **H** occur most commonly in mid to late adult life, with a peak incidence at about 60 years of age. Most are caused by **rupture** of ***Charcot-Bouchard microaneurysms*** in an hypertensive.

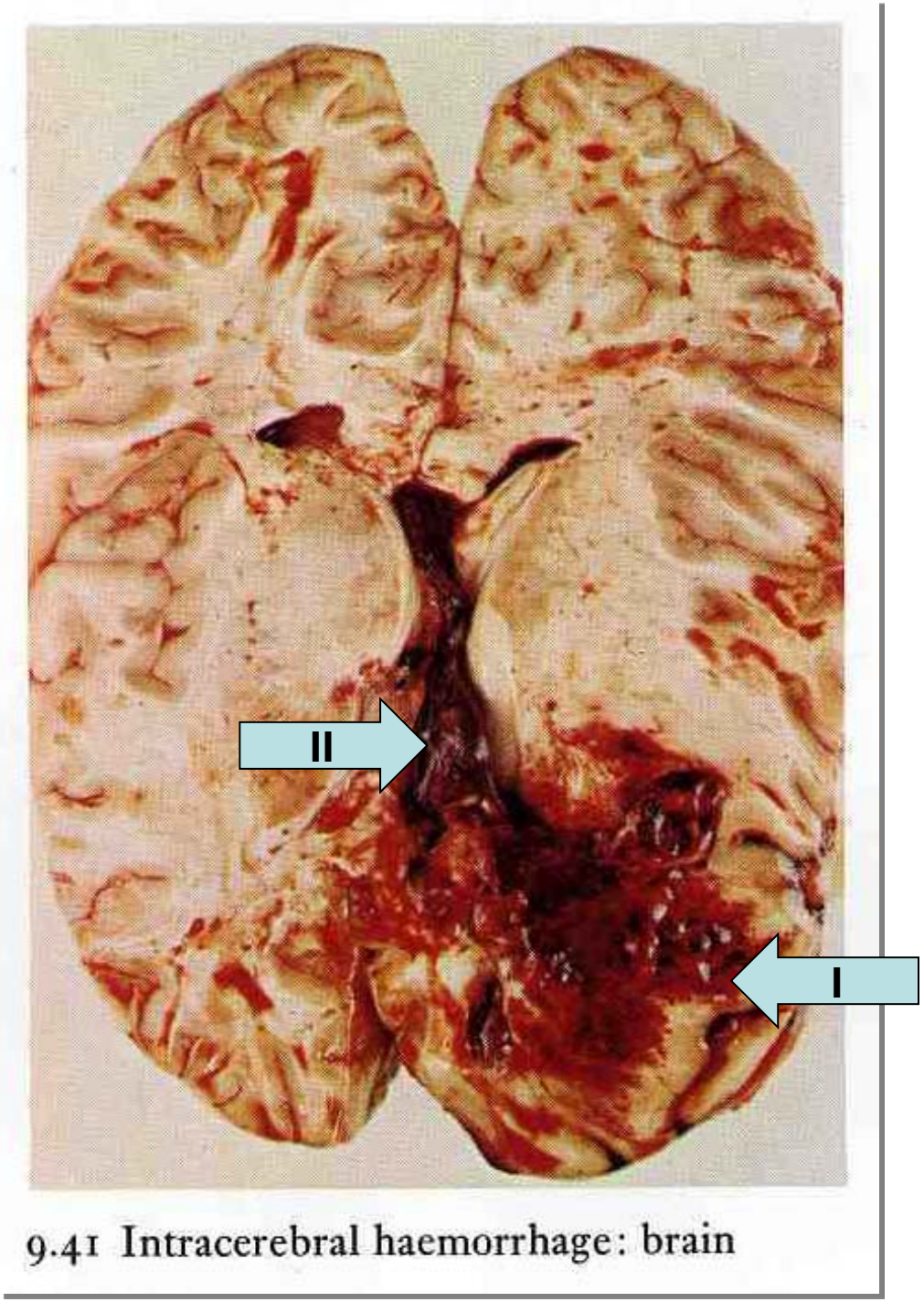
★**Hypertension** is the most common underlying cause & brain **H** accounts for **15%** of deaths among chronic hypertensives.

★Typically, hypertensive intraparenchymal H occurs in **basal ganglia, thalamus, pons, & cerebellum** (F23-8,9-42 & 43),

☠ Intracerebral **H can be clinically devastating** & ☠ **fatal** when it affects large portions of the brain; & it may extends into the ventricular system; or 😐 Intracerebral **H can affect small regions & be clinically silent.**

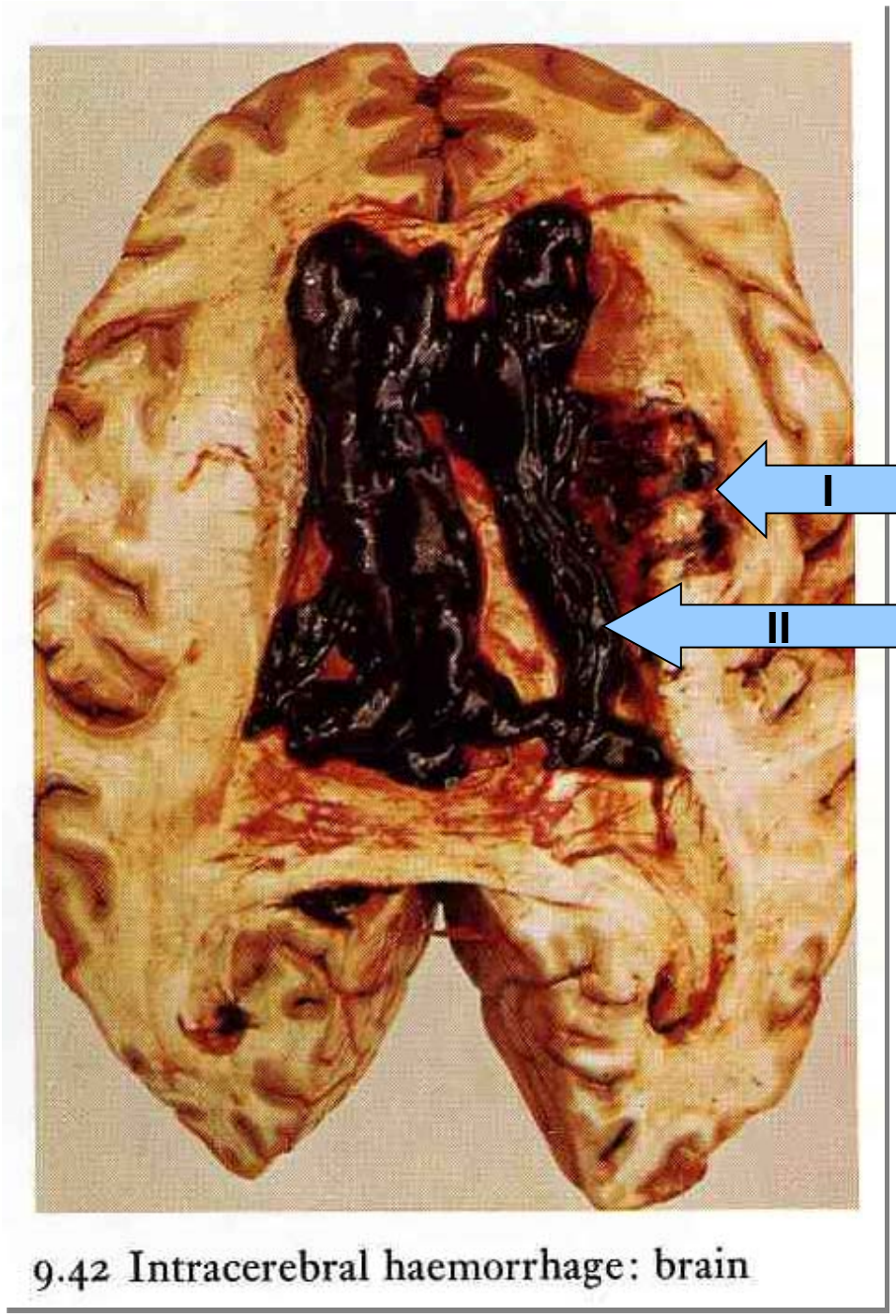
Over weeks or months there is a *gradual resolution* of the hematoma, sometimes with considerable clinical improvement. 😐 Again, the **site & size** of the **H** will determine the clinical manifestations.

F23-8: **Cerebral hemorrhage.**
Massive hypertensive hemorrhage rupturing into a lateral ventricle.



9.41 Intracerebral haemorrhage: brain

F 9-41: **Recent intracerebral hemorrhage: brain.**
(I) Recent, large hemorrhage in the right occipital pole, extending to **(II)** the lateral ventricle.

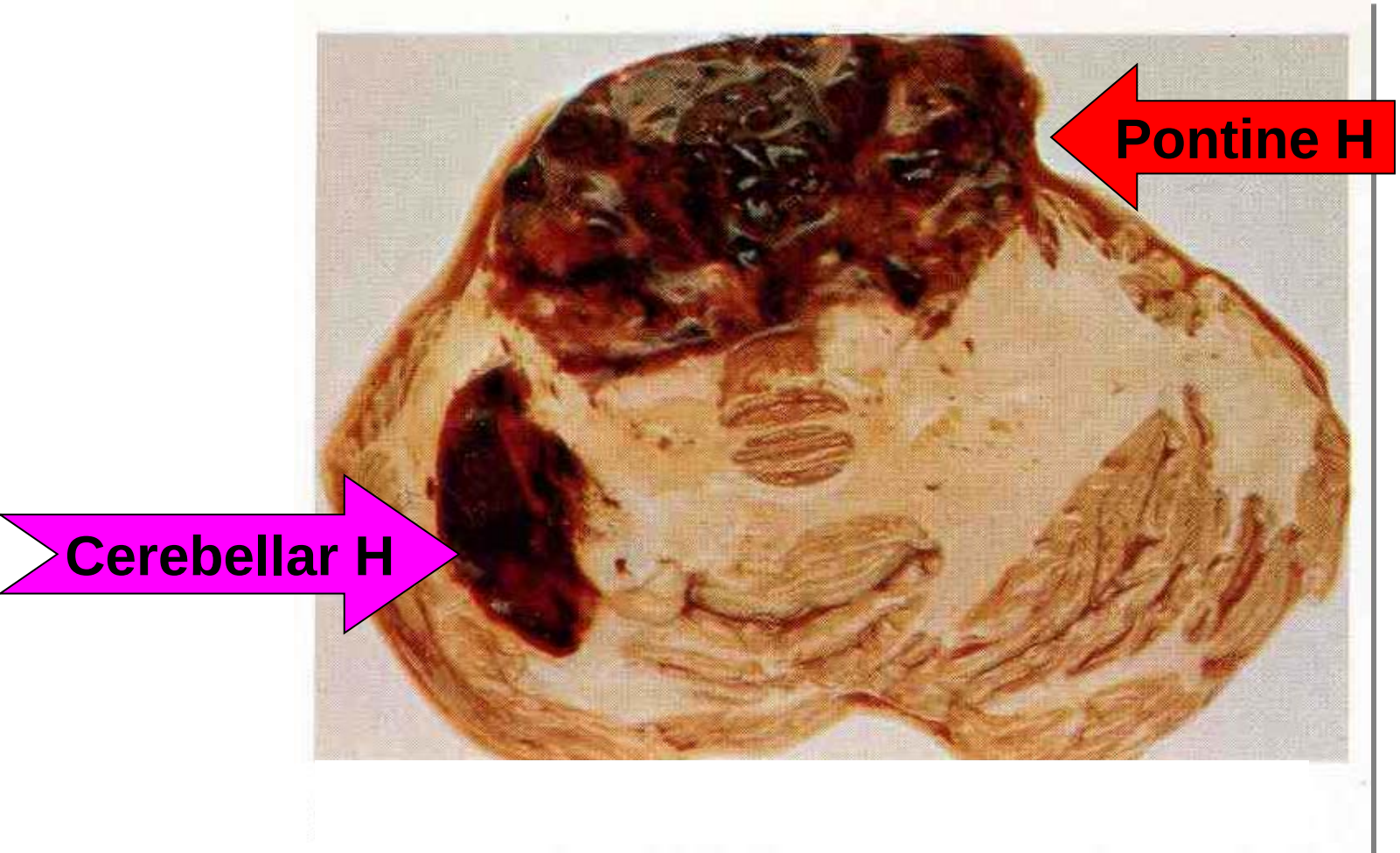


9.42 Intracerebral haemorrhage: brain

F 9-42: **Intracerebral hemorrhage: brain.**
(I) There is ragged hypertensive intracerebral hemorrhage in the region of **right lentiform nucleus** (top right) which ruptured into & fills **(II)** both lateral ventricles.

NB. This **intraventricular hemorrhage** may pass through the foramina of the fourth ventricle **into…Where?**

F 9- 43: **Massive** (more than 1.5 cm in ∅) **recent hemorrhage** destroying the **pons** (above ⇦), & with 2nd hemorrhage in the central white matter of the **cerebellar hemisphere**(⇨).
☠ The occurrence of **any one** of the above 2 hemorrhages alone, is almost always, rapidly ☠ fatal.



Morphology of *Brain Parenchymal Hemorrhage (H)*

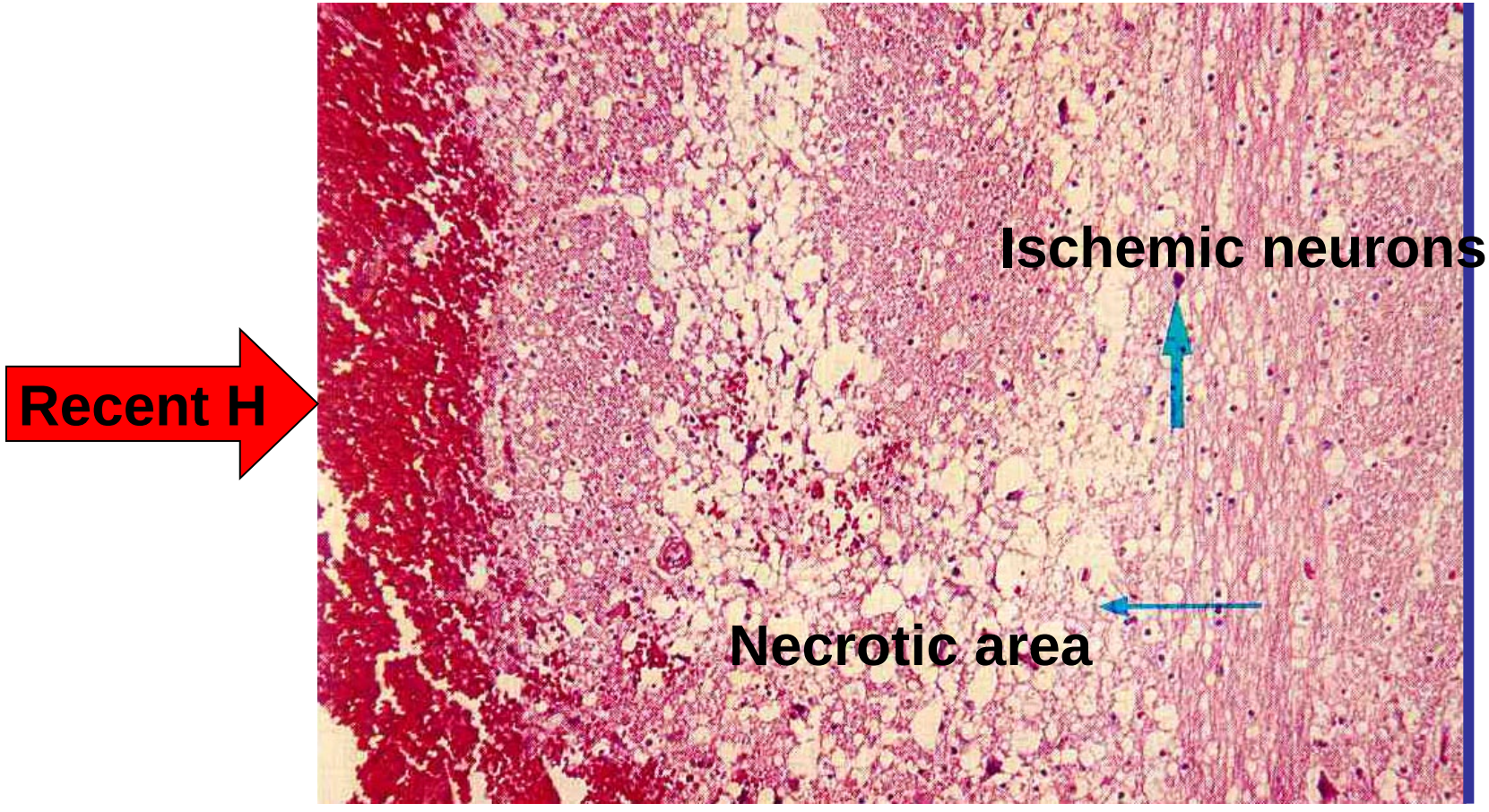
► **Acute H,** Grossly (F 9-41, 42 ,& 43) show extravasation of blood with compression of the adjacent parenchyma, &
◘ H, (◘ 4.5) consists of a (I) **central core of clotted blood** surrounded by a (II) **rim of necrotic & edematous neuronal & glial brain tissue.**

►**Old H,** Grossly, (F9-44) show:
(I) central cavity of brain destruction, filled by partly-organized, brown **hematoma** retracted from the surrounding brain;
(II) surrounded by thick capsule of reactionary astrocytic proliferation; Both…

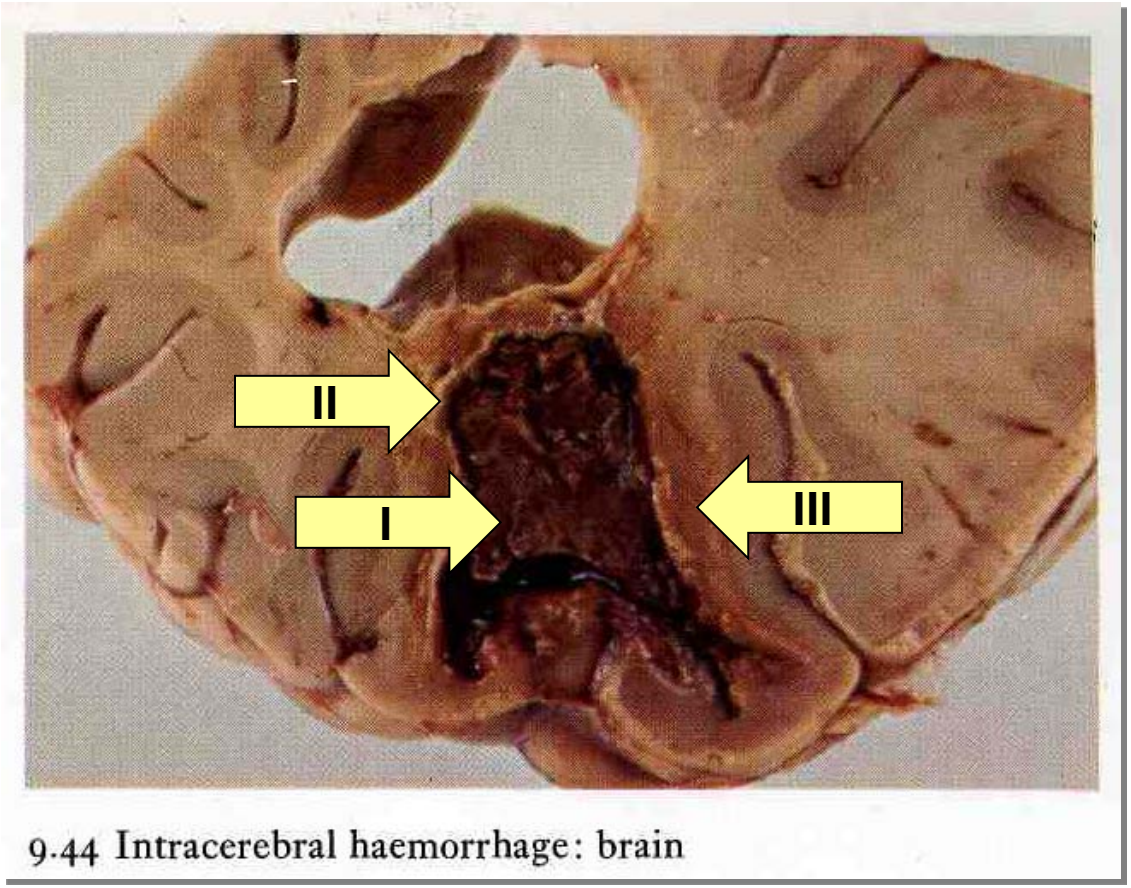
(III) the thick capsule & the adjacent brain rim are stained **golden-brown** by breakdown products of hemoglobin.

◘ H, at the periphery of the lesion, there is (1) **astrocytes** proliferation with (2) pigment & lipid-laden **macrophages.**
The cellular events then follow the same time course observed after cerebral infarction.

◘ 4.5: **Recent Cerebral hemorrhage: Brain X145.** Edge of the hemorrhage. On the left, there is red zone of **recent blood clot**. Adjacent to it , there is an extensive **necrotic area** (thin arrow), pale, edematous & vacuolated (vacuoles contain water) & many neurons & glial cells have disappeared. Few ischemic neurons **survive** as basophilic round bodies (thick arrow)



F 9-44: **Old intracerebral hemorrhage: brain.** Coronal section of the occipital lobe, showing partly-organized old hemorrhage: **(I)** Central brown **hematoma** retracted from the surrounding brain, **(II)** thick **capsule** of reactionary astrocytic proliferation, **(III) both,** the capsule & the adjacent brain are stained **golden-brown** by breakdown products of hemoglobin.



Cerebral Amyloid Angiopathy (CAA)

►Cerebral amyloid angiopathy (CAA) is a disease in which amyloidogenic peptides-typically the same ones found in -Alzheimer disease- deposit in the walls of medium- & small-caliber meningeal & cortical BV. The deposition weakens the BV wall & ↑ the risk of H.

★Since CAA is limited to leptomeningeal & cortical BV with sparing of the vasculature of white matter & deep gray structures, the H associated with CAA have a **distribution that is different** from that of hypertensive intraparenchymal hemorrhages.

★ CAA-associated H are often referred to as ***lobar H*** because of the involvement of the **cerebral cortex**.

◘ Amyloid in the vessel walls **can be identified by Congo Red stains**. The affected vessels are rigid, with a pipe-like appearance.

Subarachnoid Hemorrhage & Saccular Aneurysms

➔The **most frequent cause** of subarachnoid H **is rupture of a *saccular (Berry) aneurysm.***

★ **Other** causes include (1) **vascular malformation**, (2) **trauma** (in which case it is usually associated with other signs of the injury), (3) 2nd to **rupture** of an intracerebral H into the ventricular system,(4) **hematologic** disturbances,&(5) **tumors**.

★Rupture can occur at any time, but in about **1/3 of cases** it is associated with **acute ↑ in intracranial pressure**, such as with **straining at stool or sexual orgasm**.

★ Arterial blood is forced into the subarachnoid space, & with sudden, severe **excruciating headache** (the **worst headache** ever been felt) with **rapid lose of consciousness**.

☠ **50% of individuals die with the first rupture;**
☺ those who survive (due to **vasospasm**) typically improve & recover consciousness in minutes.

★ But in the early period after a subarachnoid H, there is a risk of **additional ischemic injury from vasospasm.**

▼**Without treatment, recurring bleeding is common in** survivors & prognosis worsens with each episode of bleeding.

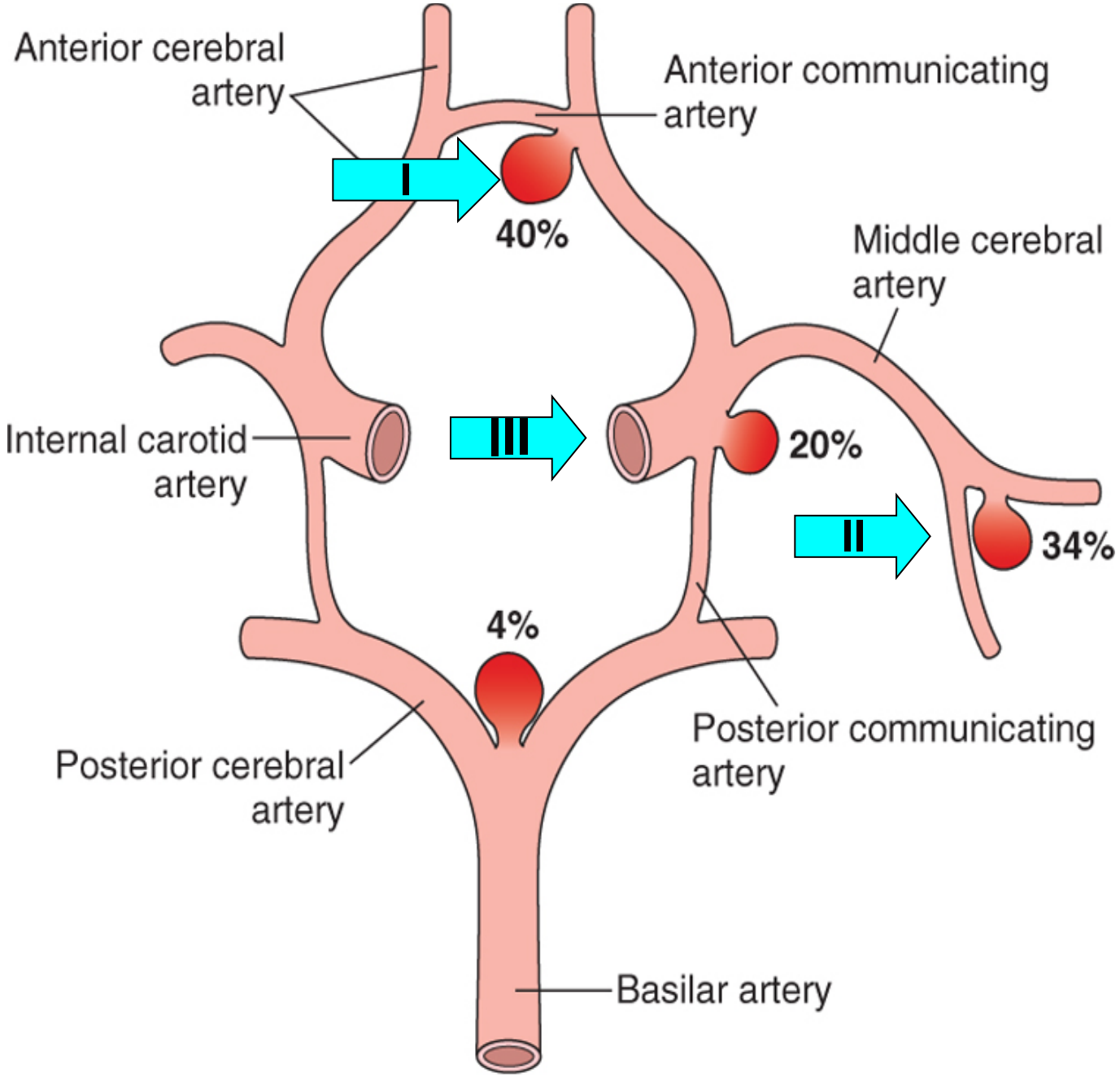
►90% of saccular aneurysms occur in the **anterior** circulation near major arterial branch points (F23-9); **multiple** aneurysms exist in **20% to 30% of cases**.

★ Although they are **sometimes referred to as *congenital,* they are not present at birth** but develop over time because of underlying defects in the arterial media.

★There is an ↑ **risk of aneurysms** (1) in individuals with **autosomal dominant polycystic kidney disease; & in** (2) in an association with disorders of ECM

★ The probability of rupture ↑ with the aneurysm size, aneurysms >1cm have a roughly 50% risk of bleeding per year.

☹ In the **healing phase** of subarachnoid H, **meningeal fibrosis & scarring** occur, sometimes leading to **obstruction of CSF** flow as well as **interruption of the normal pathways of CSF resorption.**



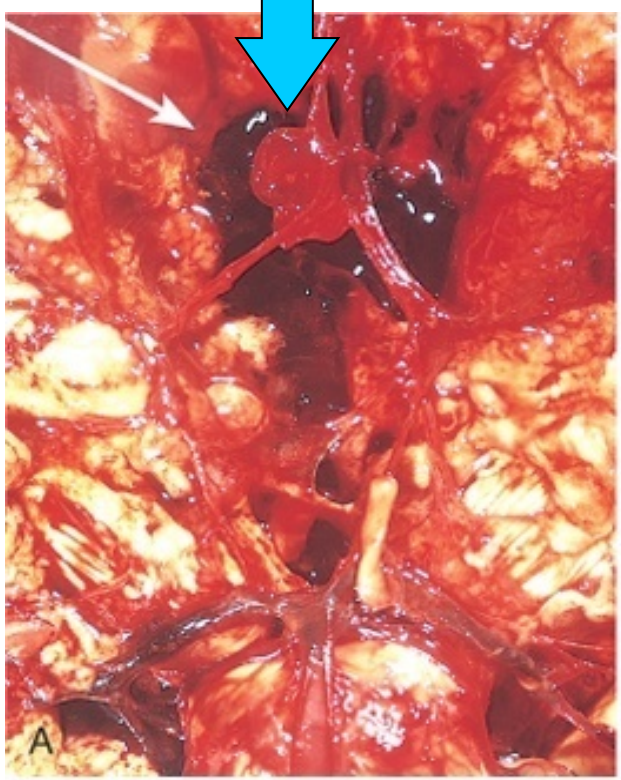
F23-9: Relative frequency of common **sites of saccular (Berry) aneurysms** in the circle of Willis.

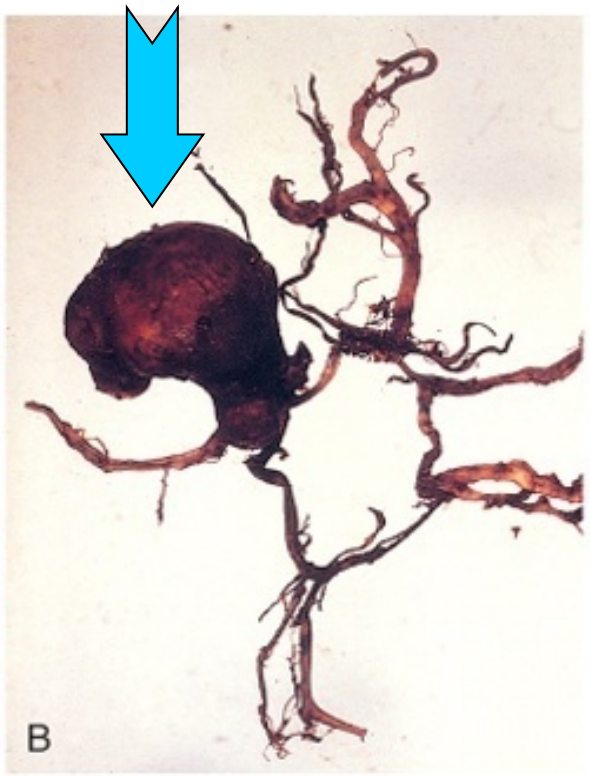
►**GROSSLY,** ★ Berry saccular aneurysm is a thin-walled outpouching of an artery. At the neck of the aneurysm, the muscular wall & intimal elastic lamina stop short & are absent from the aneurysm sac itself and the **sac is made up of thickened hyalinized intima**. The adventitia covering the sac is continuous with that of the parent artery (F23-10).
☹ **Rupture usually occurs at the apex** of the sac with extravasation of blood (mostly) into the **subarachnoid space**, or, less commonly in the substance of the **brain, or in both**.

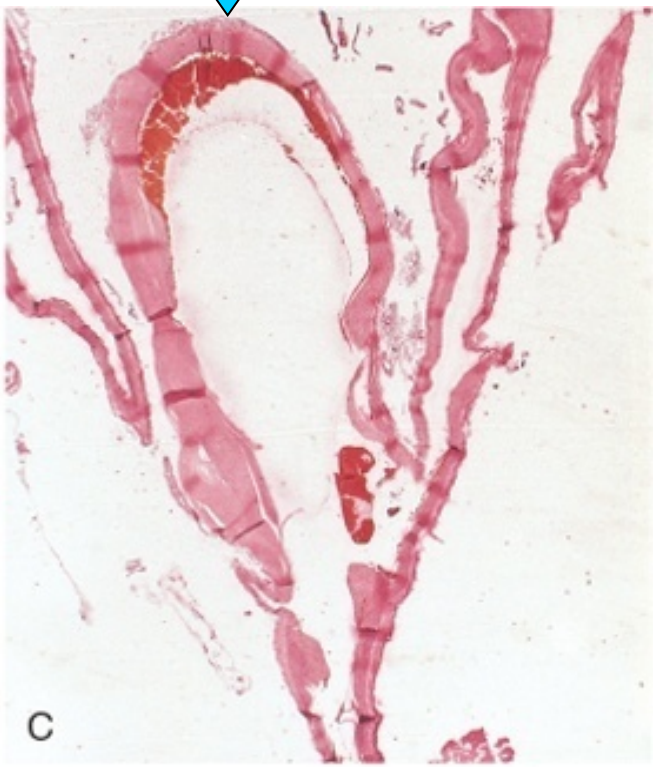
➔ **Berry saccular aneurysms are the most common type of intracranial aneurysm**, in addition,

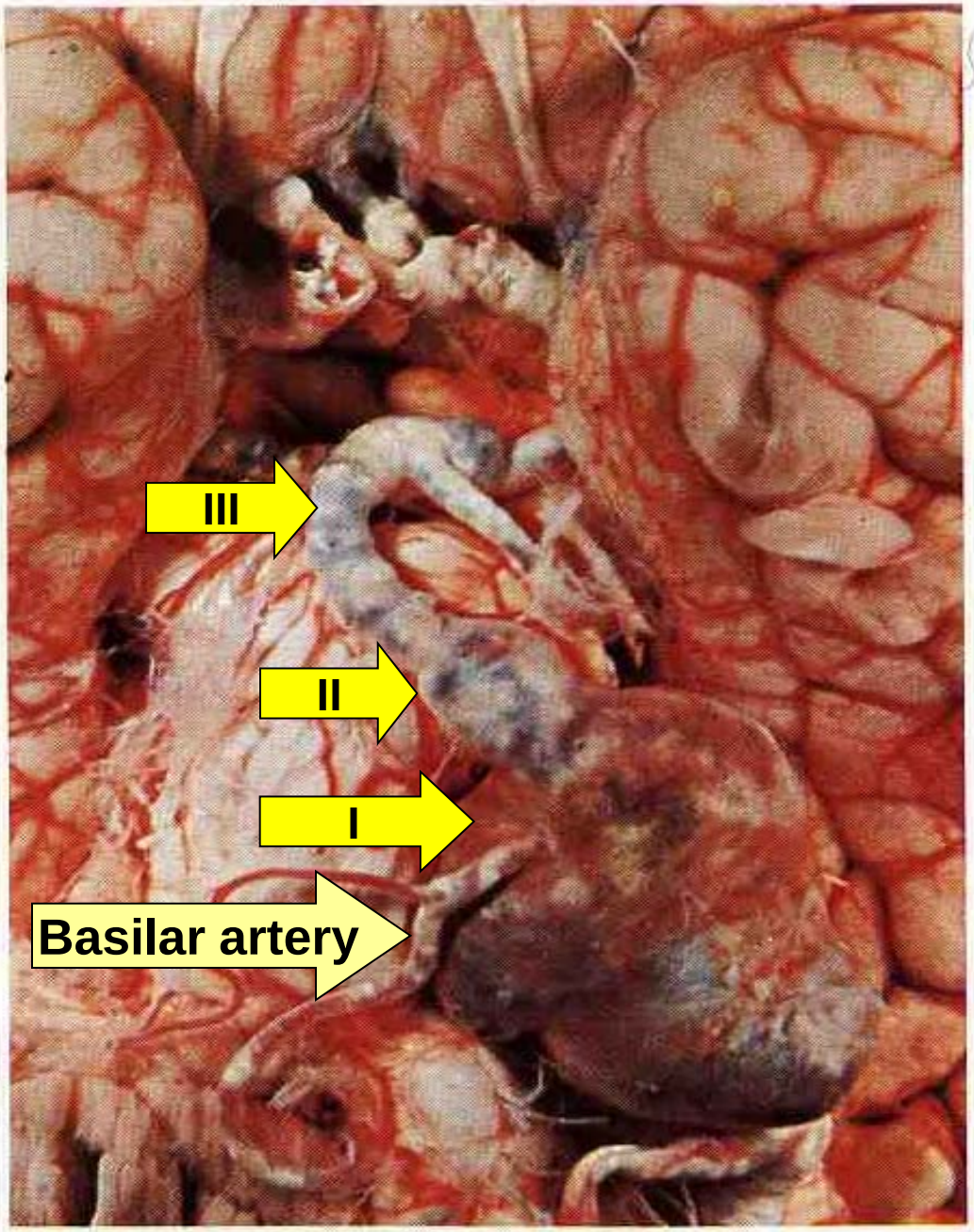
➧ Less commonly, other types of intracranial aneurysms, include **atherosclerotic** (fusiform, mostly of the basilar artery, **F 9.39**); & **Mycotic, Traumatic, & Dissecting aneurysms,** the latter 3, as with saccular aneurysms, are most often found in the **anterior** circulation.
☹ The 4 aneurysms usually **present with cerebral infarction from vascular occlusion** instead of subarachnoid H.

F23-10: **Berry saccular aneurysms**.
A, View of the base of the brain, dissected to show the circle of Willis with an aneurysm of the anterior cerebral artery (arrow).
B, Dissected circle of Willis to show the large aneurysm.
C, Section through a saccular aneurysm showing the hyalinized fibrous vessel wall (H&E).









9.39 Aneurysm: basilar artery

F 9.39: Atherosclerotic aneurysm of basilar artery.

Large, bluish –black, part- **(I)** saccular & **(II)** fusiform part of the 1st part of the artery; **(III)** Above the site of aneurysm, the basilar artery is dilated with scattered atheromatous plaques seen.

Vascular Malformations

Vascular malformations of the brain are classified into 4 main types, based on the **nature** of the abnormal vessels:

(1) Arteriovenous malformations (AVM),

(2) ***Cavernous angiomas,***

(3) Capillary telangiectasias,

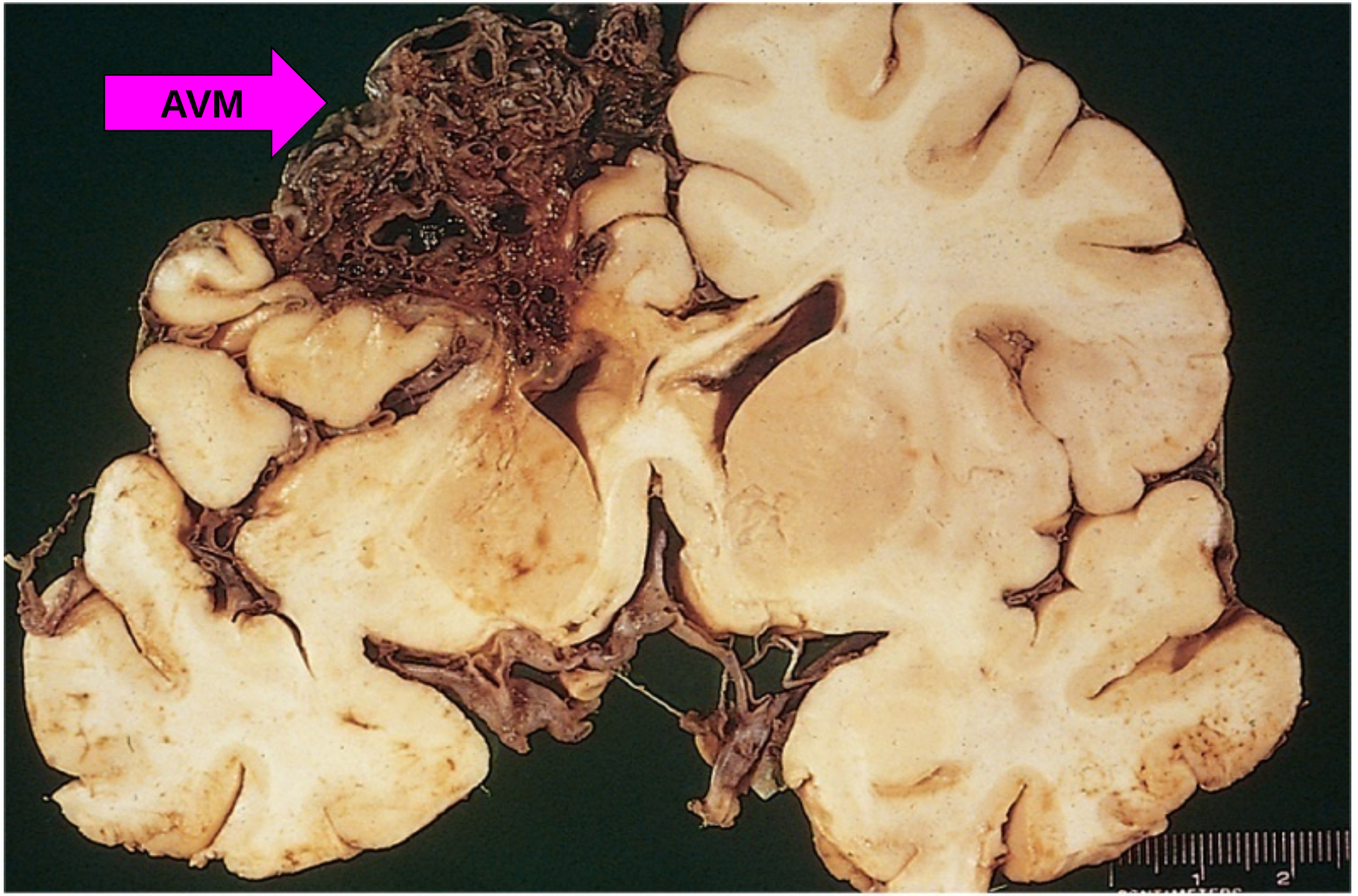
(4) Venous angiomas.

(1) Arteriovenous malformations (AVM), **the most common,** affect males twice as frequently as females; the lesion is most often recognized clinically between the ages of 10 & 30 years, **presenting** as a (1) **seizure** (epilepsy), Or (2) **H (intracerebral** or **subarachnoid, depending on their location).**

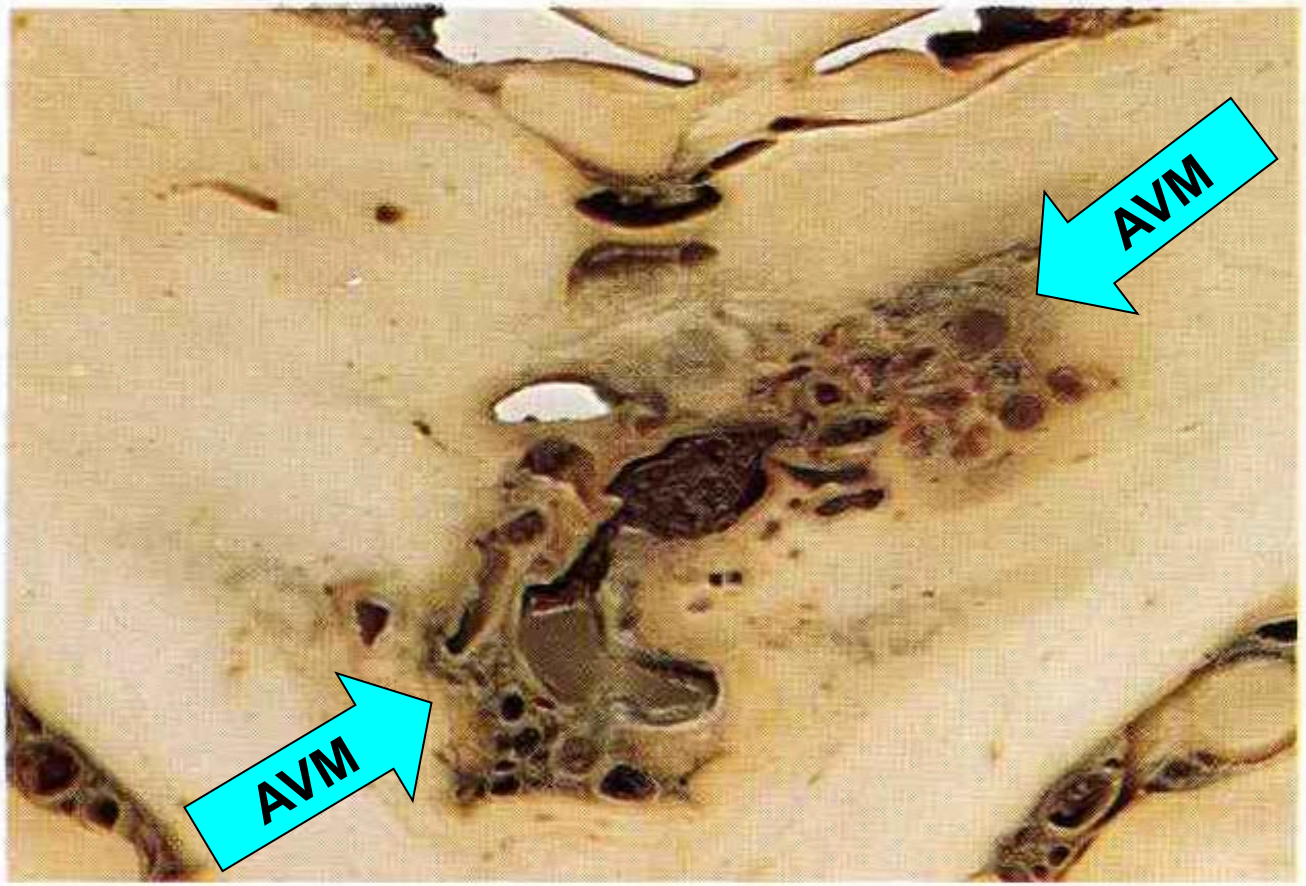
★Large AVMs occurring in the newborn period can lead to high-output congestive heart failure because of blood shunting directly from arteries to veins.

☠ The risk of bleeding makes AVM the **most dangerous** type of vascular malformation **(F23-11 & 9-35)** .

F23-11: **Arteriovenous malformation** in subarachnoid space.



F 9-35: **Arteriovenous malformation (hamartoma) : brain.** A large complex intracerebral AVM is present within the thalamus & basal ganglia. The greyish-white vessels are thick-walled & many are thrombosed. The adjacent brain contains much brown hemosiderin pigment as a result of previous hemorrhages.



9.35 Arteriovenous hamartoma: brain

►**GROSSLY,** the **AVMs** resemble a tangled **network of wormlike vascular channels** involve vessels either in the **(I) subarachnoid space (F23-11) extending into brain parenchyma** or they may occur **(II) exclusively within the brain (F9-35).**

◘ H, they are enlarged BV **separated by gliotic tissue**, often with evidence of previous H. Some BVs can be recognized as **arteries with duplicated & fragmented internal elastic lamina**, while others show marked thickening or partial replacement of the media by hyalinized connective tissue.

(2) Cavernous hemangiomas consist of aggregates of distended, loosely organized vascular channels with thin collagenized walls; **devoid of intervening nervous tissue** (thus distinguishing them from capillary telangiectasias).

They occur most often in the **cerebellum, pons, & subcortical regions**.

Old foci of **H** , infarction, & calcification frequently surround the abnormal lesion.

(3) Capillary telangiectasias (◘ 4.40) are microscopic foci of dilated, thin-walled vascular channels **separated** by relatively **normal brain** parenchyma & occurring mostly in the **pons.**
(4) Venous angiomas (varices) consist of aggregates of ectatic (dilated) venous channels (F 9-34).
Lesions 3 & 4 are unlikely to bleed or cause symptoms, & are most commonly discovered **incidentally.**

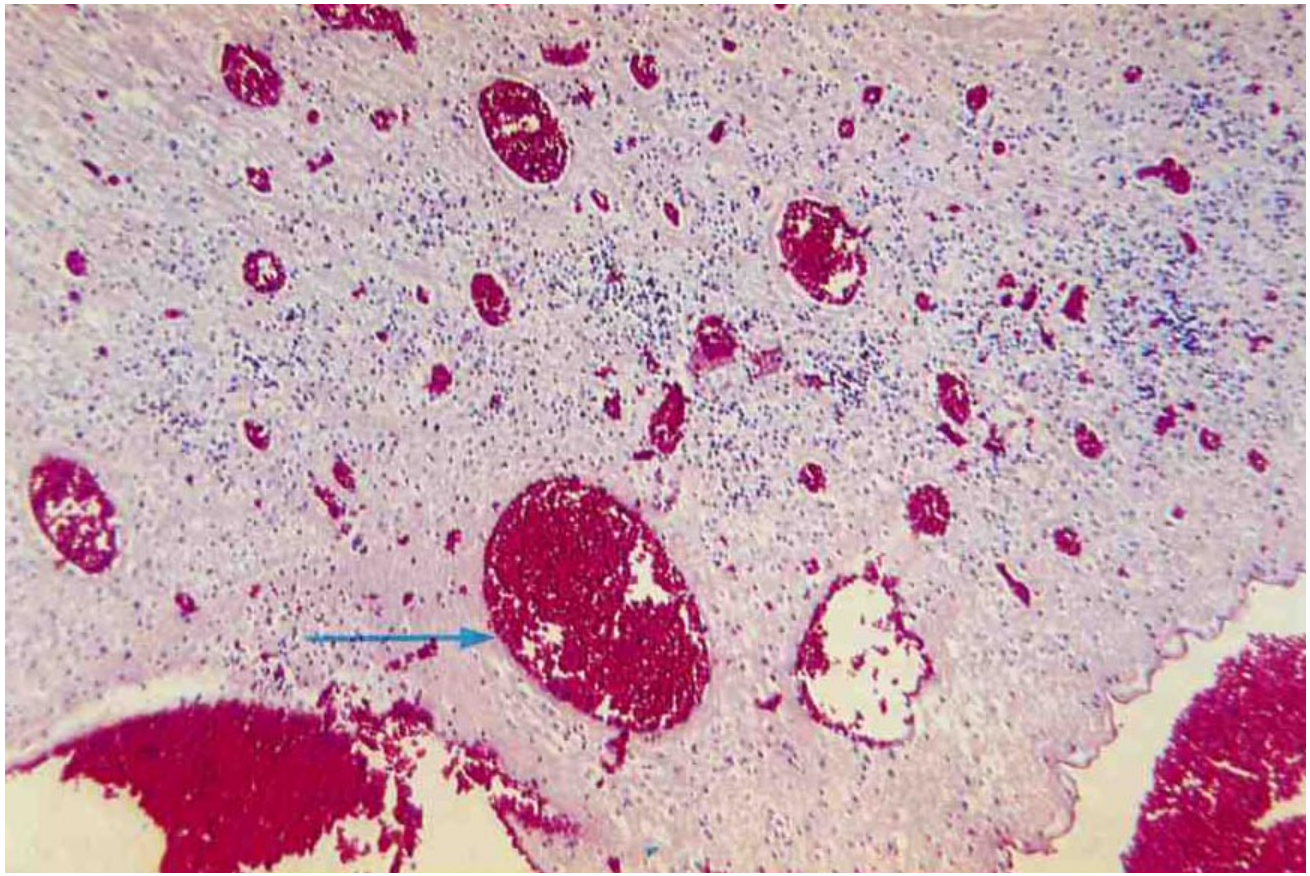
Hypertensive cerebrovascular disease

Over the past few decades there has been a 🡻 threshold for ☺ treatment of hypertension & more extensive screening for early disease, both of which have contributed to an overall 🡻 in the incidence of these complications.
Nevertheless, hypertension continues to be important, due to **poor patient compliance or inadequate access to health care.**

►Hypertension affects the deep penetrating arteries & arterioles that supply the basal ganglia & hemispheric white matter & the brain stem.

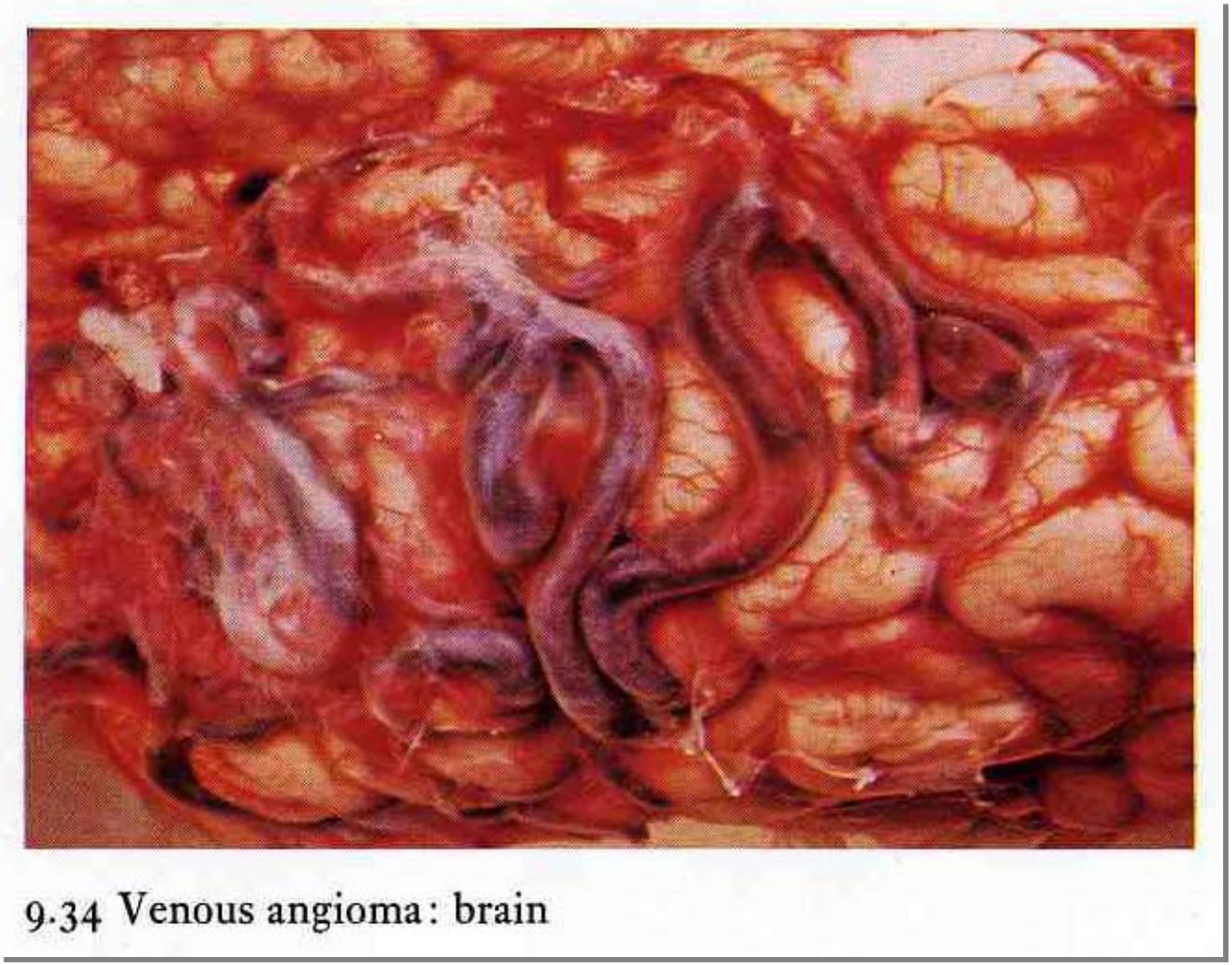
☹4 Most important **effects of hypertension** on the brain are:

◘ 4.40: **Capillary telangiectasia: Brain X 80.** A solitary lesion, consists of **abnormally dilated capillaries**, each with a very thin wall (arrow), surrounded by thin layer of eosinophilic hyaline amorphous material. The capillaries are **separated by neural tissue & not by fibromuscular tissue (compare** with those seen in an ordinary capillary/ cavernous hemangiomas). Complete resection of this lesion may be difficult or, impossible.



F 9-34: **Venous angioma: brain,** forming a complex tangle of dilated & thrombosed veins within the leptomeninges (arachnoid & pia mater) over the left parietal lobe. ☺ **This rare lesion is** unlikely to bleed or cause symptoms

& is most commonly discovered **incidentally.**



9.34 Venous angioma: brain

(1) ***Massive*** *hypertensive intracerebral H (2)* ***Lacunar*** *infarcts (3)* ***Slit*** *H (4)* ***Hypertensive encephalopathy***

(1) ***Massive*** *hypertensive intracerebral H (see above),* in which chronic hypertension is associated with the development of minute ***Charcot-Bouchard microaneurysms*** in vessels that are less than 300 μm in ∅, these aneurysms can rupture, resulting in **Spontaneous** intraparenchymal **H.**

(2) Hyaline arteriolar sclerosis , in which **arterioles** become weaker than normal & are more vulnerable to rupture; the important clinical & pathologic outcome of which is the development of ***lacunes*** **or** ***lacunar infarcts***. These small cavitary infarcts are <15 mm, are found **most commonly in deep gray matter (basal ganglia & thalamus); internal capsule, deep white matter, & pons**, & they consist of tissue loss ***cavities***, with scattered lipid-laden macrophages & surrounding gliosis.

Depending on their location in the CNS, lacunes can either be **clinically silent** or cause **significant neurologic impairment.**

(3) Hypertension also gives rise to rupture of the small-caliber penetrating vessels & the development of small H. In time, these H resorb, leaving behind a slitlike cavity **(*slit hemorrhage*)** surrounded by brownish discoloration.

(4) Acute hypertensive encephalopathy is a clinicopathologic syndrome characterized by **diffuse cerebral dysfunction**, **including headaches, confusion, vomiting, & convulsions, sometimes leading to coma.**

➔Rapid intervention to reduce the accompanying ↑ intracranial pressure is required, since the syndrome **does not usually remit spontaneously.**

☠ Postmortem examination of fatal cases show an **edematous brain**, with/or without **transtentorial or tonsillar herniation.**
◘ H, Fibrinoid necrosis of arterioles & petechiae (of malignant hypertension) may be seen microscopically in the gray & white matter.

Vasculitis

►A variety of inflammatory processes that involve BV may lead to luminal narrowing & cerebral infarcts.

Infectious arteritis of small & large BV was **previously** seen in association with **syphilis & tuberculosis**, but now more commonly occurs in the setting of immunosuppression & opportunistic infection (such as toxoplasmosis, aspergillosis, & CMV encephalitis).

★ Some of the systemic forms of vasculitis, such as **polyarteritis nodosa (PAN),** may involve cerebral BV & cause single or multiple **infarcts** throughout the brain.

★***Primary angiitis of the CNS*** is an inflammatory disorder that involves multiple, small to medium-sized parenchymal & subarachnoid vessels, & is characterized by **chronic inflammation, multinucleated giant cells (with or without granuloma formation)**, & destruction of the BV wall.

Affected individuals manifest a diffuse encephalopathic clinical picture, often with cognitive dysfunction; improvement occurs with steroid & immunosuppressive treatment.

CENTRAL NERVOUS SYSTEM (CNS) TRAUMA

★Trauma to the brain & spinal cord is a significant cause of death & disability. Site & Severity of injury affect the outcome: **Injury** of several cubic centimeters, of brain, **(1)** in the frontal lobe parenchyma may be **clinically silent , or (2) severely disabling** (spinal cord), or **(3) ☠ fatal** (involving the brain stem)

★Magnitude & distribution of traumatic brain lesions depend on the **shape** of the object causing the trauma, the **force** of impact, & whether the head is **in motion at the time of injury**.

★**A blow to the head** may cause: (1) ***penetrating open injury,*** **or (2)** ***blunt closed injury***.

☹ From **medico-legal point of view**, severe brain damage can occur in the absence of external signs of head injury, &

☺ **Conversely,** severe scalp lacerations & even skull fractures do not necessarily indicate damage to the underlying brain.

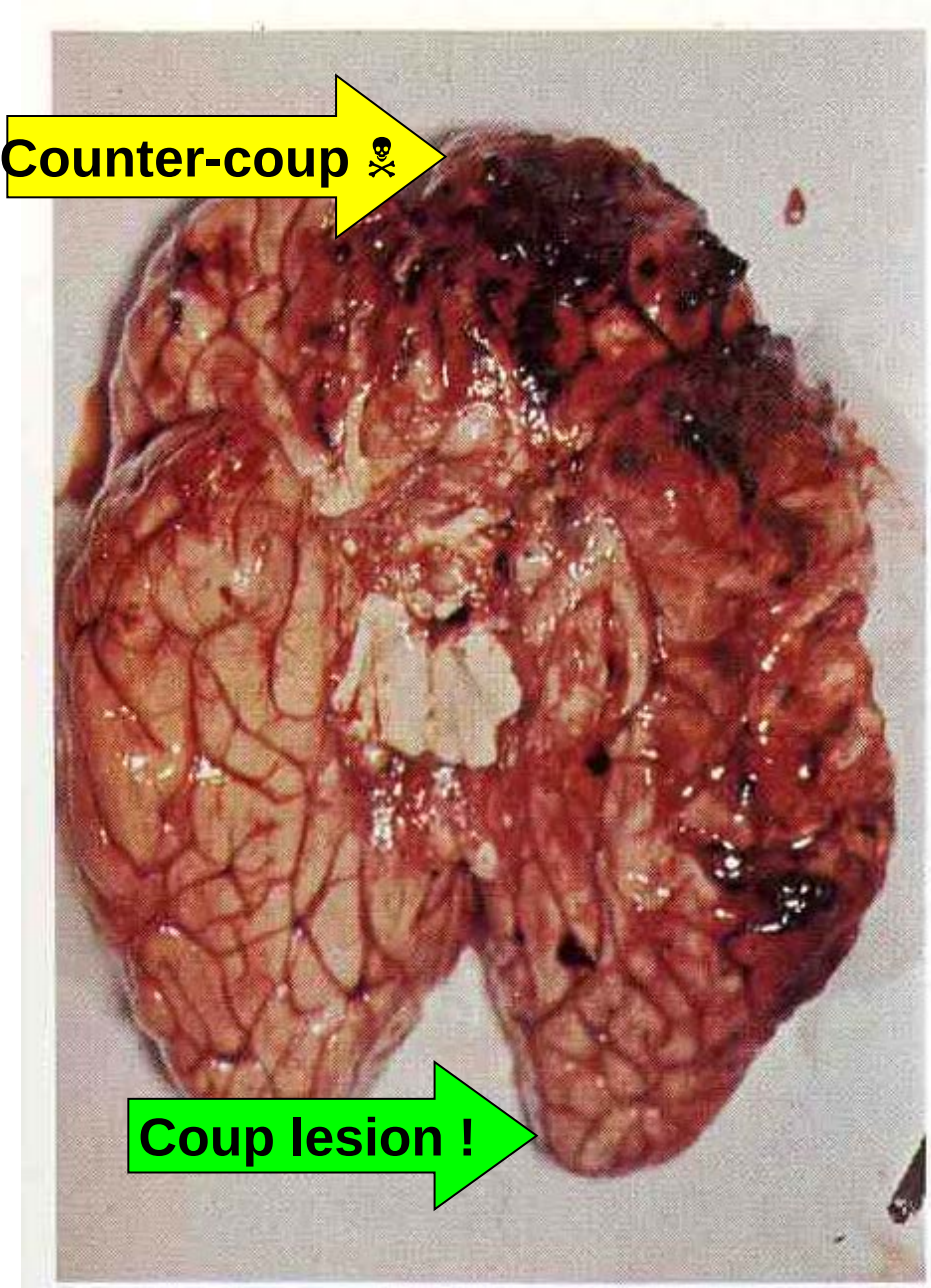
☹ Trauma can cause (1) **fractures(Basal, Depressed, Linear)** of skull, or of the spine, (2) **parenchymal & (3) vascular injuries**; ***combinations*** are common.

Traumatic Parenchymal Injuries

▼ When there is impact of an object with the head, injury may occur from collision of the *brain* with the *skull* (I) at the site of impact (a ***coup*** injury, e.g., at frontal pole) or (II) on the opposite side {***contrecoup, at the occipital area in the above case of (I)}*****,** Both coup & contrecoup lesions are… (F 9-19)
☹ **Contusions,** caused by rapid tissue displacement with **disruption of BVs**, & subsequent **H**, **tissue injury**, & **edema**.

★Since they are the points of impact, **crests of gyri are most susceptible**, whereas cerebral cortex along the sulci is less vulnerable. The **most common locations** where contusions occur correspond to the most frequent sites of (I) **direct impact** & to (II) **regions of the brain that overlie a rough & irregular inner skull surface**, including, (A) orbital gyri of frontal lobes & (B) temporal lobes (F23-12).

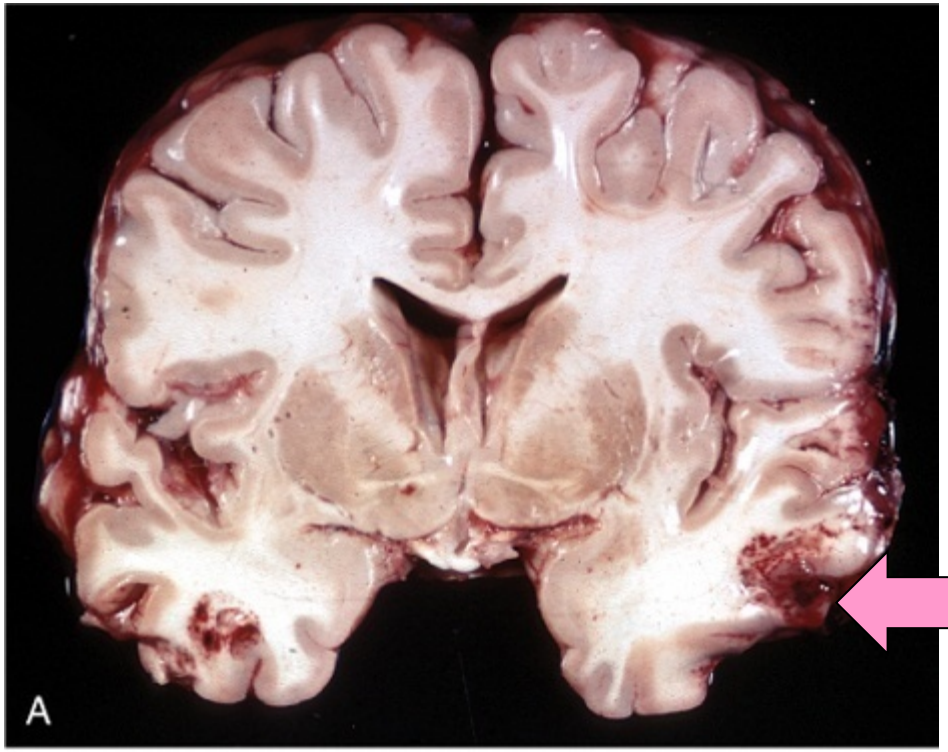
▼**Penetration of the brain**, either by a (1) projectile, e.g., **bullet** or (2) a skull bone **fragment from a fracture**, results in **laceration**, with tissue **tearing**, vascular disruption, hemorrhage, & **injury, along a linear path [focal lesion].**

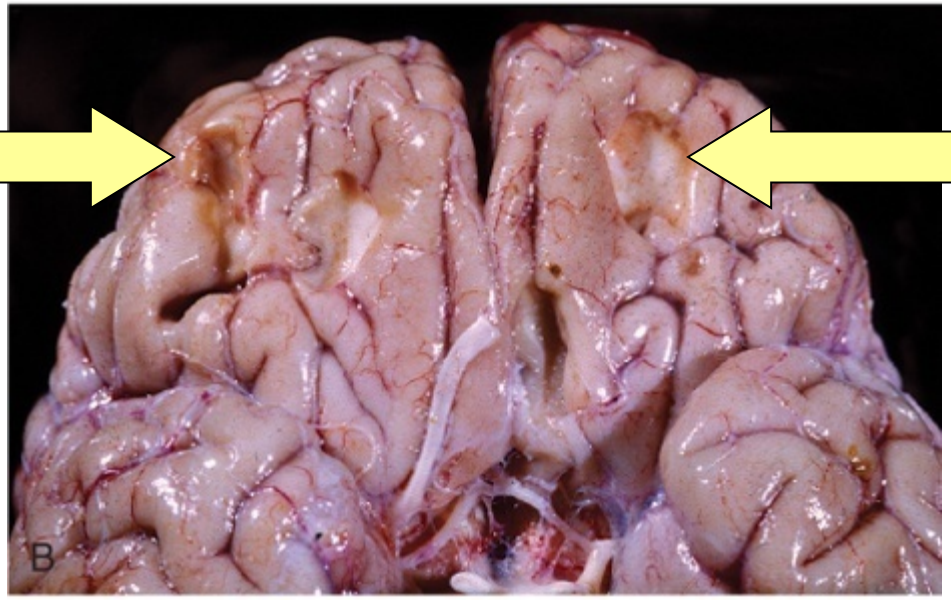


9.19 Contusions: brain

F 9-19: **Contusions: brain.**

★This patient sustained severe **trauma to the left occipital region of the head** which has caused extensive fronto-temporal (Counter-coup) contusions & lacerations of the brain (at top center & bottom right).
😐 In this case, the counter-coup lesion is **much more extensive than the coup lesion** which are at the point of impact (occipital area)





F23-12: **Cerebral trauma. A, Acute contusions** with areas of hemorrhage & tissue disruption, present in both temporal lobes,

B, Old contusions are present on the inferior, (orbital gyri) of frontal lobes surfaces of this brain.

►**GROSSLY,** ★contusions, when seen on cross-section, are ►**wedge shaped,** with the broad base ▼ spanning the surface & centered on the point (impact). The histologic appearance of contusions is independent of the type of trauma (F23-12A) .

★In the earliest stages there is **edema & hemorrhage**, with **blood extravasates** throughout the damaged tissue, **across the width of the cerebral cortex, & into the white matter & subarachnoid spaces**.

☼ Although **functional effects are seen earlier**, the…
◙ H, the neuronal cell necrotic changes of injury (***red neurons)*** **takes about 24 hours to appear,** followed by the usual course of inflammatory response, with neutrophils followed by macrophages.

☹ **In contrast to ischemic lesions,** in which the superficial layer of cortex may be preserved, ► **trauma affects the superficial layers most severely ▼.**

★**Grossly, old traumatic lesions** have a characteristic depressed, retracted, yellowish brown patches involving the crests of gyri (Fig. 23-12B).

More extensive H regions of brain trauma give rise to **larger cavitated lesions**. In sites of old contusions, there are ➔ gliosis + predominate residual hemosiderin laden macrophages

☺***Concussion***

☺***Concussion*** **is Reversible loss of consciousness from head injury, in the absence of contusion.**

☺ The characteristic transient neurologic dysfunction includes loss of consciousness + temporary respiratory arrest + loss of reflexes. Although neurologic recovery is complete, **amnesia** for the event persists.

😐 **?** The **pathogenesis** of ***Concussion*** *with* the sudden disruption of nervous activity is **unknown.**

☠ Diffuse axonal injury

★ Although injury to the surface of the brain is often the most ★ dramatic, however, widespread injury to axons within the brain (called ***diffuse axonal injury***) can be even **more devastating**
✱The movement of one region of brain relative to another lead to the disruption of axonal integrity & function.
➔ **Angular acceleration alone, in the absence of impact, may cause axonal injury as well as H.**

★ 50% of patients who develop coma shortly after trauma, ★ even without cerebral contusions, are believed to have white matter damage & diffuse axonal injury. Although these changes may be widespread, **lesions are most commonly** found near the **angles of the lateral ventricles & in the brain stem.**

Diffuse axonal injury characterized by the **wide, but often, ★ asymmetric distribution of axonal swellings (spheroids) that appears within hours of the injury** & may persist for much longer. These are best demonstrated with silver stains or by immunohistochemistry for proteins within axons.

Traumatic Vascular Injury

★Vascular injury is a frequent component of CNS trauma & results from direct trauma & disruption of the BV wall, leading to H. Depending on which BV rupture, H may occur in any of several compartments (sometimes in combination): *epidural, subdural, subarachnoid, & intraparenchymal* (F23-13A).

★ Subarachnoid & intraparenchymal H most often occur at sites of contusions & lacerations.

Epidural (extra-dural) H

☼ The dura is normally fused with the skull periosteum. **BV that run in the dura**, most importantly the **middle meningeal artery**, are vulnerable to injury, particularly with skull **fractures**.

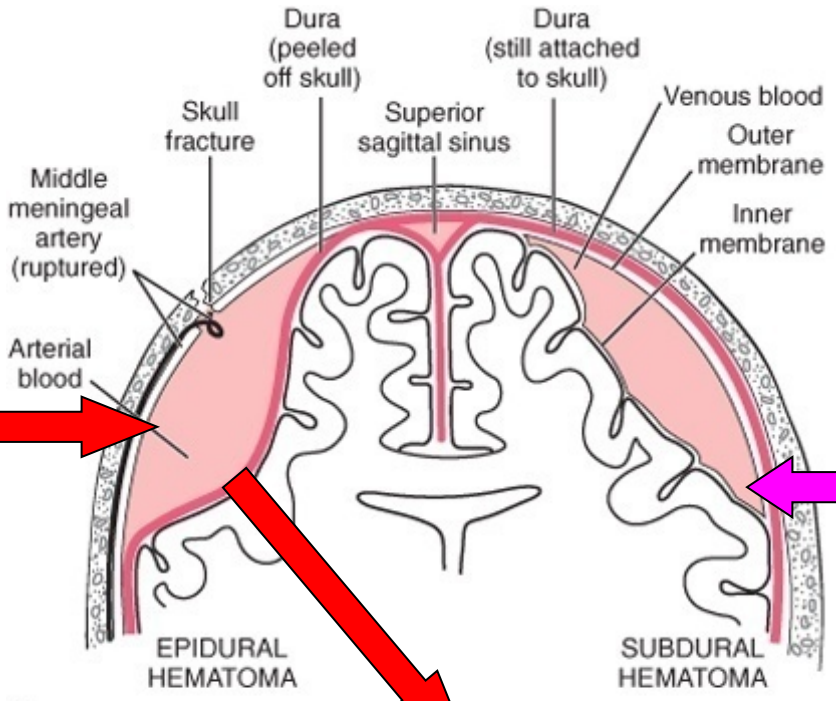
☹ In children, in whom the skull is deformable, a temporary displacement of the skull bones may **tear a BV in the absence of a skull fracture**.

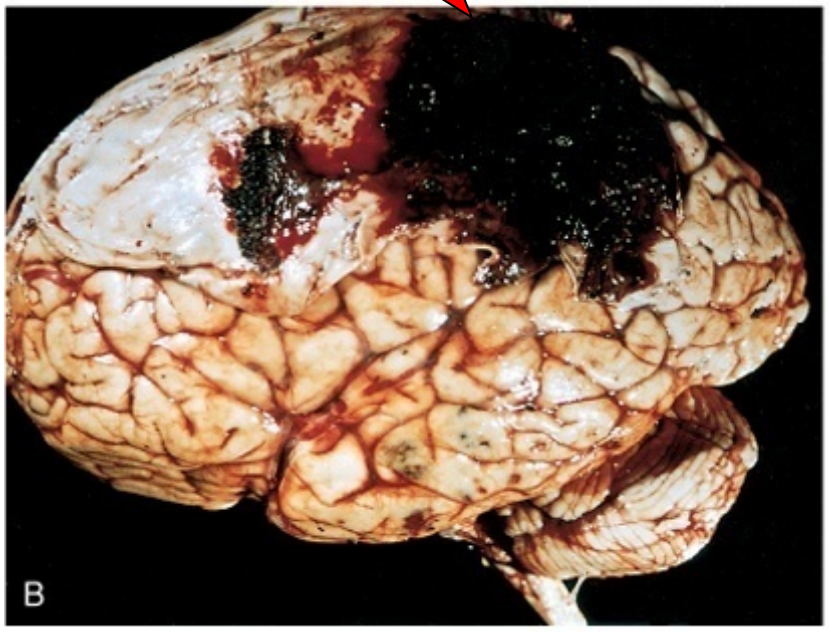
★ Once torn, the accumulation of **arterial** blood under **arterial pressure** cause separation of the dura from the inner surface of the skull (F23-13B). The expanding hematoma has a smooth inner contour that compresses the brain surface.

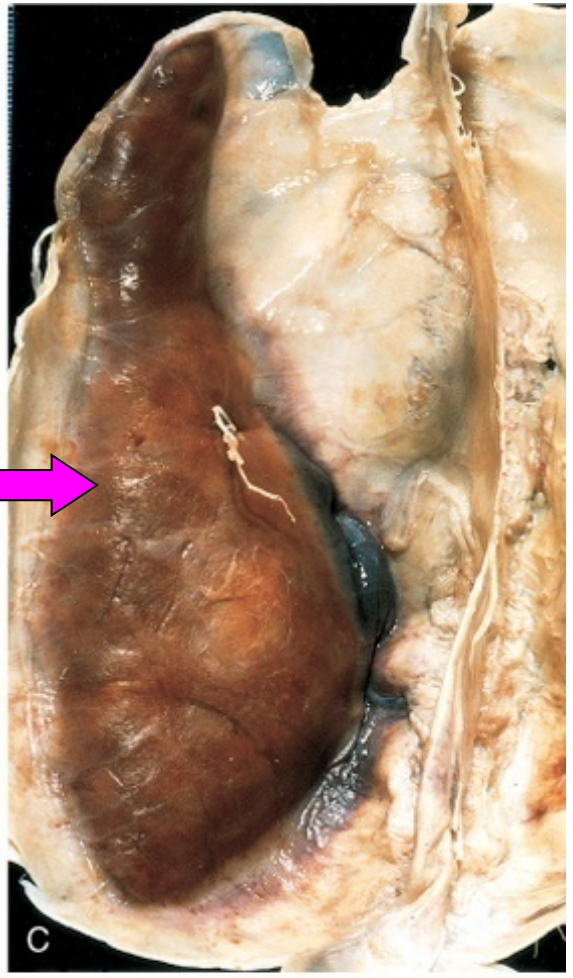
F23-13: Traumatic intracranial hemorrhages

A, Epidural hematoma Rupture of a middle meningeal artery, usually following skull fracture, leads to accumulation of arterial blood between the dura & the skull.

B, Epidural hematoma covering a portion of the dura.







C, Large organizing **subdural hematoma** attached to the dura

★***Clinically,*** *patients can be* ***lucid*** *for several* ***hours*** *between the moment of trauma & the development of neurologic signs.*
The arterial epidural H may expand rapidly & …
is a ☠ neurosurgical emergency requiring prompt drainage, (usually through Burr hole).

Subdural Hemorrhage

★The rapid movement of the brain that occurs in trauma can **tear the bridging veins,** majority of which **extend from the ➔ cerebral hemispheres through the ➔ subarachnoid & subdural space ➔ to empty into superior sagittal dural sinuses.** These veins are particularly **prone to tearing**, & their rupture leads to H into the subdural space, most lesions begin in the parasagittal region

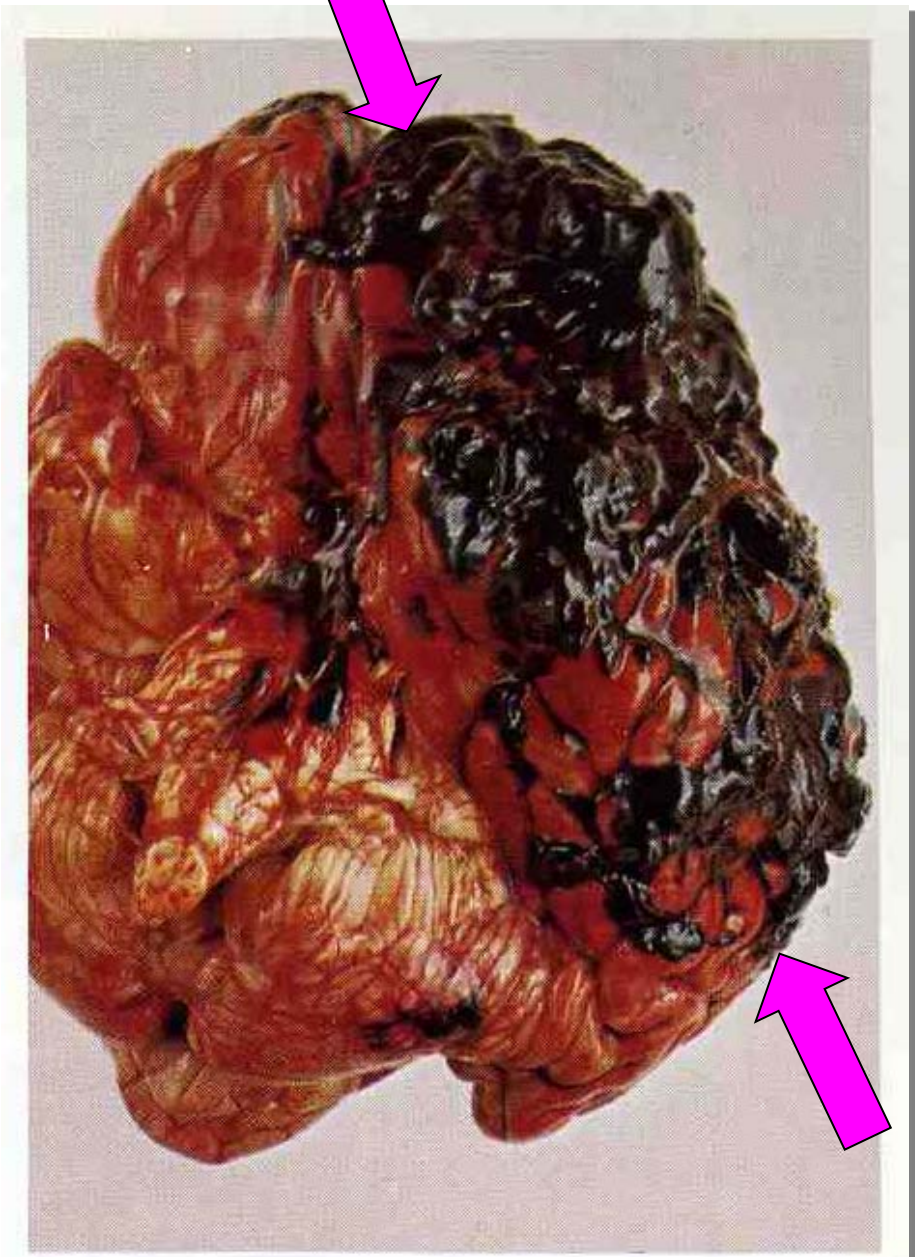
☹ In **elderly patients,** with brain atrophy, the bridging veins are stretched out & the brain has additional space for movement, accounting for the higher rate of subdural H in **elderly** patients, even after relatively **minor head trauma**.

☹ **Infants** are also susceptible to subdural H, because **their bridging veins are thin-walled.**

►Subdural H **most** often become **manifest within the first 48 hours after injury.** They are most common over the lateral aspects of the cerebral hemispheres & are bilateral in about 10% of cases. (I) **Focal neurologic signs** are attributable to the pressure exerted on the adjacent brain, but (II) often the clinical manifestations are **nonlocalizing** & include headache or confusion. ☹ In time there may be slowly progressive neurologic deterioration, **rarely** with acute decompensation.

►**Grossly**, the acute subdural H appears as a **collection of freshly clotted blood apposed along the contour of the brain** surface, without extension into the depths of sulci (F23-13C & 9- 21). The underlying **brain is flattened.**

➔ Subdural H is **venous bleeding**, & is self-limited; breakdown & organization of the H take place over time:
(1) by lysis of the RBC (in about 1 week),
(2) growth of fibroblasts from the dural surface into the H (in 2 weeks), & (3) early development of hyalinized connective tissue (in1-3 months), which is ***attached to the inner surface of the dura*** & is not adherent to the underlying arachnoid.



9.21 Subdural haemorrhage (subdural haematoma): brain

F 9-21: **Subdural hemorrhage (hematoma): brain.**

☠ A massive subdural hemorrhage over the left **fronto, temporo, parietal** regions extends over the inferior surface of the hemisphere.

★ **Most** subdural hemorrhages follow **blunt** injury to the skull ; & in the elderly they may occur without a history of direct injury to the head.

But in this case, the cause was an ☠ **extensive fracture of the skull.**

►Subdural hematomas commonly rebleed (**chronic subdural hematomas**), presumably from the thin-walled vessels of the granulation tissue.

▲The treatment of subdural hematomas is to remove the organized blood & associated organizing tissue.

INFECTIONS OF THE CNS

★The brain & its coverings can be affected by many infectious agents, some have a **relative or absolute predilection for the nervous system** (e.g., **rabies)**, **others can affect many other organs** as well as the brain (e.g., *Staphylococcus aureus*).

★ Damage of the infectious agents to nervous tissue may be the consequence of:
(1) Direct injury by the **infectious agent** to neurons or glia, or
(2) Indirectly, through the **microbial toxins**, or through the
(3) Destructive effects of the inflammatory response, or the
(4) Influence of immune-mediated mechanisms.

➔The **4 Routes** of entry of infectious agent to the CNS are:

(1) Arterial blood spread is the most common route of entry. **Retrograde venous** spread through the anastomoses between **veins of the face** & the venous sinuses of the skull, can occur.

(2) Post-traumatic direct implantation of microorganisms through introduction of foreign material.
☹ In rare cases, it can be **iatrogenic**, as when microbes are introduced with a lumbar puncture needle.

(3) Local extension from an established infection in the skull or the spine. The infection may originate from:
(1) **air sinus**, mostly **mastoid or frontal;** (2) **infected tooth**;
(3) congenital malformation, such as **meningomyelocele**
(4) **surgical site** in the cranium or spine causing **osteomyelitis (OM)** ⇨ bone erosion & spread of the infection into the CNS;

(4) Peripheral nerves can serve as the path of entry of a few pathogens, in particular viruses, e.g., **rabies & herpes zoster.**

Epidural (extradural) & Subdural Infections

Both can occur, usually through **direct local spread** to cause:
(I) **Epidural abscess**, commonly associated with **OM**, arises from an adjacent focus of infection, such as sinusitis or a surgical procedure (e.g., craniotomy).

Spinal epidural abscess may cause spinal cord compression, which is an important **neurosurgical emergency**.

(II) **Subdural abscess**, which can produce **mass effect**.
😐 The underlying arachnoid & subarachnoid spaces are usually unaffected.

☹ **Thrombophlebitis may develop in the bridging veins** that cross the subdural space **abscess**, resulting in **venous occlusion & infarction of the brain.**

★ Symptoms include (1) those referable to the **source** of the infection. Most patients are (2) **febrile**, **with headache & neck stiffness**, & if untreated may develop (3) **focal** neurologic signs, lethargy, & coma.

☺ With prompt treatment {including surgical drainage}, complete recovery is usual.

Meningitis

★ ***Meningitis*** means inflammation of the leptomeninges (arachnoid & pia mater) & CSF within the subarachnoid space.

Spread of the infection from the meninges into the adjacent brain results in inflammation of both **(meningoencephalitis)**.

★ ***Infectious meningitis*** is broadly classified, on the basis of the characteristics of inflammatory exudate on CSF examination & the clinical evolution of the illness into: (1) ***acute pyogenic*** (usually bacterial), (2) ***aseptic*** **(usually viral**), & (3) ***chronic*** (usually TB, spirochetal, or cryptococcal).

Acute Pyogenic (Bacterial) Meningitis

There is a relationship between the age of the patient & the most common causative organisms:

★ In **neonates**, *Escherichia coli* & group B streptococci;

★ In **elderly**, *Strep. pneumoniae* & *Listeria monocytogenes;*

★ In **adolescents & in young adults**, *Neisseria meningitides* with occasional clusters of cases representing public health concerns.

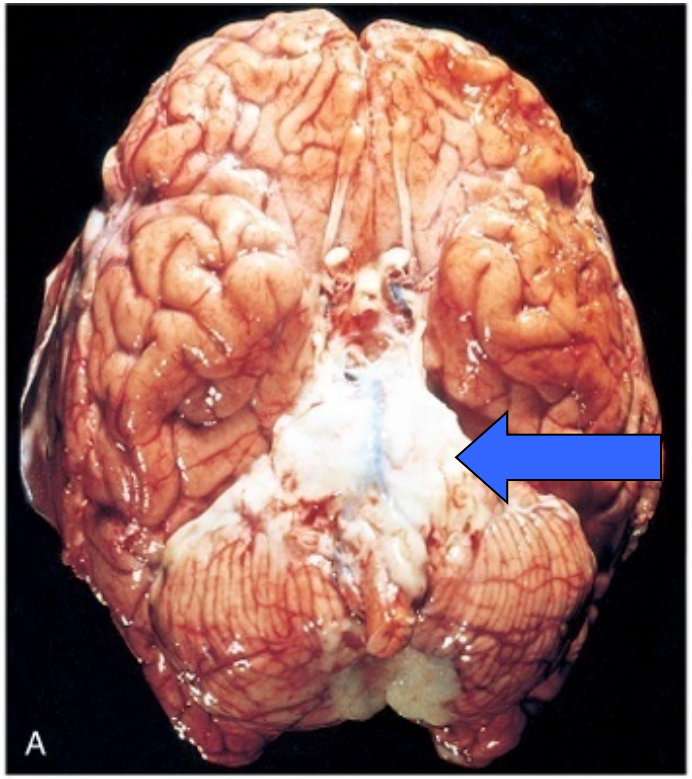
►All patients typically show (1) **systemic signs of infection** superimposed on clinical evidence of (2) **meningeal irritation** & neurologic impairment-including, headache, **neck stiffness**, photophobia, irritability, & clouding of consciousness.

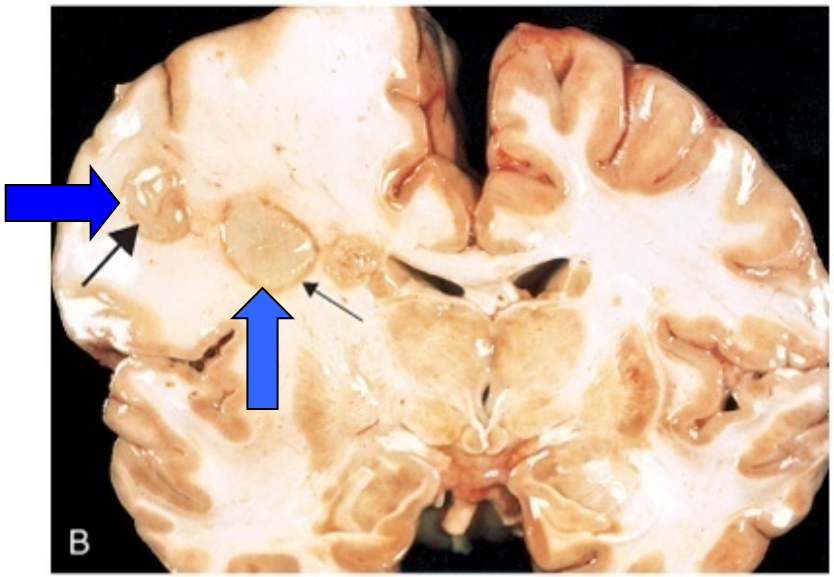
▼**CSF exam. is essential for diagnosis.** It reveals an: ↑ pressure +↑ neurophils +↑ protein & ↓ glucose. Bacteria may be seen on a smear or can be culture.

☠ If untreated, pyogenic meningitis can be **fatal;** but effective antimicrobial agents have markedly reduced the mortality.

►**Grossly,** in acute meningitis, there is an:
(1) **Pus** or fibrinous exudate within the subarachnoid space **covering the surface of the brain** (F23-16A &1-6 & 9-13).
(2) **Congested BVs**.

☹ When the meningitis is fulminant, the inflammatory cells infiltrate the walls of the leptomeningeal veins & **may spread** into the substance of the brain **(focal cerebritis),** or the inflammation may extend to the **ventricles, producing ventriculitis**.





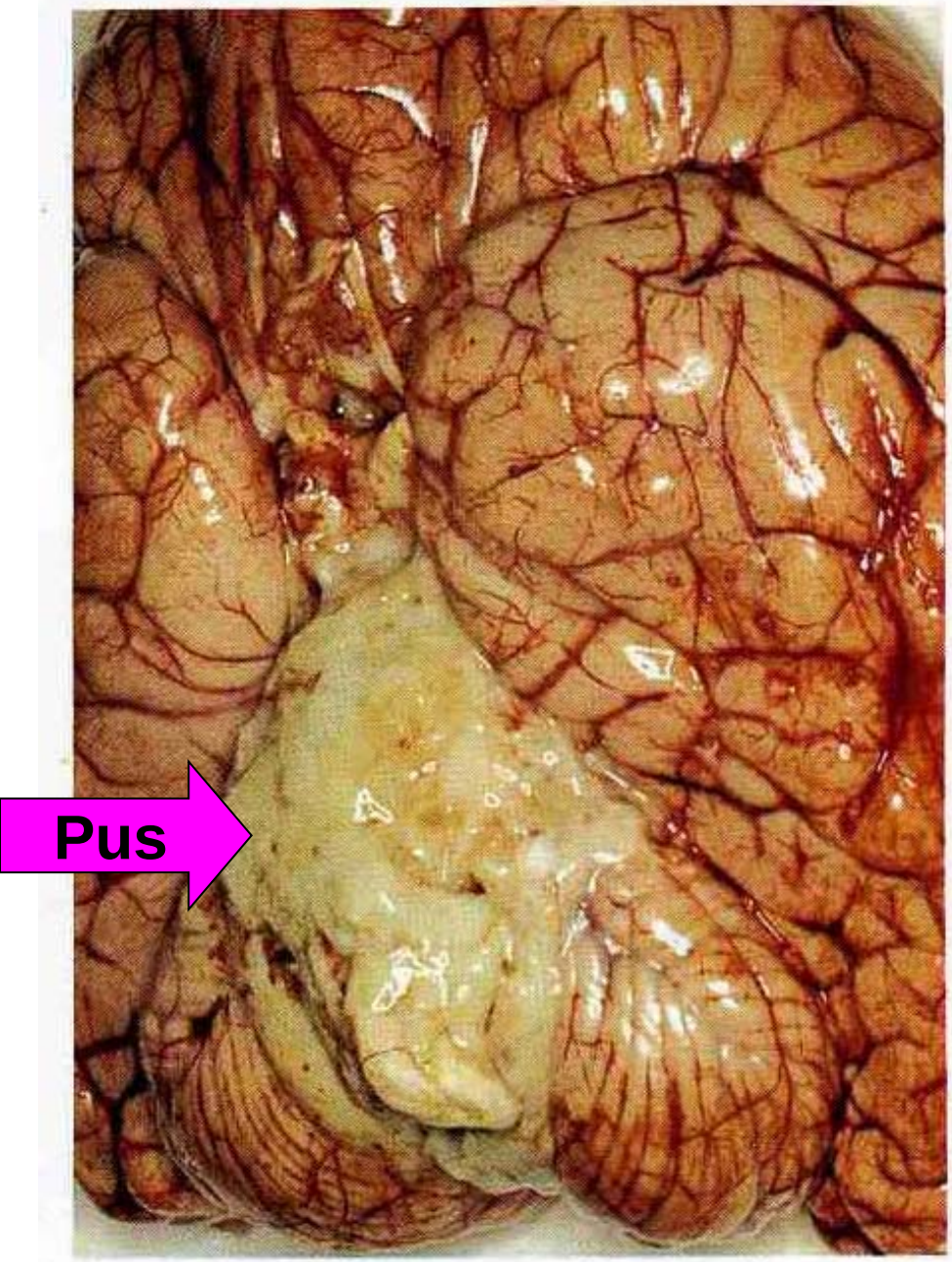
F23-16: **CNS Bacterial infections.**

A, Pyogenic meningitis.

☹ A thick layer of white pus covers the brain stem & cerebellum.

B, Two cerebral abscesses in the frontal white matter (arrows) .

Q: What is the possible route of infection in this case?

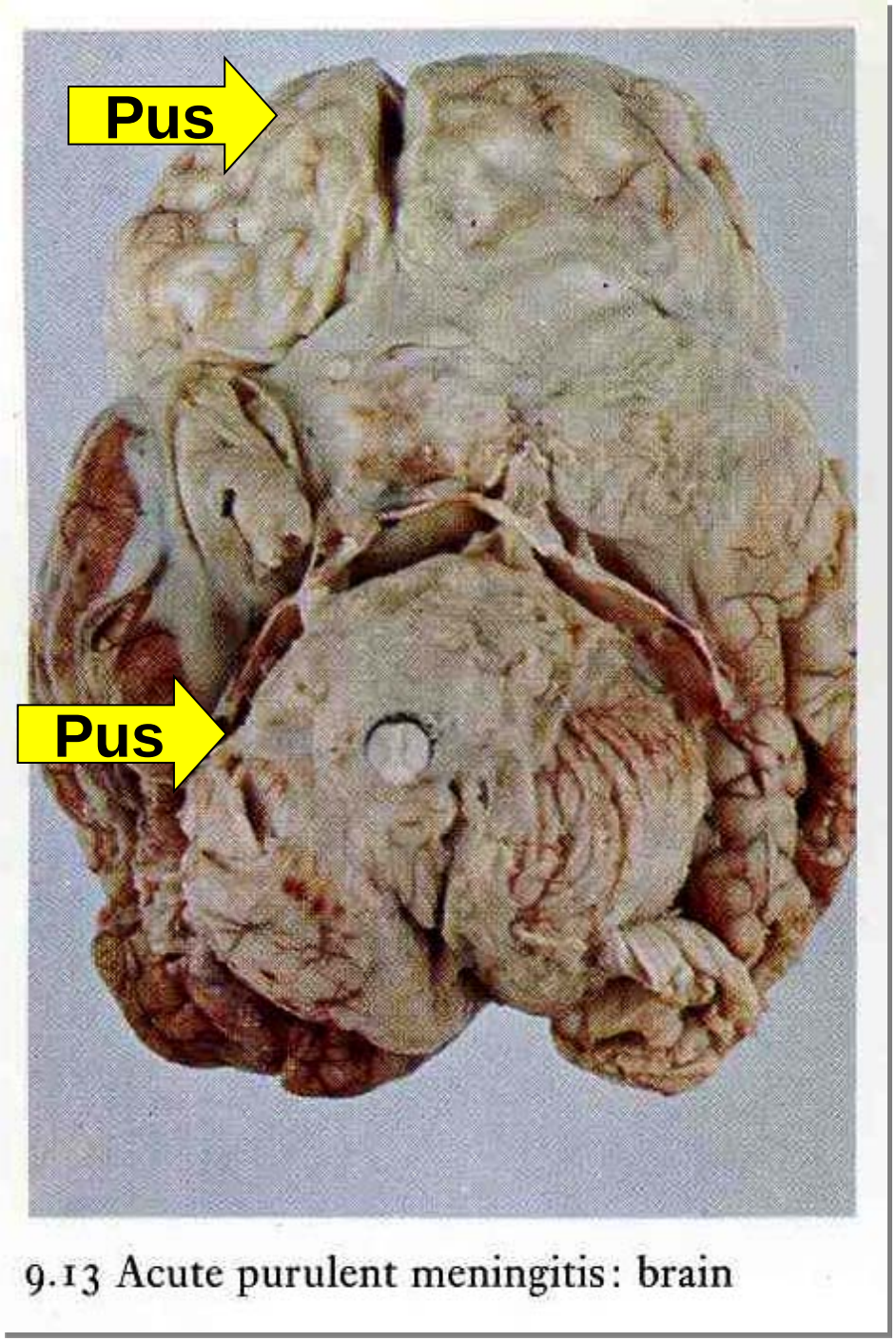


1.6 Purulent meningitis

F 1-6: **Purulent meningitis.**

Brain under surface showing thick yellowish green purulent exudate (**Pus)** filling the subarachnoid space over the brain-stem & cerebellum.

✱ The patient had acute meningitis caused by staphylococcus aureus.



9.13 Acute purulent meningitis: brain

F 9-13: **Acute purulent meningitis: brain.**

This shows the undersurface of the brain of a 5-month-old boy. The surface is covered by a shaggy greyish-green purulent pus.

► A recent **ventriculo-atrial shunt** had been inserted for an obstructive hydrocephalus secondary to a craniopharyngioma.
The causative bacteria was *Streptoccous pneumoniae.*

◘ H, **neutrophils (pus) fill** the entire **subarachnoid space** (◘ 4.7) in severely affected areas, or may be found predominantly around the leptomeningeal BVs. In untreated meningitis, Gram stain reveals varying numbers of the causative organism. Bacterial meningitis may be associated with:

(1) Brain abscesses (F23-16B).

(2) Phlebitis (inflammation of veins) may also lead to thrombosis & venous occlusion & hemorrhagic infarction of the underlying brain.

Aseptic (viral) Meningitis

★Is an acute onset illness, characterized by meningeal irritation, fever, & alterations of consciousness. The clinical course is less fulminant than in pyogenic meningitis, usually self-limiting, & most often is treated symptomatically.

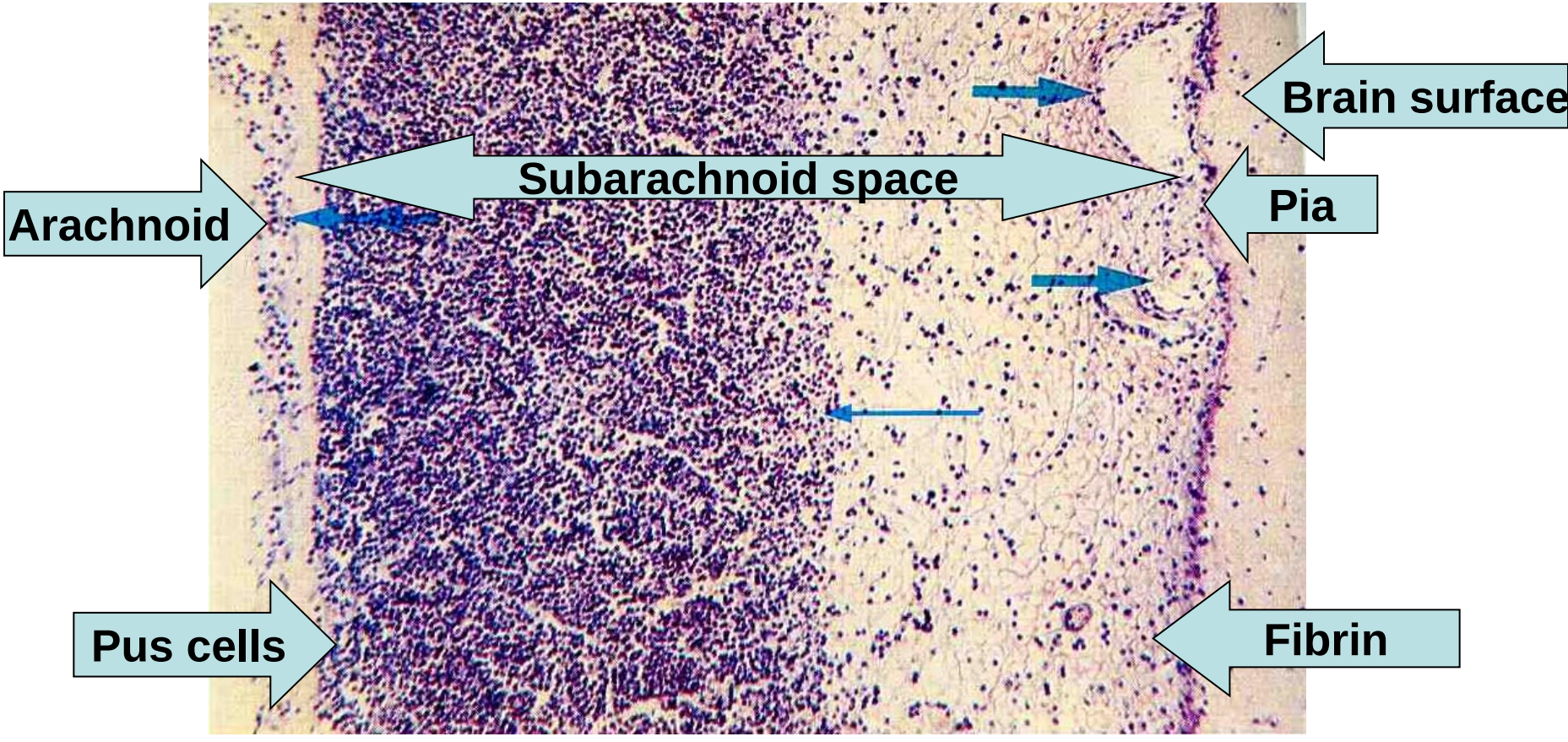
★**CSF** shows • ↑ lymphocytes, • moderate protein elevation, • **NORMAL glucose content &** • **NO bacteria.**

▼In **70% of cases**, a virus can identified, most commonly an **enterovirus.**

►**Grossly,** brain swelling can be seen in some instances.

◘ H, the leptomeninges are either normal, or show mild to moderate infiltration by lymphocytes.

◘ 4.7: **Acute pyogenic (purulent) meningitis. Brain X120.** Brain surface on the right & is covered by pia. ●The small BV on the surface of the cerebral cortex (thick arrows) are markedly dilated. ● The arachnoid membrane (double arrow) is infiltrated by a blue line of basophilic neutrophils. ● The subarachnoid space (between pia & arachnoid) is filled by thick layer of neutrophils (pus cells, thin arrow) & fibrin strands.



Chronic Meningitis : **Tuberculous (TB) Meningitis**

★Usually presents with generalized symptoms of headache, malaise, mental confusion, & vomiting.

★ **CSF** shows: • moderate ↑ in mononuclear cells, or a mixture of polymorphonuclear & mononuclear cells;
• markedly elevated ↑ protein level &
• the glucose content typically is moderately reduced or normal.

►**Grossly:(1)** There may be **discrete white granulomas scattered over the leptomeninges, these granulomas may encase the cranial** nerves leading to their **paralysis.**

(2) Arteries running through the subarachnoid space may show inflammatory infiltrates in their walls & marked intimal thickening (**obliterative endarteritis)** which may cause paranchymatous ischemia of brain tissue.

(3) The TB meningitis may ***spread*** through the CSF to the choroid plexuses & it may also result in a well-circumscribed intraparenchymal (brain) mass **(*tuberculoma*).**

(4) Chronic TB meningitis causes arachnoid fibrosis, which may produce **hydrocephalus** (F9-14).

◘ H, there are typical well-formed **granulomas** (with/without caseation) with giant cells, or there may be a mixtures of lymphocytes, plasma cells, & macrophages.

Similar findings are observed in tuberculomas within the brain.

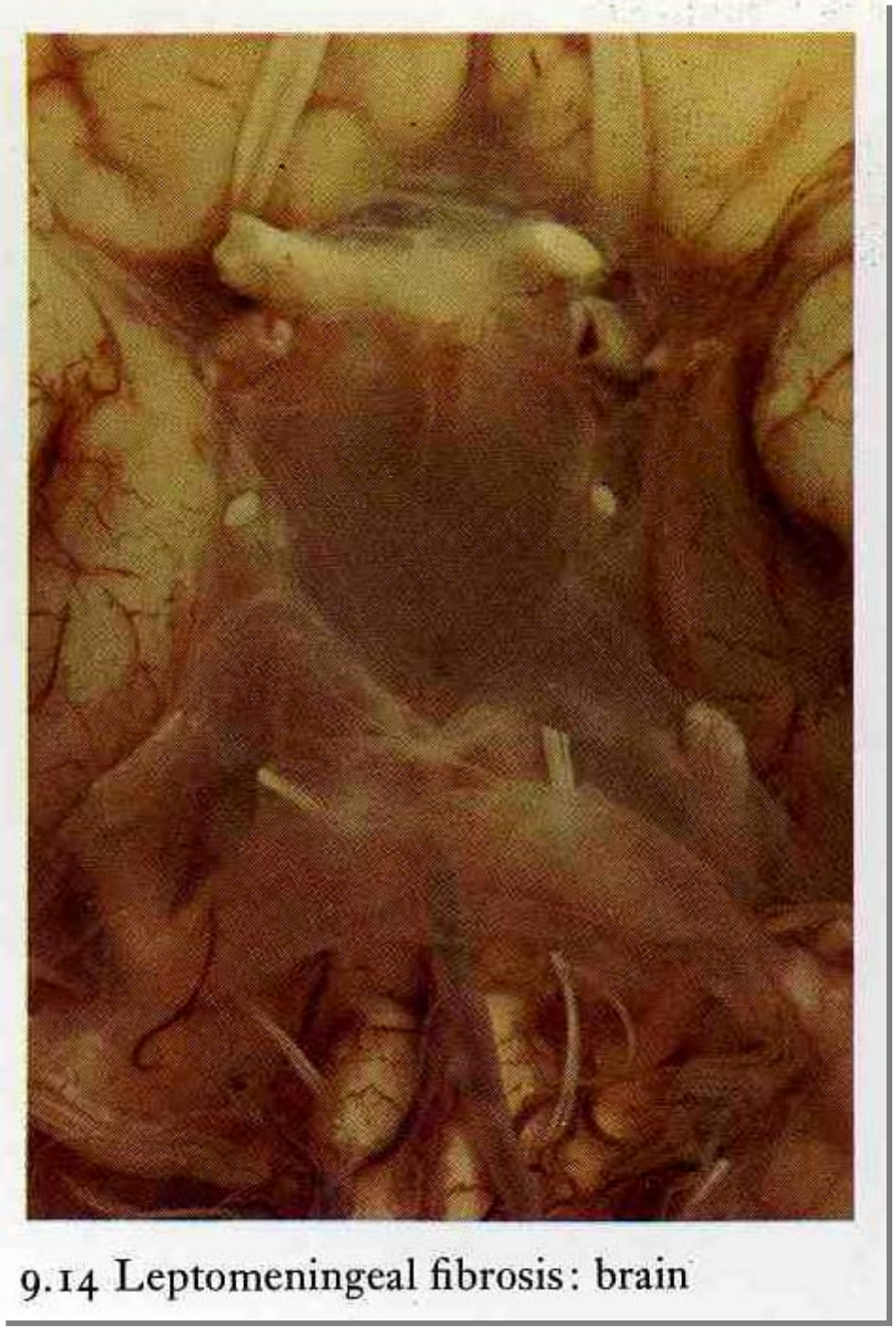
Neurosyphilis

★ Neurosyphilis is manifestation of tertiary syphilis.

★ Neurosyphilis include 4 lesions:

(1) Paretic neurosyphilis (General Paralysis of Insane, GPI), caused by invasion of the brain by *Treponema pallidum* & manifests as insidious, progressive **loss of mental & physical** functions with mood alterations (including delusions of grandeur), **terminating in severe dementia.**

◘ H, there is parenchymal damage particularly in the frontal lobe, characterized by **loss of neurons** with proliferation of microglia & **gliosis**.



9.14 Leptomeningeal fibrosis: brain

F9-14: **Leptomeningeal fibrosis: brain.**

★ Organization & fibrosis of exudate (in pyogenic or TB meningitis) cause marked fibrotic thickening of the leptomeninges over the base of the cerebrum & brain-stem seen in this patient.

☹ **Effects?**

fibrous scarring may:

(I) compress cranial nerves, leading to **paralysis**, &

(II) obstructs the CSF flow causing communicating **hydrocephalus**

(1) Tabes dorsalis (◘ 4.31) results from damage to sensory nerves in the dorsal roots of the spinal nerves, producing (2) **loss of pain & sensation**, leading to skin & joint damage **(Charcot joints);** &

(2) loss of deep joint position sensation result in **locomotor ataxia &**

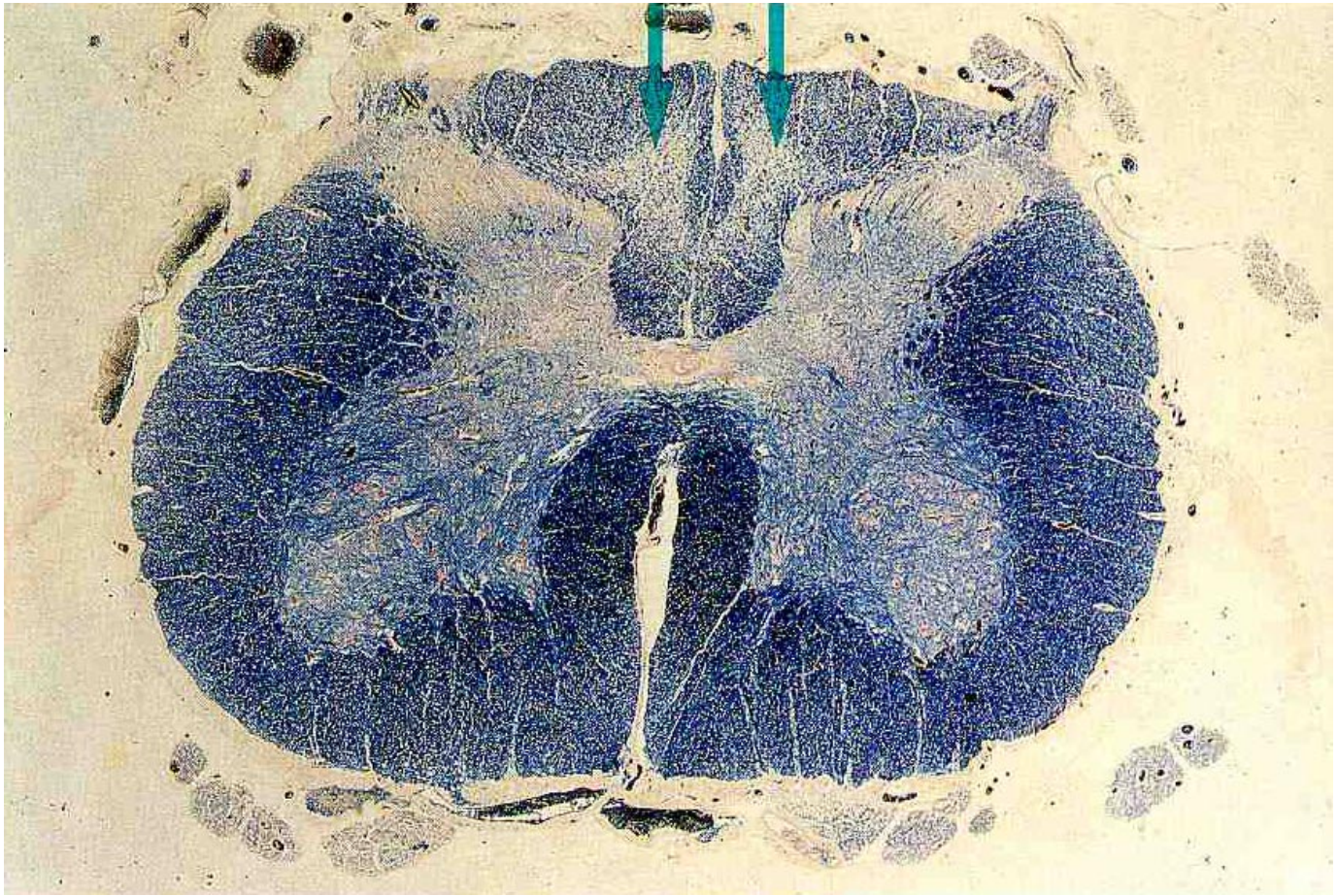
(3) **absence of deep tendon reflexes.**

◘ H, there is loss of axons & myelin in the dorsal roots, with **pallor & atrophy in the dorsal columns of the spinal cord.**

(3) Meningovascular neurosyphilis is a major manifestations of neurosyphilis, it is (1) **chronic meningitis**, usually involving the base of the brain & sometimes the cerebral convexities & the spinal leptomeninges, & as in TB meningitis, there may be an associated (2) **obliterative endarteritis.**

(4) Gummas (yellow necrotic mass surrounded by plasma cells) may also occur in the meninges & brain.

◘ 4.15: **Tabes dorsalis: Spinal cord X11.** SC section through L4 segment, stained by the Loyez for myelin, showing an area of **pallor** in each of the **posterior columns** (thick arrows) in the middle root zone, caused by the **loss of the myelinated** fibers; causes **loss** of pain & deep sensations in the muscles & joints of the legs with **ataxia** & **absence of deep tendon reflexes**.



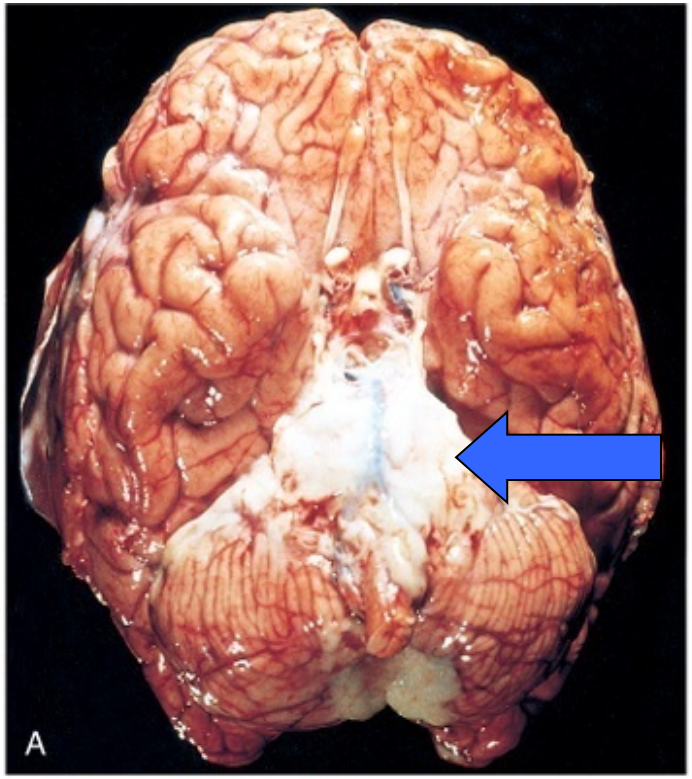
Parenchymal Infections

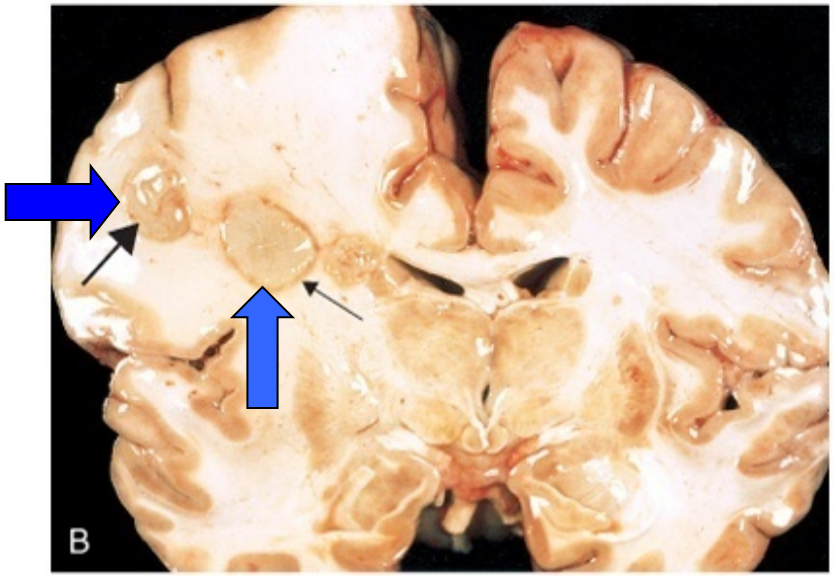
★Most microbes (virus to parasites) can potentially infect the brain. Different pathogens have different patterns of involvement (although the distinctions are not absolute).
In general, **viral infections produce the most diffuse involvement,** ***bacteria*** (when not associated with meningitis) produce the ***most localized***, & other organisms give more mixed patterns. In patients with underlying immunosuppression, more widespread involvement with any agent is typical.

Brain Abscesses **(**F 9-11)

☹ Brain abscesses are nearly always **bacterial infections**; arise by:

- **Direct implantation** of organisms (open skull # fracture),
- **Local extension from adjacent infected foci** (mastoiditis, sinusitis, or skull base fracture communicating with sinuses), or
- **Hematogenous** spread (F23-16B, **usually multiple)** abscesses, from a primary site in the heart, lungs, or distal bones or after tooth extraction.





F23-16: **CNS Bacterial infections.**

A, Pyogenic meningitis.

☹ A thick layer of pus covers the brain stem & cerebellum.

B, Two cerebral abscesses in the frontal white matter (arrows) .

Q: What is the possible route of infection in this case?

☹ Predisposing conditions for hematogenous infection include:

- Acute bacterial **endocarditis;**
- **Cyanotic** congenital HD, in which there is a right-to-left shunt & loss of pulmonary filtration of organisms; &
- Pulmonary sepsis, **i.e., bronchiectasis** & **lung abscess**.

► Abscesses are destructive lesions, & patients almost invariably present clinically with
(1) progressive **Focal** deficits, & **(2)** signs of ⇧ **ICP**.

★**CSF** white cell count & protein level are raised (?), but the glucose content is normal.

- A systemic or local source of infection may be apparent.

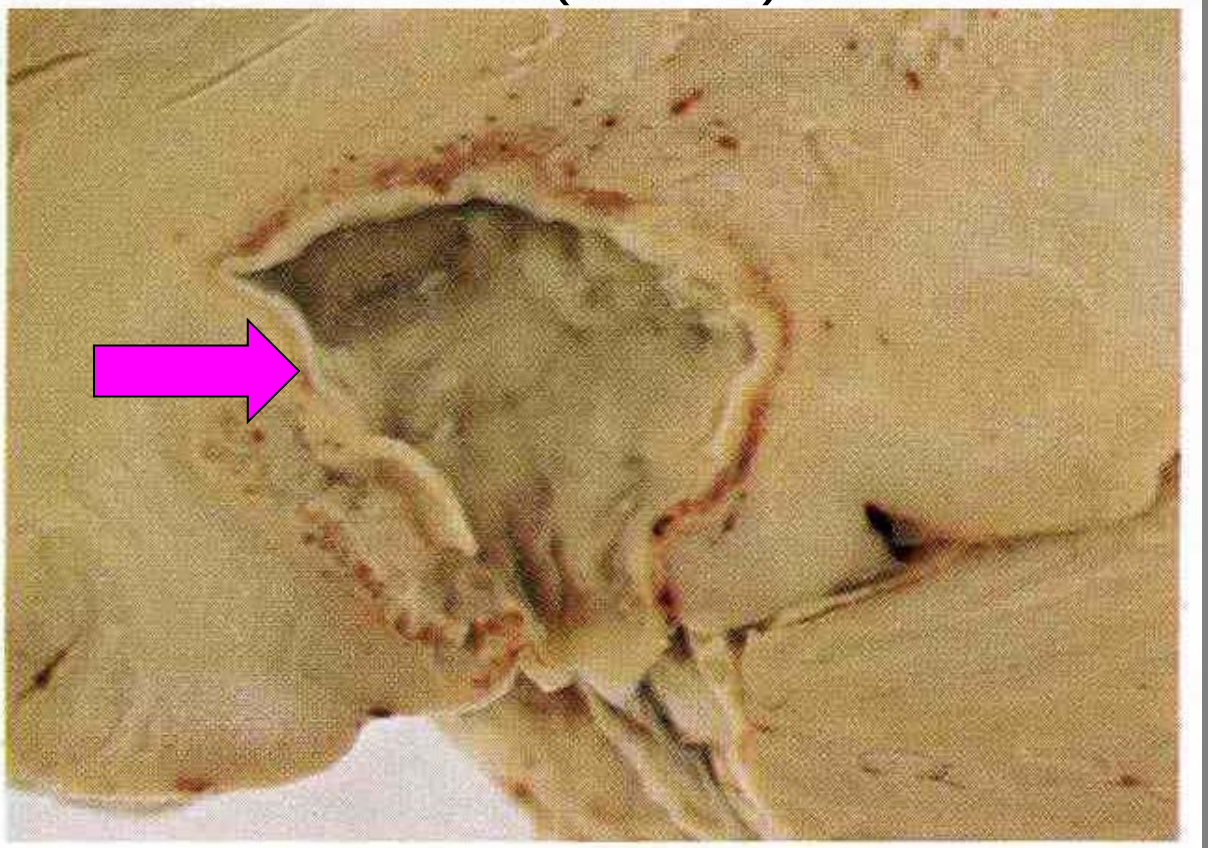
Effects & complications:

☹ **(I) the** ⇧ ICP can be **fatal,** &

(II) abscess rupture can lead to ventriculitis, meningitis, & venous sinus thrombosis.

☺ Prognosis: With surgery & antibiotics, the previous high mortality rate is reduced.

F 9-11: **Chronic brain abscess** in the inferior part of the temporal lobe, with an irregular ragged cavity, the inner wall of which is lined by greyish-green **pus**. The abscess is enclosed by a **capsule** consisting of granulation tissue & fibrosis. ☠ This abscess results from extension of infection from chronic suppurative otitis media (CSOM) & chronic mastoiditis.



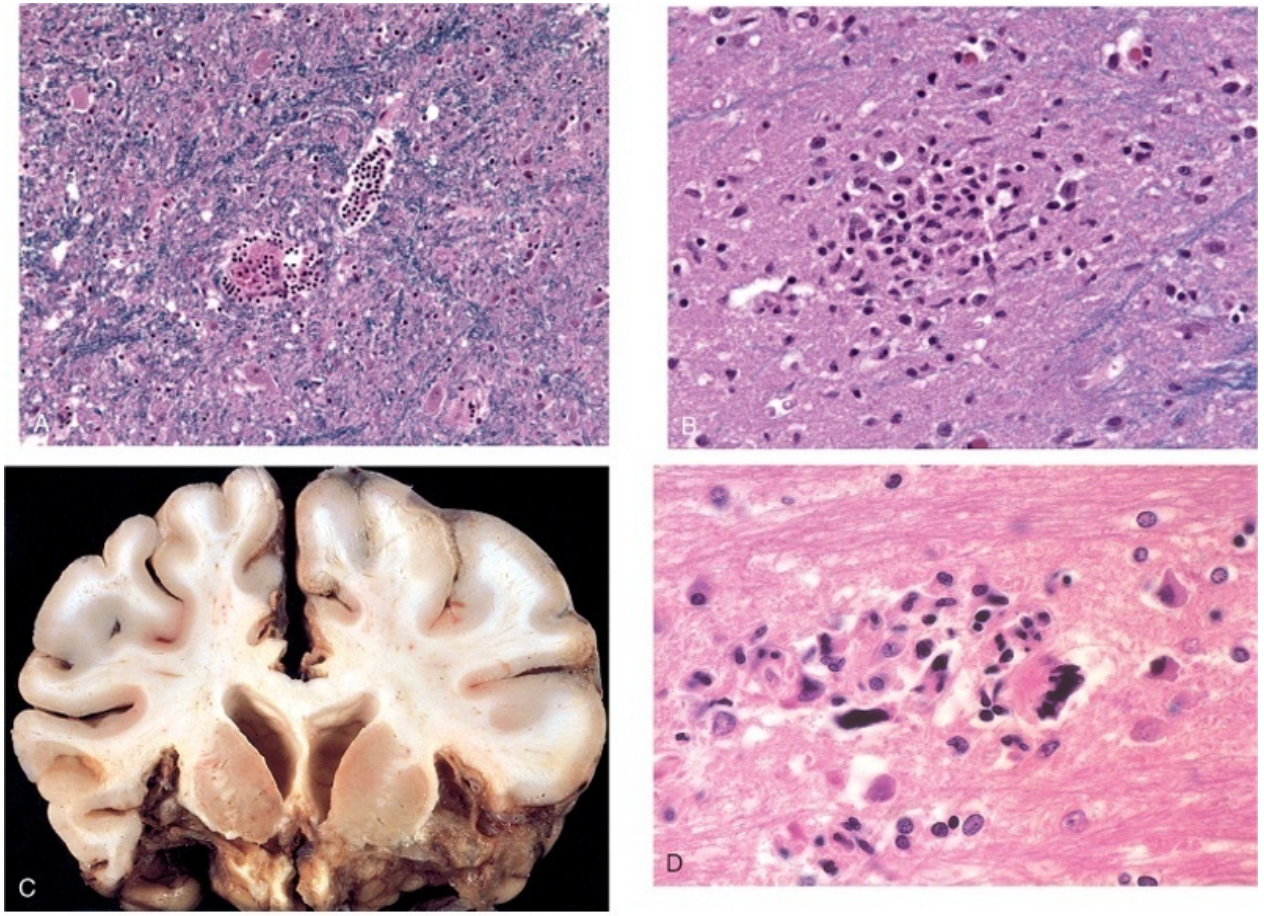
9.11 Chronic abscess: brain

►**GROSSLY,** Abscesses are **discrete** (isolated) lesions, with **central liquefactive necrosis** & surrounding **fibrous capsule** (9-11). ◘ H, there is (1) central necrosis, surrounded by (2) granulation tissue that is responsible for the marked edema, (3) fibrous capsule & a zone of reactive gliosis.

Viral Encephalitis

• Viral encephalitis is a parenchymal infection of the brain that is **almost invariably associated** with meningeal inflammation **(*meningoencephalitis*).** While different viruses may show varying patterns of injury, (F23-17A, B), the most characteristic ◘ histologic features are:
(1) perivascular & parenchymal **mononuclear** cell infiltrates,
(2) microglial nodules, &
(3) neuronophagia; certain viruses may form
(4) inclusion bodies.
★ The CNS is particularly susceptible to viruses such as rabies & polio. Some viruses infect specific CNS cell types, while others, because of their routes of entry, preferentially involve particular areas of the brain (such as medial temporal lobes, limbic system)

F23-17: **CNS Viral infections.** Characteristic findings of viral meningo-encephalitis include **(A)** perivascular **cuffs** of lymphocytes & **(B)** microglial nodules. **(C) Herpes encephalitis** showing extensive destruction of inferior frontal & anterior temporal lobes. **(D) HIV encephalitis**. Note the microglial nodule & multinucleated giant cell.



★In addition to direct infection, the CNS can also be injured by **immune mechanisms** after systemic viral infections.
★ Intrauterine viral infection may cause *congenital malformations,* as occurs with **rubella**.

Arboviruses

Arboviruses (arthropod-borne viruses) are an important cause of **epidemic encephalitis**; the more commonly encountered types are **Eastern & Western equine encephalitis** & **West Nile virus**.

★ **Animal hosts act as disease reservoirs for the arboviruses**, which are mostly **transmitted by ★ mosquitoes**.
★ CSF is: • colorless, • slightly ⇧ pressure, • ⇧ protein level, • initially, a neutrophilic, that rapidly converts to lymphocytes; but • **sugar content is normal**.

◘ H, there is • perivascular lymphocytic **cuff** meningoencephalitis (F23-17A), Multifocal gray & white matter **necrosis** with •**Neuronophagia &** • **Microglial nodules**(F23-17B). In severe cases there may be a • **necrotizing vasculitis with associated focal hemorrhages.**

Herpes Simplex Virus Type 1

Produces encephalitis that occurs in any age group but is ★ **most common in children & young adults.**

😐 Only, some patients have previous oral herpetic lesions.

★Commonly causes **alterations in mood, memory & behavior** reflecting the involvement of frontal & temporal lobes.

►**Grossly,** there is **necrotizing** & **hemorrhagic** ★ ***meningoencephalitis*****,** *starting in & most severely involves, the inferior & medial regions of the temporal lobes & the orbital gyri of the frontal lobes* (F23-17C). **Cowdry type A intranuclear viral inclusion bodies** can be found in both neurons & glia.

Herpes Simplex Virus Type 2

CNS Infection usually manifests (1) in adults as meningitis; while (2) disseminated severe encephalitis occurs in many **neonates born by vaginal delivery to women with active primary HSV Type 2 genital infections.**

The dependence on route of delivery indicates that the infection is acquired during passage through the infected birth canal rather than transplacentally**.**

Varicella-Zoster Virus (Herpes Zoster)

★Varicella-zoster virus (VZV) **causes chickenpox during its primary infection,** usually without any evidence of neurologic involvement. The virus establishes…

★ **latent infection in neurons of dorsal root ganglia;**

★Reactivation in adults manifests as a painful, vesicular skin eruption in the distribution of one or a few **dermatomes (*shingles*),** usually a self-limited process, but there may be a persistent pain in the affected region **(*post-herpetic neuralgia*)**

★VZV may cause a granulomatous arteritis, which may cause infarcts. In immunosuppressed patients, acute herpes zoster encephalitis can occur. **Inclusion bodies** can be found in glia & neurons.

Cytomegalovirus (CMV)

★ CMV infects the CNS in **fetuses & immunosuppressed** patients. • **In utero infection cause severe brain destruction** in the periventricular area with necrosis, followed by microcephaly and calcification. • CMV is a common opportunistic viral pathogen in individuals with **AIDS.**

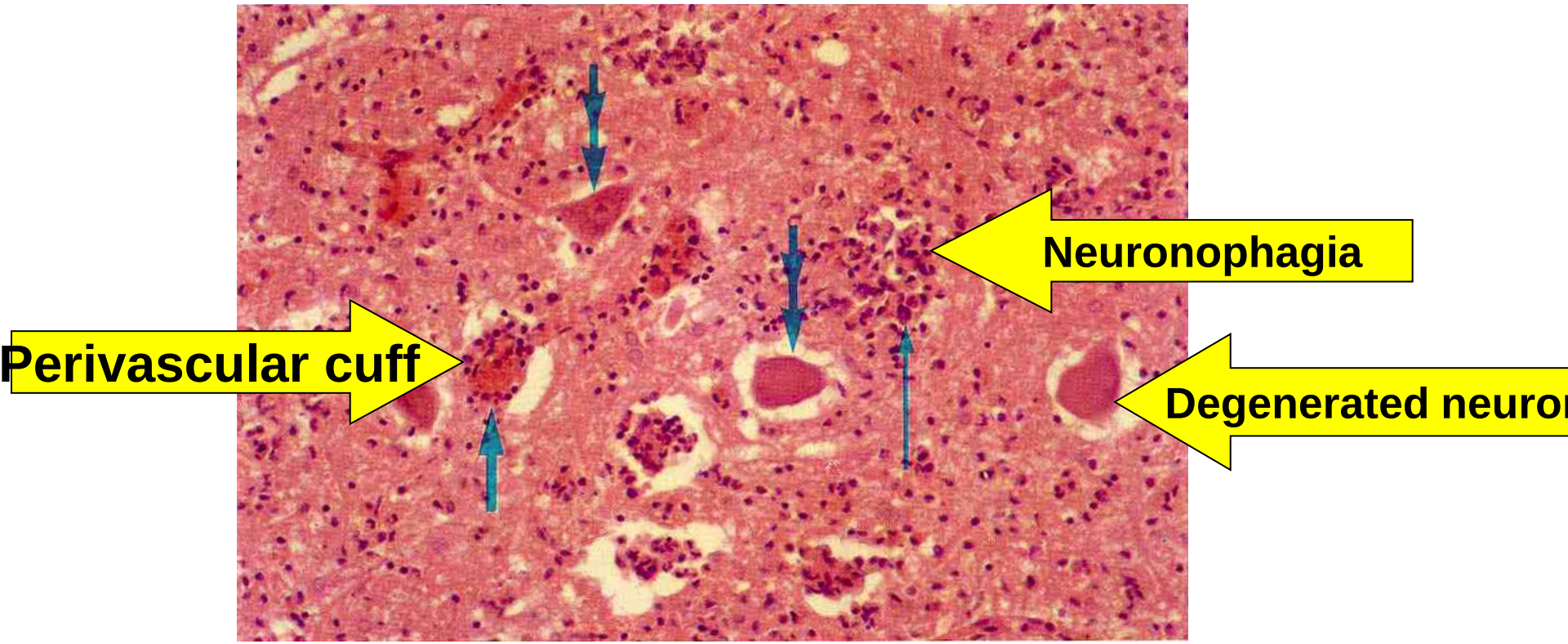
◘ **H, subacute CMV encephalitis is associated with inclusion-bearing cells,** is the most common pattern of involvement in the immunosuppressed patient. Although any type of cell within the CNS can be infected by CMV, there is a tendency for the **virus to localize in the paraventricular subependymal regions of the brain.** This results in a severe hemorrhagic necrotizing ventriculoencephalitis & choroid plexitis.

Poliovirus (◘ 4.19 & 20)

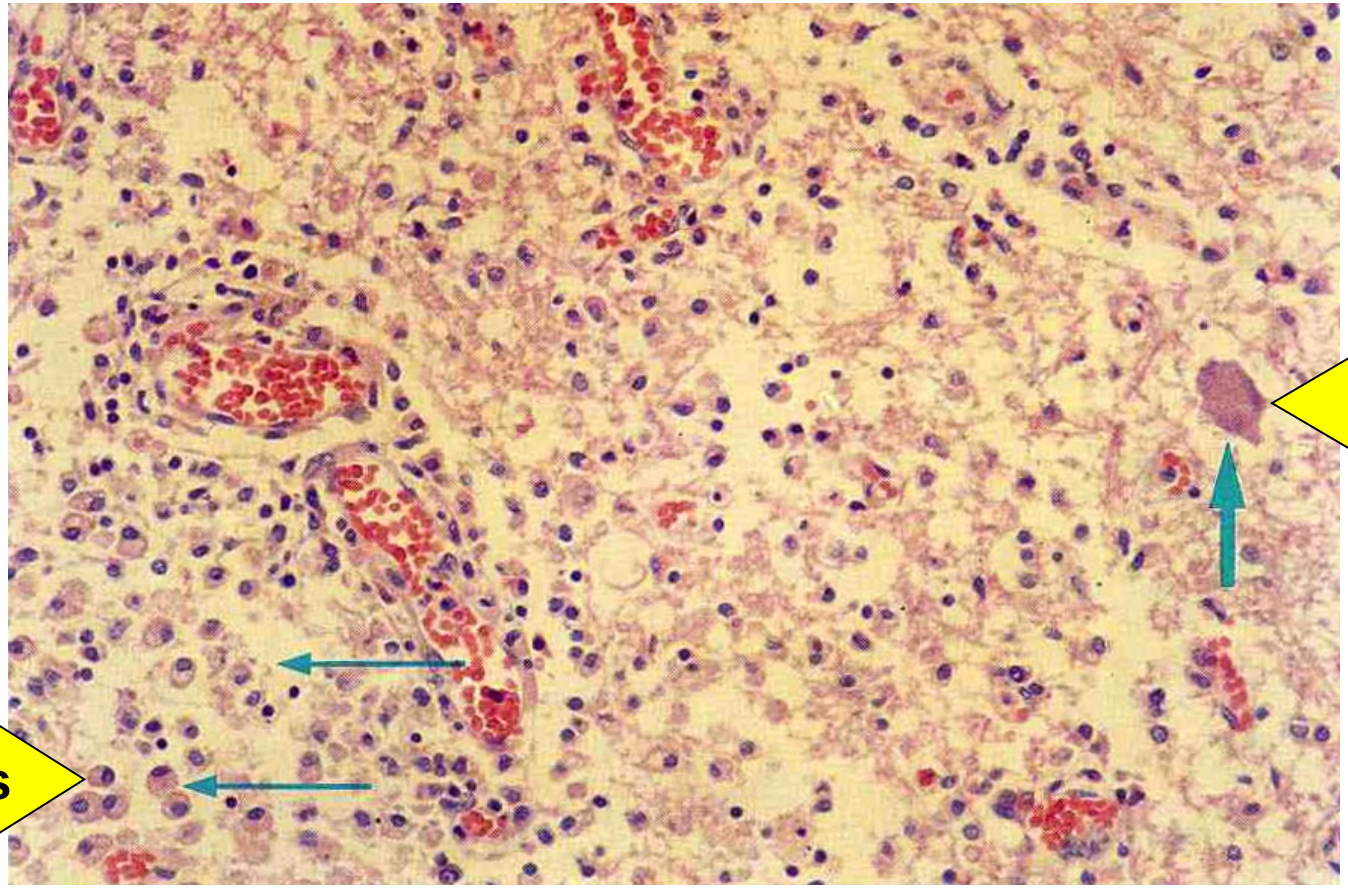
- Is an enterovirus that causes **paralytic poliomyelitis**.
- It has been **eradicated by immunization** in many parts of the world, but there are still many affected regions.
- Infection with poliovirus most often causes a subclinical or mild gastroenteritis; but
- **In few (1%) of cases it secondarily invades the CNS** & causes damage & loss of **motor neurons in the spinal cord & brain stem,** resulting in flaccid paralysis, muscle wasting & hyporeflexia in the corresponding region.

☠ **In the acute disease, death can occur from paralysis of respiratory muscles**.

◘ 4.19: **Poliomyelitis: X235 Spinal cord** anterior horn in a patient who die 6 days {Cause?} after the onset of illness. There is neutrophils, lymphocytes & macrophages cell infiltration, some as a **perivascular cuff** (thick A). **All neurons are degenerated**, having no nucleus & contain little or no Nissl substance & some are shrunken & occupy large **vacuoles** (double thick A). Several necrotic neurons are being phagocytosed **(neuronophagia** (thin A)**).**



◘ 4.20: **Poliomyelitis: x235. Spinal cord** anterior horn in a patient who die 7 days after the onset of illness {**Cause**?}. There is extensive destruction of all neurons, except a degenerating & shrunken **single neuron** (thick arrow). There is infiltration by lymphocytes, plasma cells ,& macrophages which are swollen with pale granular lipid [foamy macrophages, thin arrow] pushing the nucleus to one side of the cell



Foamy macrophages

Rabies

★Rabies is **severe encephalitis** transmitted to humans by the **bite of a rabid animal**; various animals (Such as?) are the natural reservoir for the virus. Exposure to some species of **bat, even without a bite,** is a risk factor for developing infection.

★ **Virus enters the CNS by ascending along the peripheral nerves from the wound site,** so the incubation period depends on the distance between the wound & the brain, usually taking **few weeks, or months**.

☹ As the infection advances, the patient shows extraordinary CNS **excitability**; the slightest touch is painful, with violent motor responses progressing to **convulsions**.

☹ **Contractions of the pharyngeal muscles may create an aversion (hate) to swallowing, even to water (hydrophobia).**

☠ Periods of alternating mania & stupor progress to coma & **death from respiratory center failure.**

Human Immunodeficiency Virus (HIV)

★HIV can have direct effects on the nervous system as well as setting the stage for opportunistic infections or tumors that can involve the nervous system Table 23-1.

➔ 60% of individuals with AIDS develop neurologic dysfunction during the course of their illness; in some, it dominates the clinical picture. Patterns of direct injury to the brain include:

(1) Aseptic HIV-1 meningitis occurring in about 10% of patients within 1 to 2 weeks of seroconversion.

(2) HIV-1 meningoencephalitis (subacute encephalitis) causing **AIDS-dementia** complex.

◘ H, the brain show chronic inflammatory reaction with widely distributed infiltrates of microglial nodules containing macrophage-derived multinucleated giant cells (F23-17D).

(3) Vacuolar myelopathy involving the tracts of the spinal cord can **resemble subacute combined degeneration**, although serum levels of vitamin B12 are normal.

Progressive Multifocal Leukoencephalopathy (PML)

★PML is caused by JC virus, a **polyomavirus** which preferentially infects **oligodendrocytes**, so **demyelination is its principal pathologic effect.**

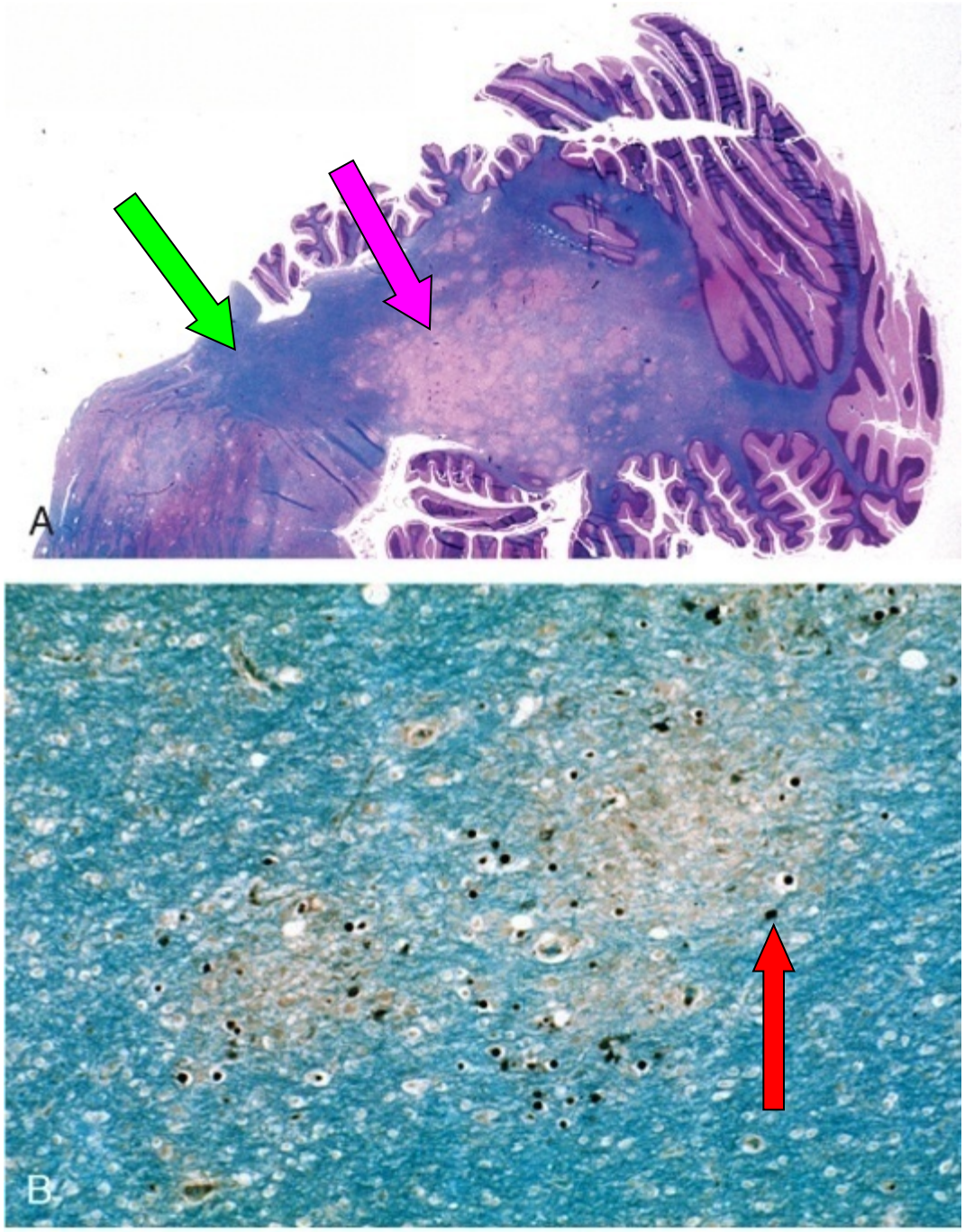
★ The disease occurs invariably in **immunosuppressed** individuals.

★ Most people show serologic evidence of exposure to JC virus during childhood & **it is believed that PML results from virus reactivation because of immunosuppression.**

★ Imaging studies show extensive, multifocal, ring-enhancing lesions in the hemispheric or cerebellar white matter.

►**Grossly,** the lesions consist of patches of irregular, ill-defined **destruction of the white matter** that enlarge as the disease progresses (F23-18).

Each lesion is an area of demyelination, in the center of which are scattered lipid-laden macrophages & a reduced number of axons, & at the edge of are greatly enlarged **oligodendrocyte** nuclei whose chromatin is replaced by glassy amphophilic viral **inclusion.**



F23-18: **Progressive multifocal leukoencephalopathy (PML).**
A, Section stained for myelin, showing irregular poorly defined areas of **demyelination**, which become confluent in places.
B, Enlarged oligodendrocyte nuclei stained for viral antigens surround an area of early myelin loss.

Fungal Encephalitis

• *Candida albicans,* • *Mucor,* • *Aspergillus fumigatus*, & • *Cryptococcus neoformans* are the most common fungi that can cause encephalitis, but in endemic areas, • *Histoplasma capsulatum,* • *Coccidioides immitis*, & • *Blastomyces dermatitidis* can also infect the CNS, especially in the setting of immunosuppression.

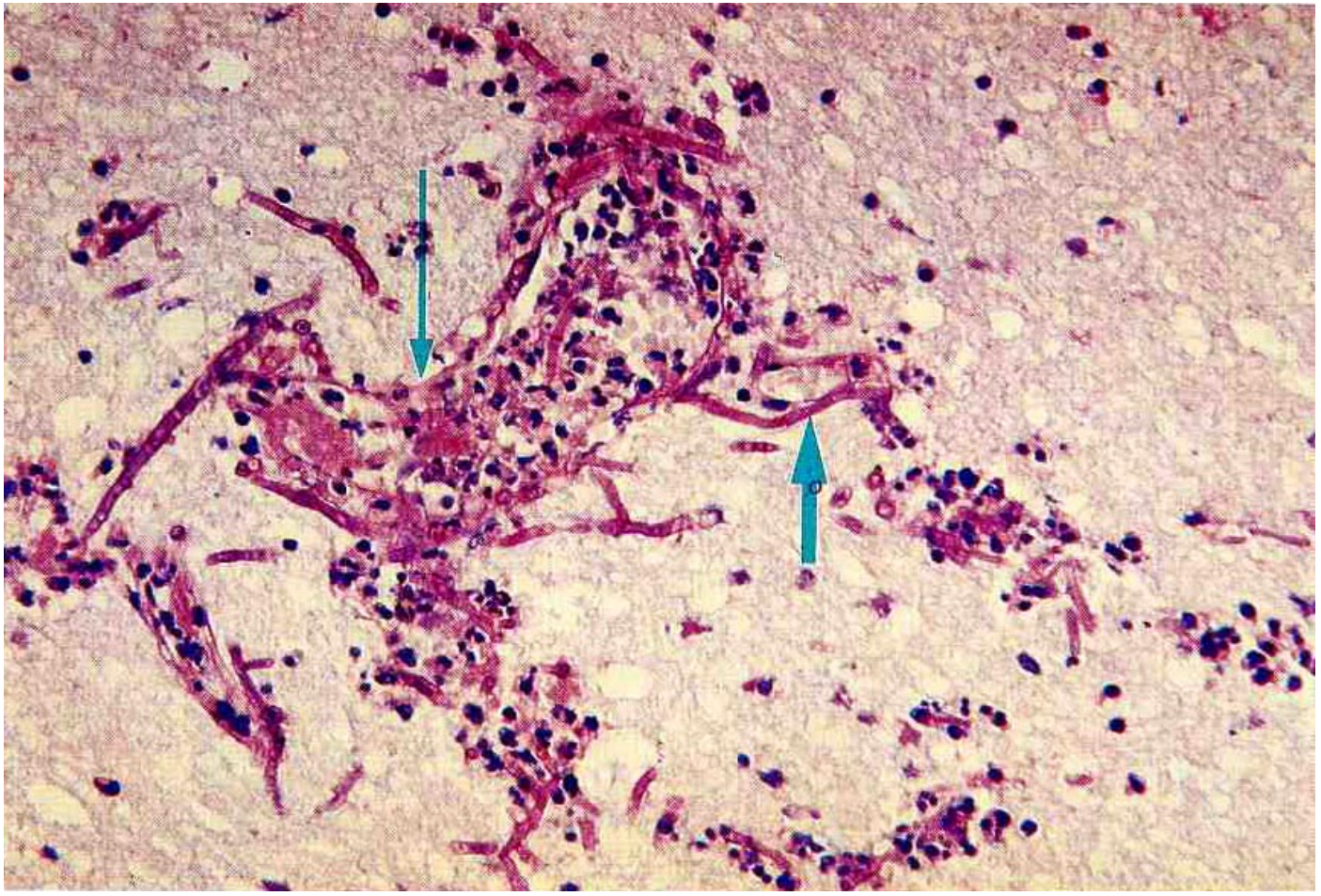
★ *Parenchymal invasion,* usually in the form of **granulomas or abscesses,** can occur with most of the fungi & often coexists with meningitis. *Candida* usually produces multiple microabscesses, with or without granuloma formation.

• Although most fungi invade the brain by **blood dissemination**,

• Direct extension may also occur, particularly with ***Mucor,*** most commonly in **diabetics with ketoacidosis**.

• ***Aspergillus*** tends to cause a distinctive pattern of widespread septic hemorrhagic infarctions because of its marked predilection for **invasion of blood vessel walls** (◘ 4.10) **& subsequent thrombosis**.

◘ 4.10: **Aspergillosis: Brain.** A 13 years old girl on chemotherapy for Hodgkin's lymphoma. The branching filamentous Aspergillus fungi, with many transverse septa in the hyphae (thick arrow) are growing alongside & penetrating the small venule lumen & the adjacent white matter. Parts of the hyphae are surrounded by a moderate neutrophils infiltrate.



• *Cryptococcal meningitis & meningoencephalitis* is observed often in association with AIDS. It can be fulminant & fatal in as little as 2 weeks, or indolent, or it can evolve over months or years. ★**CSF** may have • few cells but a • high level of protein. The mucoid encapsulated yeasts can be visualized in the CSF by India ink preparations & in tissue sections by PAS & mucicarmine as well as silver stains (F23-19 & ◘ 4.11).

Prion Diseases

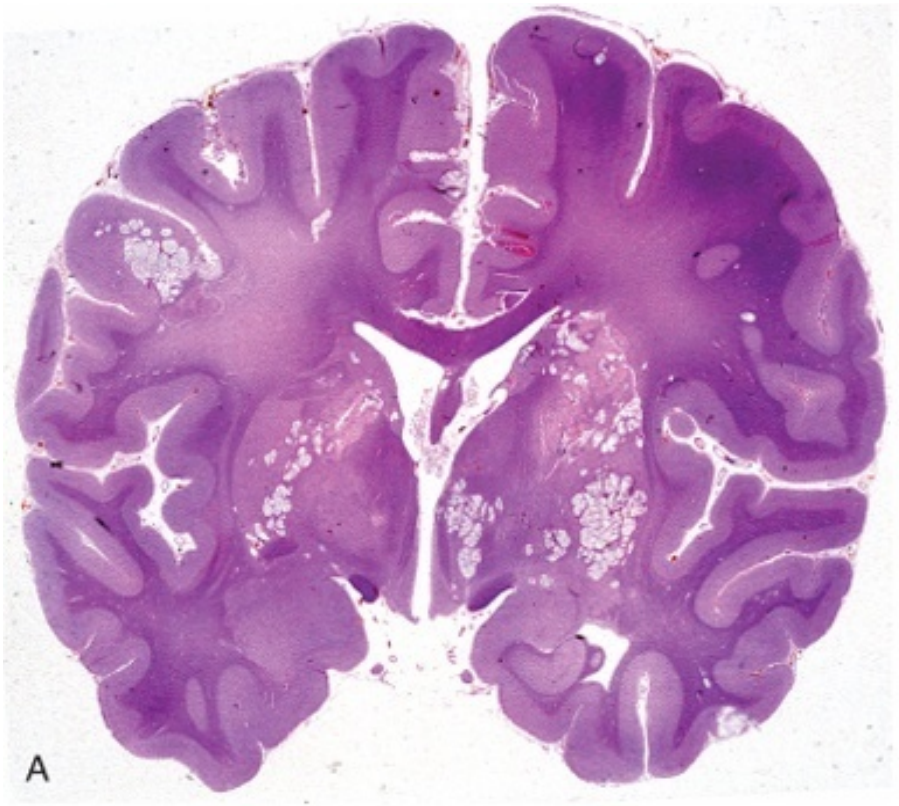
★ Group of diseases includes • sporadic, • familial, • iatrogenic & • variant forms (vCJD) of ➔Creutzfeldt-Jakob disease& Kuru

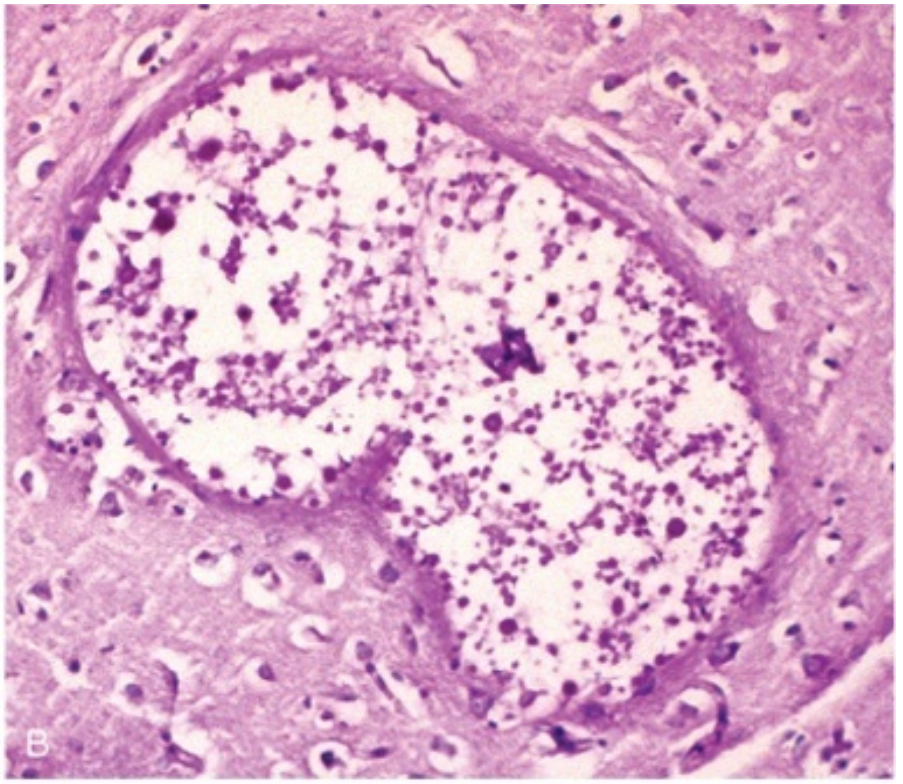
★ Several animal diseases from this group are also known, including **scrapie in sheep & goats; & bovine spongiform encephalopathy in cattle ("mad cow" disease).**

★Prion disease represents a form of protein-induced transmissible disease that is unique to the CNS.

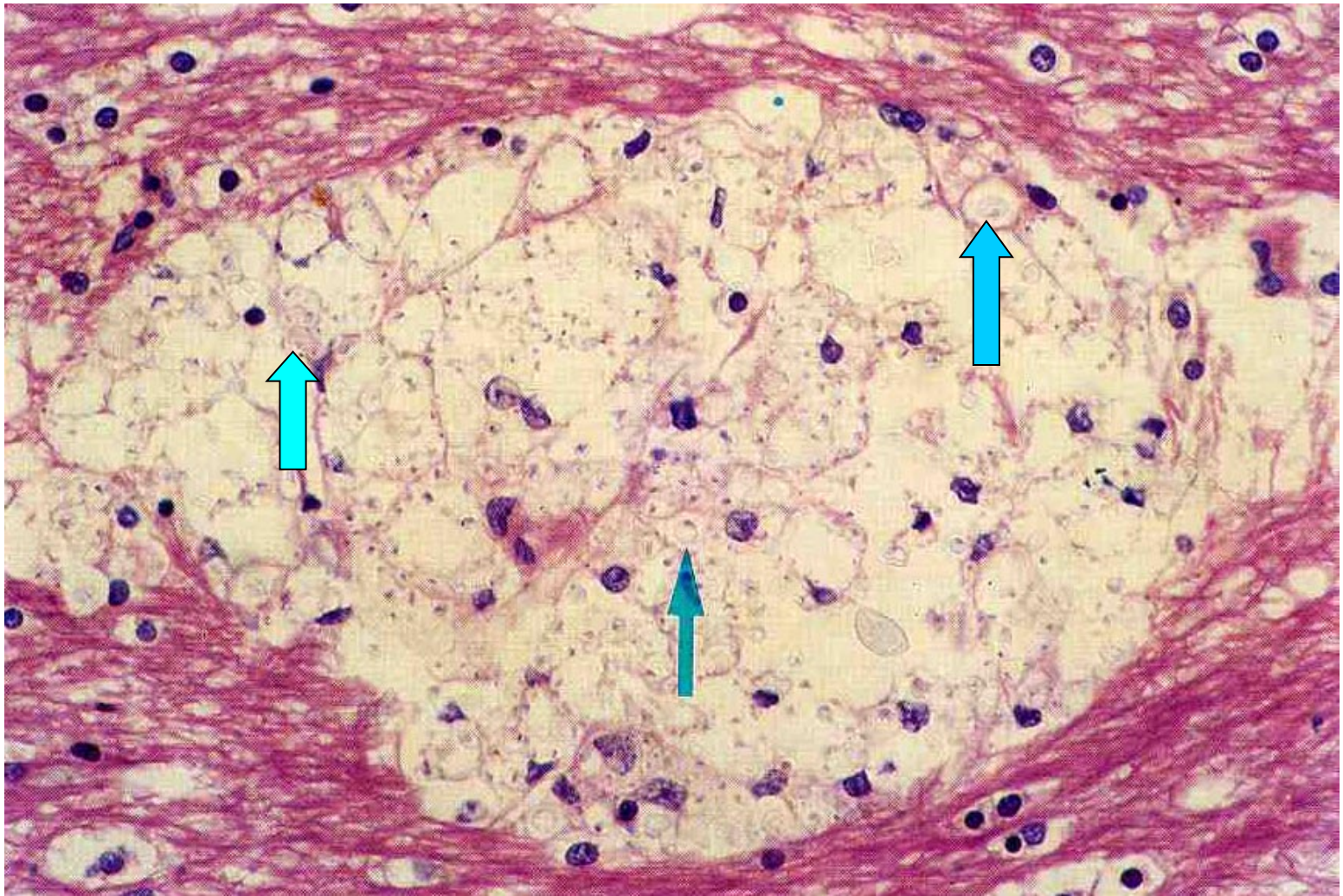
★All these disorders are associated with abnormal forms of a normal cellular protein, termed {**prion protein (PrPc)}.**

F23-19: **Cryptococcal infection.** Inhalation of the yeast from the environment (pigeon droppings) may produce lesions in the lung, which in immune depressed patient may spread to the CNS, causing meningo-encephalitis.
A, Brain section showing many areas of tissue destruction associated with the spread of organisms in the perivascular spaces. **B, Cryptococci** in the lesions at higher magnification.





◘ 4.11: **Cryptococcosis (neoformans) : brain X360.**
Typical cyst in the cerebral cortex, contains large number of **Cryptococci**, each is 5-20 microns in ∅, is dark-colored & enclosed within a thick pale grey mucoid capsule (thick arrow) with little, if any , inflammatory reaction!



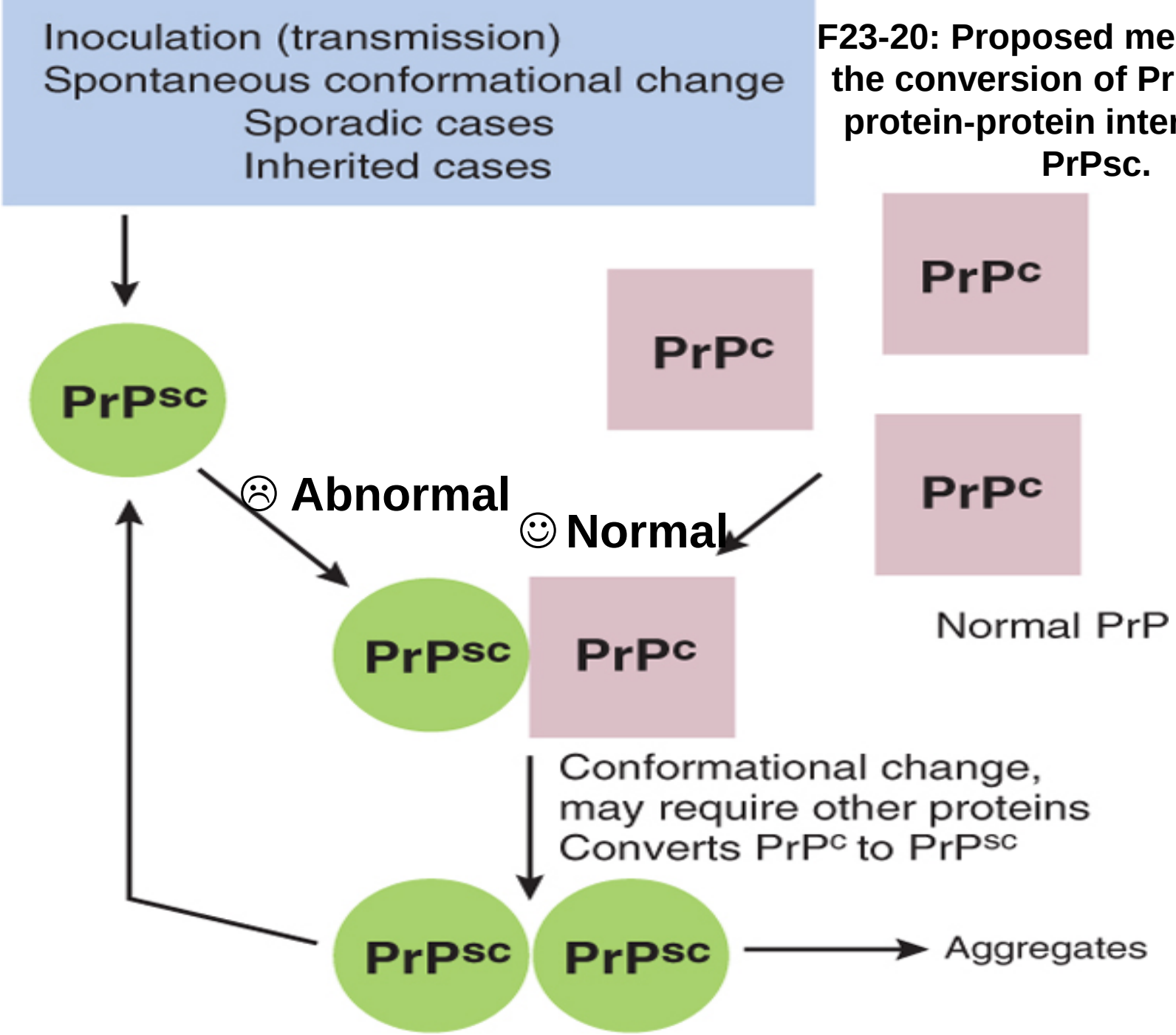
➔**The abnormal form of this protein can act as an infectious agent,** since it propagates itself & injures the cells in which it is present. Most cases of prion disease are either sporadic or associated with mutations in the gene that encodes PrPc.

➔The **unique pathogenesis** of prion diseases is related to changes in the conformation of PrP from its **native PrPc** form to an abnormal configuration called either **PrPsc** (for *s*crapie) or **PrPres** (for **P**rotease ***resistant***) (F23-20).

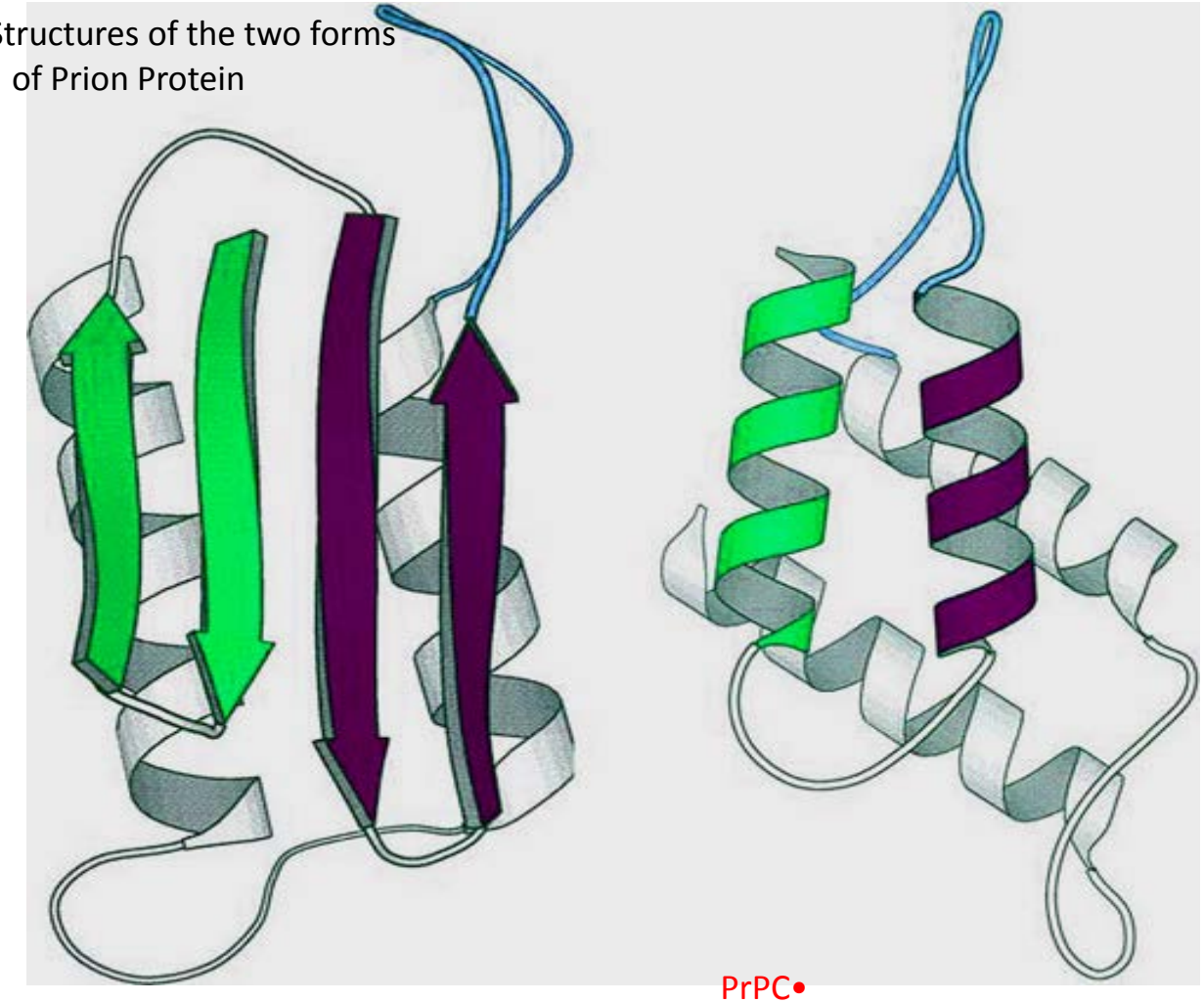
★ In the abnormal conformation, the prion protein becomes **resistant to protease digestion**. Once formed, PrPsc can then initiate comparable transformation of other PrPc molecules.

☹ The **infectious nature** of PrPsc protein comes from this ability to propagate the pathologic conformational change.
★ The conformational change can occur:
(I) **spontaneously** at an extremely low rate & accounts for **sporadic cases** of prion disease **(1per million person).**
(II) If there is a **mutation** in the gene encoding PrPc, then the change can occur at a higher rate; this results in **familial forms** of prion disease.

F23-20: Proposed mechanism for the conversion of PrPc through protein-protein interactions to PrPsc.



Protein Structures of the two forms of Prion Protein



PrPSc

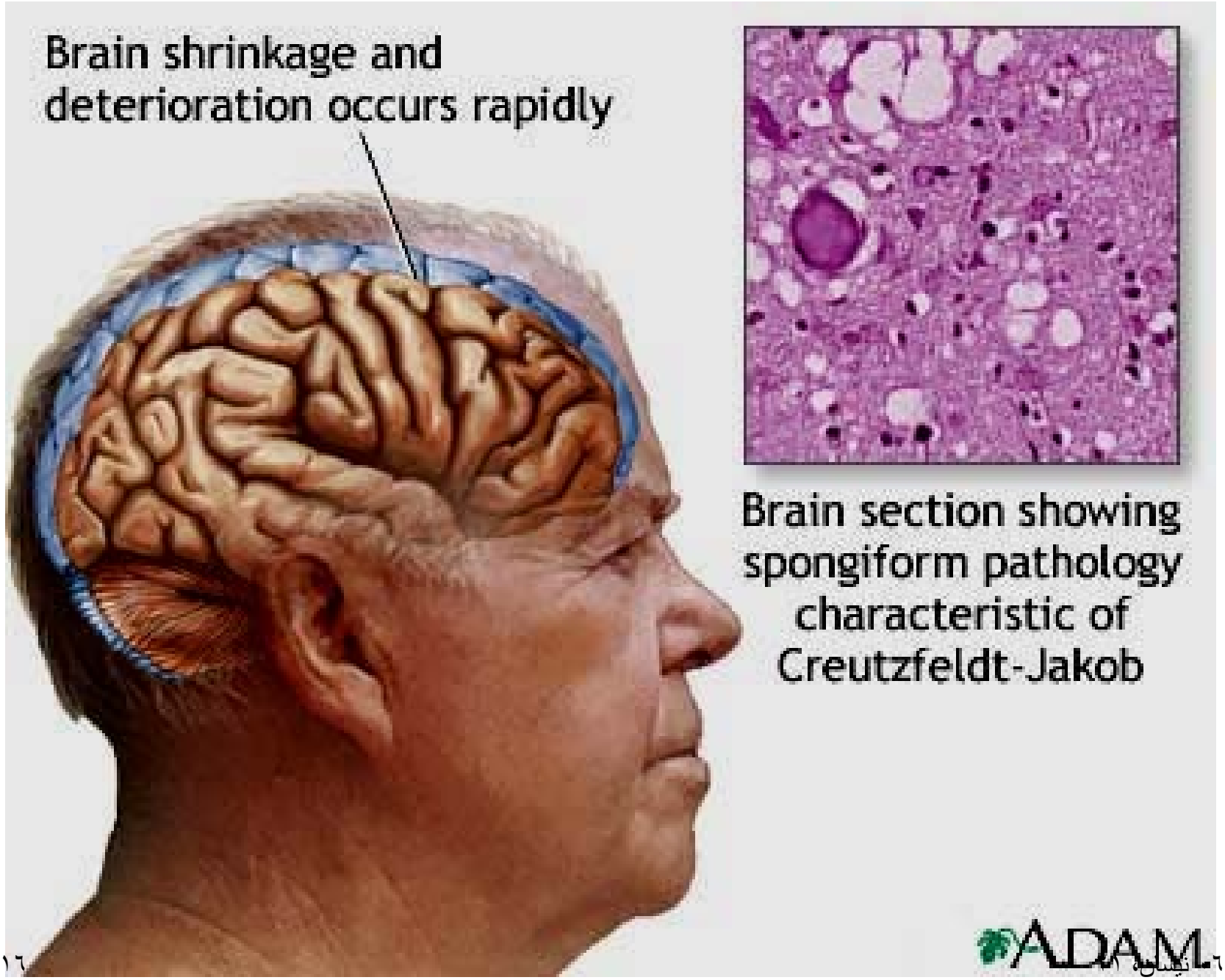
Infectious form(normal form of protein folded incorrectly)..

Sc= 'scrapie

PrPC•

The normal form of the protein.•

C= 'cellular' or 'common •


Brain shrinkage and deterioration occurs rapidly
Brain section showing spongiform pathology characteristic of Creutzfeldt-Jakob
A.D.A.M.

★ Accumulation of PrPsc in neural tissue seems to be the cause of cell injury, but **how** this material leads to the development of cytoplasmic vacuoles & eventual neuronal death is still **unknown!**

Creutzfeldt-Jakob Disease (CJD)

- CJD is a rare (first described in 1920, up till 1980 was of unknown cause!) but well-characterized prion disease that manifests clinically as a **rapidly progressive dementia**.
- It is sporadic in about 85% of cases, with a worldwide annual **incidence of about 1 per million**; familial forms also exist. The disease has a peak incidence in the 7th decade.

☹ There are well-established cases of **iatrogenic transmission by deep implantation electrodes & contaminated preparations of human growth hormone (GH)**

★Presentation begins with mild changes in *memory & behavior* that rapidly progress to **dementia**. The disease is **uniformly fatal**, with an average duration of only 7 months.

◘ H, the pathognomonic finding is a **spongiform transformation of the cerebral cortex & deep gray matter structures** (caudate, putamen); this consists of a multifocal process that results in the uneven formation of **small**, **empty, microscopic vacuoles** of varying sizes within the cerebral substance(“ **neuropil”** ◘ 4.17) & sometimes in the perikaryon of neurons (F23-21A).

• In advanced cases, there is **severe neuronal loss, reactive gliosis**, & sometimes expansion of the vacuolated areas into **cystlike spaces** ("status spongiosus").
✱ **No inflammatory infiltrate is present !**

▼In all forms of prion disease, **immunohistochemical staining** demonstrates the presence of proteinase K-resistant **PrPsc in tissue (**◘ 4.16).

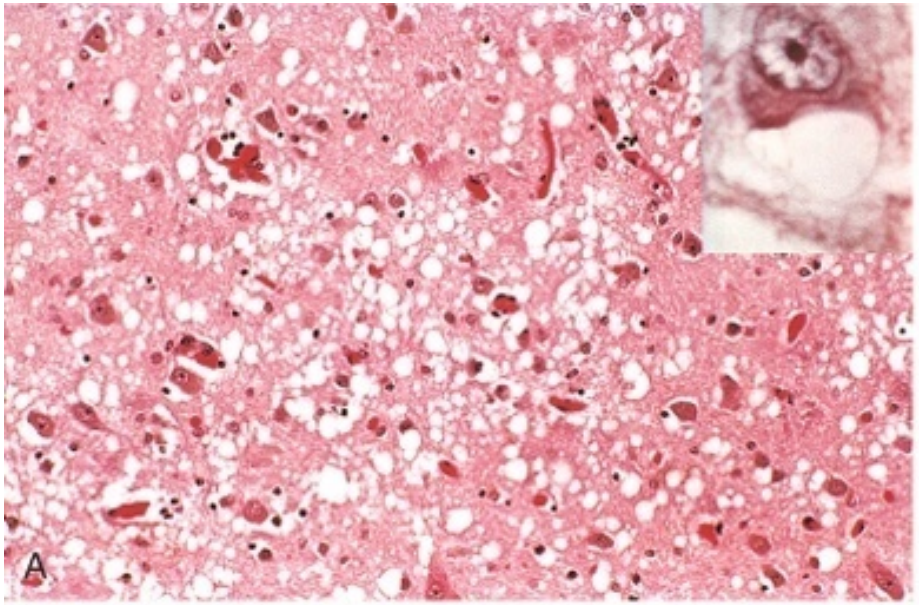
▼**Western blotting of tissue extracts** after partial protease digestion allows detection of diagnostic PrPsc.

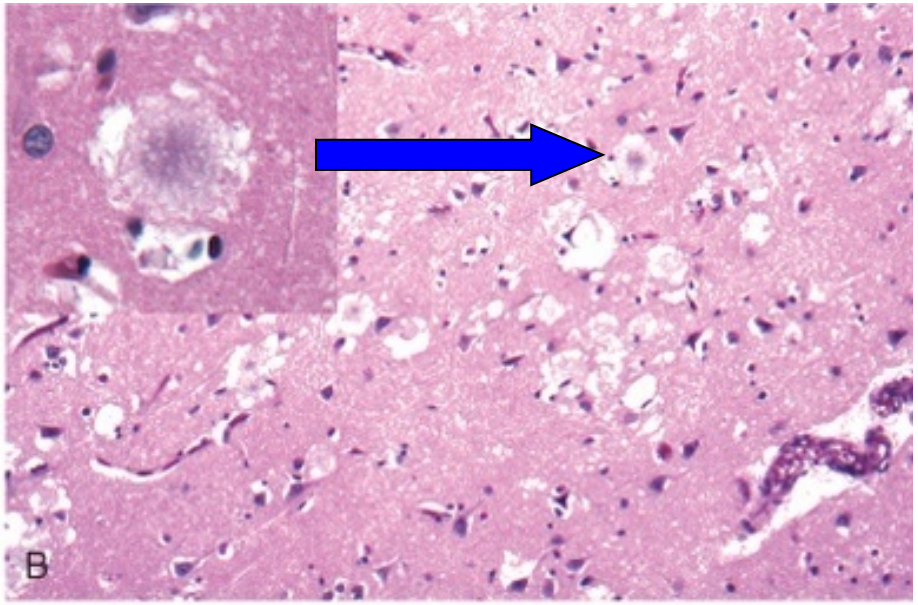
F 23-21: **Prion disease.**

A, Histology of CJD showing spongiform change in the cerebral cortex.

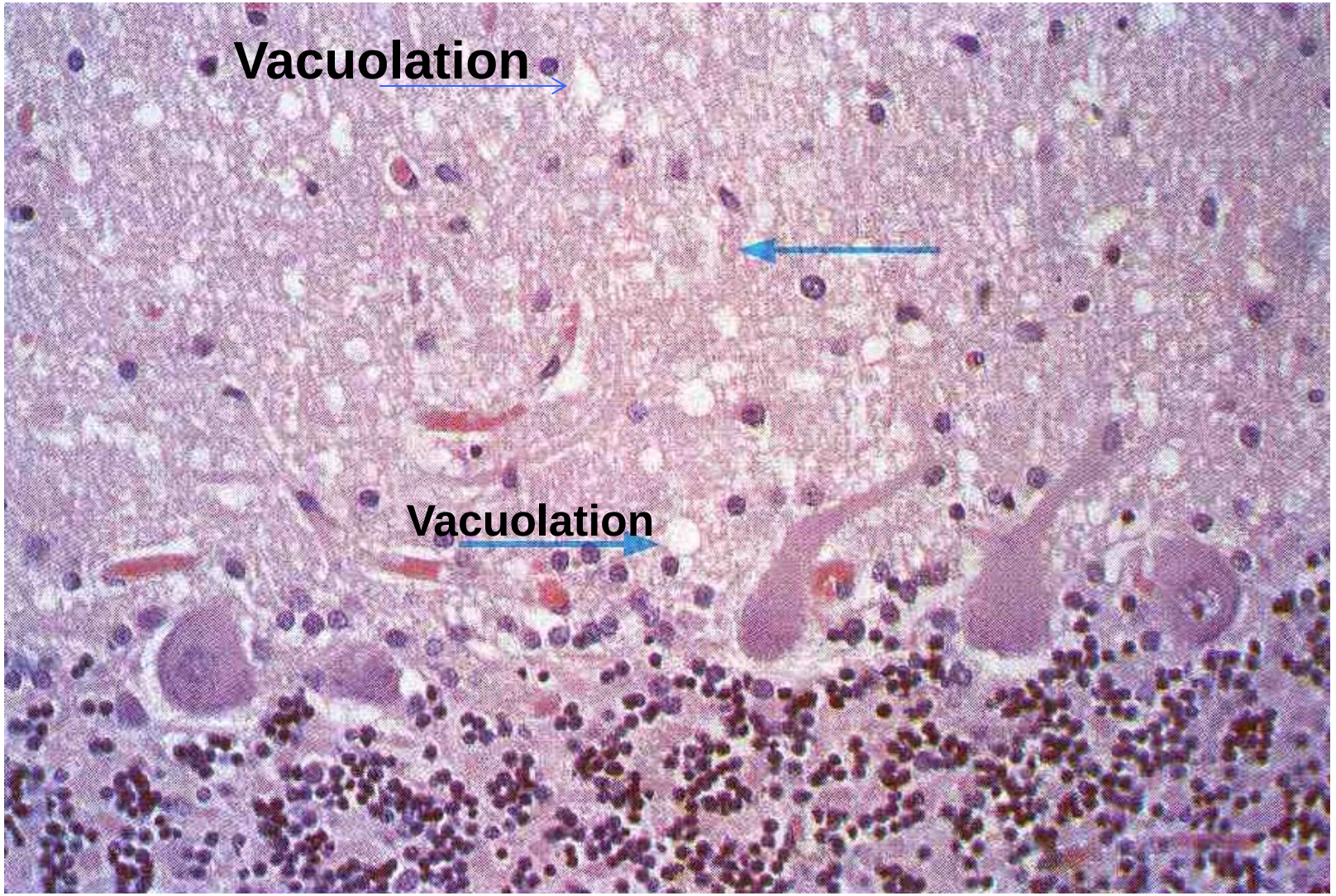
Inset, High magnification of neuron with vacuoles.

B, Variant CJD (vCJD) is characterized by abundant cortical **amyloid plaques** (see **inset**), **surrounded by spongiform change**.

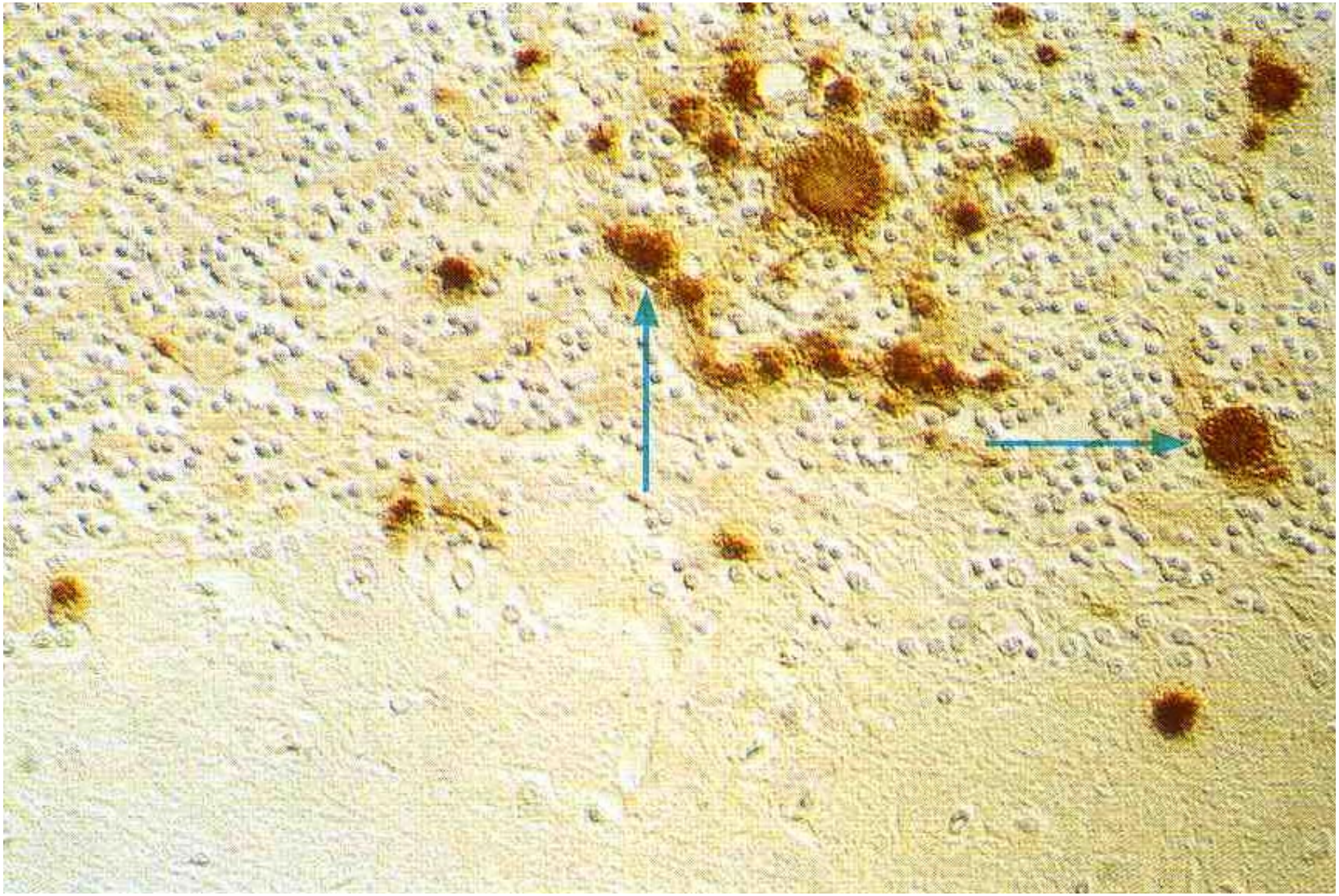




◘ 4.17: **Creutzfeldt-Jakob disease: Brain.** The main features are **loss of neurons**, **demyelination** & spongiform change (confluent **vacuolation** {thin arrow} of the cerebral white matter "neuropil"). However there is **no inflammatory reaction!**



◘ 4.16: **Creutzfeldt-Jakob disease: Brain.**
Immunohistochemical stain demonstrating the presence of proteinase K-resistant Prion Protein (**PrPsc) in tissue** {arrows}.



Variant Creutzfeldt-Jakob Disease

➔ **Starting in 1995**, a series of cases with a CJD-like illness appeared in the United Kingdom. They differed from typical CJD in several important respects: the disease affected
(1) Young adults,
(2) Behavioral disorders are prominent in the early stage; &
(3) the neurologic syndrome **progressed more slowly** than in individuals with other forms of CJD.

😐 The neuropathologic findings & molecular features of these new cases were similar to those of CJD, suggesting a close relationship between the two illnesses.

😐 Multiple lines of evidence indicate that this new disease is a consequence of **exposure** to the prion disease of cattle, **Bovine spongiform encephalopathy**.

vCJD has a similar pathologic appearance, in general, to other forms of CJD, with spongiform change & absence of inflammation. In vCJD, however, there are abundant cortical amyloid plaques, surrounded by spongiform change (F23-21B).

TUMORS OF THE CNS

• The annual incidence of **T** of the CNS ranges from 100 to 170/ per Million persons for **intracranial** Tumors **(T)** & 10 to 20/ per Million persons for **intraspinal T**; of which 50% are primary **T** & 50% are metastatic **T**.

• **20% of all childhood cancers are CNS T** & those differ from those in adults both in histologic subtype & location: **T** in **childhood** are likely to arise in the **posterior fossa**, while in **adults** they are mostly **supratentorial.**

★ **T** of the CNS have **unique characteristics** that set them apart from **T** elsewhere in the body, these are:

😐 **(I) Histologic distinction between benign & malignant T** may be **less important** in the CNS than in other organs! **Why**

Because: (I) 😐 **infiltration,** most **T** (even the low-grade CNS **T,** which show low mitotic rate, cellular uniformity & slow growth) are **infiltrative of adjacent brain tissues,** leading to **serious clinical** deficits & poor prognosis.

😐 **(II)** The **anatomic site of the T can have ☠ lethal** consequences, irrespective of histologic classification!
For example, a **benign meningioma, by compressing the medulla, can cause fatal cardiorespiratory arrest**.
In addition, the tumor location may limits the ability to resect it !

😐 **(III)** The **pattern of spread of primary CNS T differs** from that of other body **T**.

(I)Before done craniotomy operation, even the most highly malignant gliomas **rarely metastasize** outside the CNS &
(II) the subarachnoid space does provide a pathway for **T** spread, so that seeding along the brain & spinal cord can occur

Gliomas

★ Gliomas are **T** of the glial brain cells. The three major types are: ***astrocytomas, oligodendrogliomas, & ependymomas.***

Astrocytoma

★ Several different categories of astrocytic **T** are recognized, the most common being fibrillary & pilocytic astrocytomas.

Diffuse or Fibrillary Astrocytoma

★Account for **80%** of adult primary brain **T;** • most frequent in the 4th to 6th decades;• usually found in the **cerebral hemispheres;** • most common presenting S&S are, (1) **seizures (epilepsy),** (2)**headaches** & (3) **focal neurologic deficits** related to the anatomical site.

◘ **Histologically,** classified into 3 groups: **well-differentiated**, **anaplastic astrocytoma, & glioblastoma multiforme** which correlates well with clinical course & outcome.

• **Well-differentiated astrocytomas** progress slowly, with a **mean survival of more than 5 years.** Eventually, however, patients usually enter a period of **rapid clinical deterioration** that is generally **correlated** with the appearance of **anaplastic** features & more rapid **T** growth**.**

• Many patients present with **glioblastoma multiforme from the start** rather than having their **T** evolve from a lower grade **T**

☠ Glioblastoma prognosis is **very poor;** & current **state-of-the-art treatment**, comprising resection (when feasible) together with radiotherapy & chemotherapy, yields a mean survival of only 6 **months (2007)which increased to 15 months in 2013**.

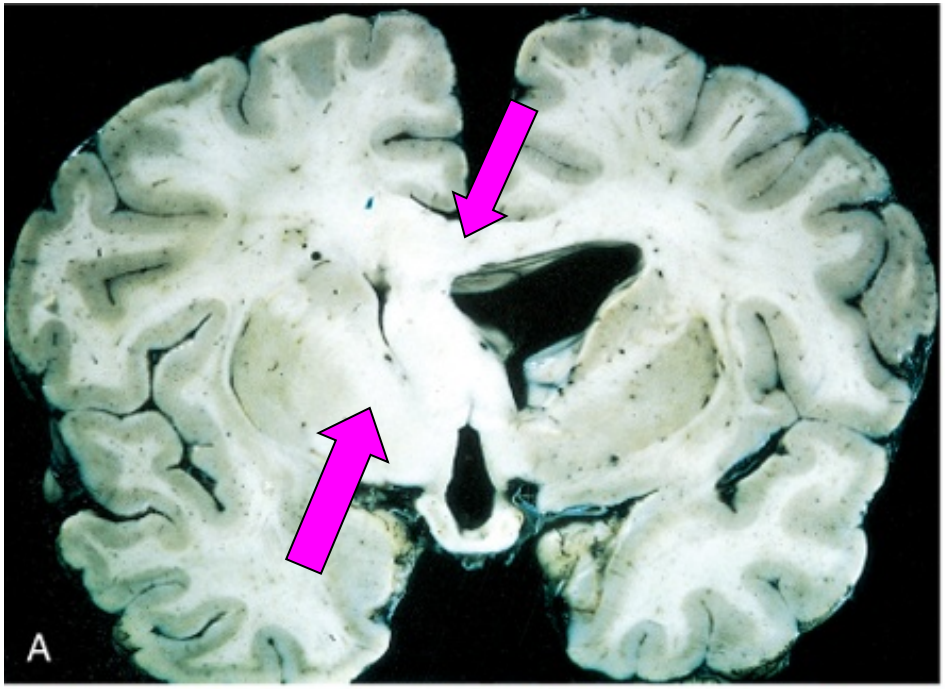
►**Grossly**, fibrillary astrocytoma is a gray, poorly defined, infiltrative **T which *always* infiltrate beyond the grossly evident margins,** expands & distorts the brain, without forming a discrete mass (F23-22A). **T** C/S is either firm or soft & gelatinous with cystic degeneration

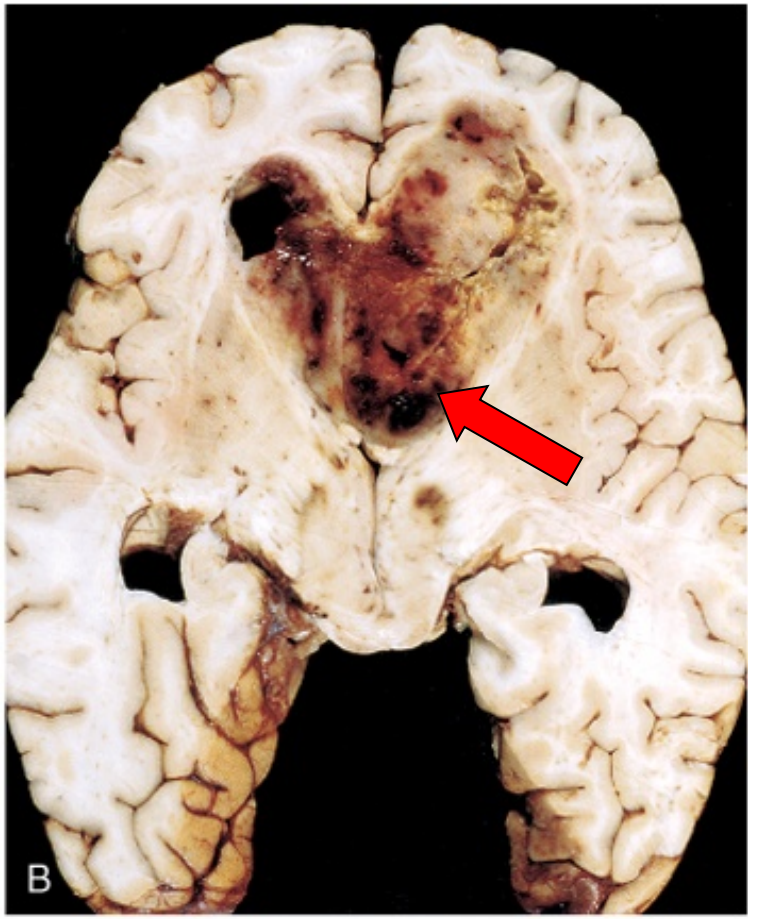
☹ In **glioblastoma multiforme**, **heterogeneity (variation in** the appearance of the **T** from region to region, is characteristic (F23-22B & F 9-67). Some areas are **firm & white**, others are soft & yellow (due to **necrosis**), & others show **cystic degeneration) & hemorrhage.**

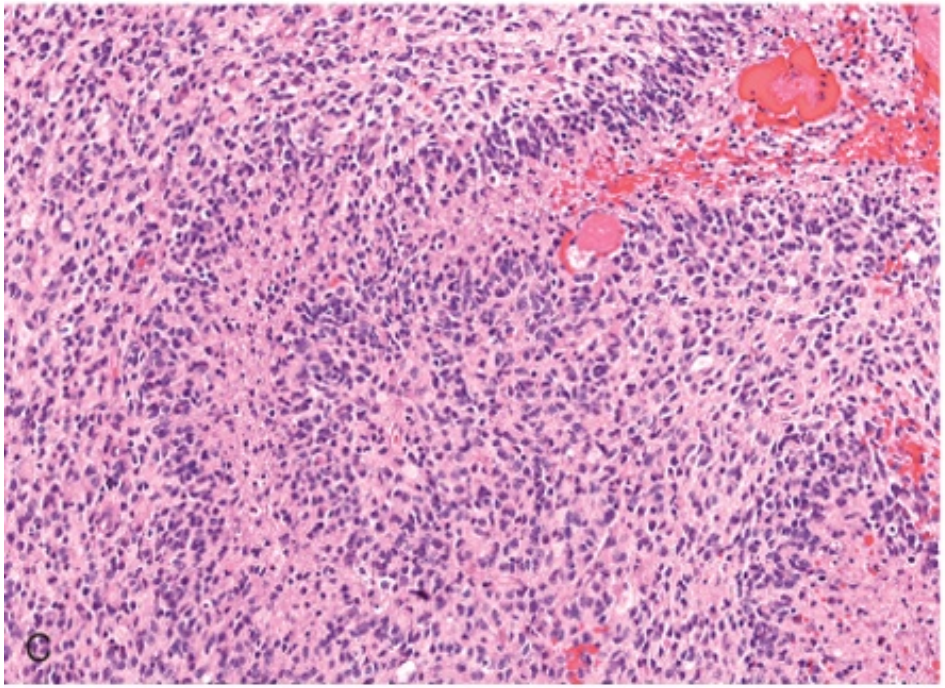
◘ **Well-differentiated fibrillary astrocytomas (**◘ 4.31) are characterized by a mild to moderate ↑ in the number of glial cell nuclei, mild nuclear pleomorphism, & an intervening feltwork of fine, GFAP-positive astrocytic cell processes that give the background a fibrillary appearance.

☹The **T is infiltrative & transition between neoplastic & normal tissue is indistinct (not clear); & T** cells can be seen infiltrating normal tissue at some distance from the main lesion.

- **Anaplastic astrocytomas** show more dense cellularity, greater nuclear pleomorphism, & ↑ mitoses.

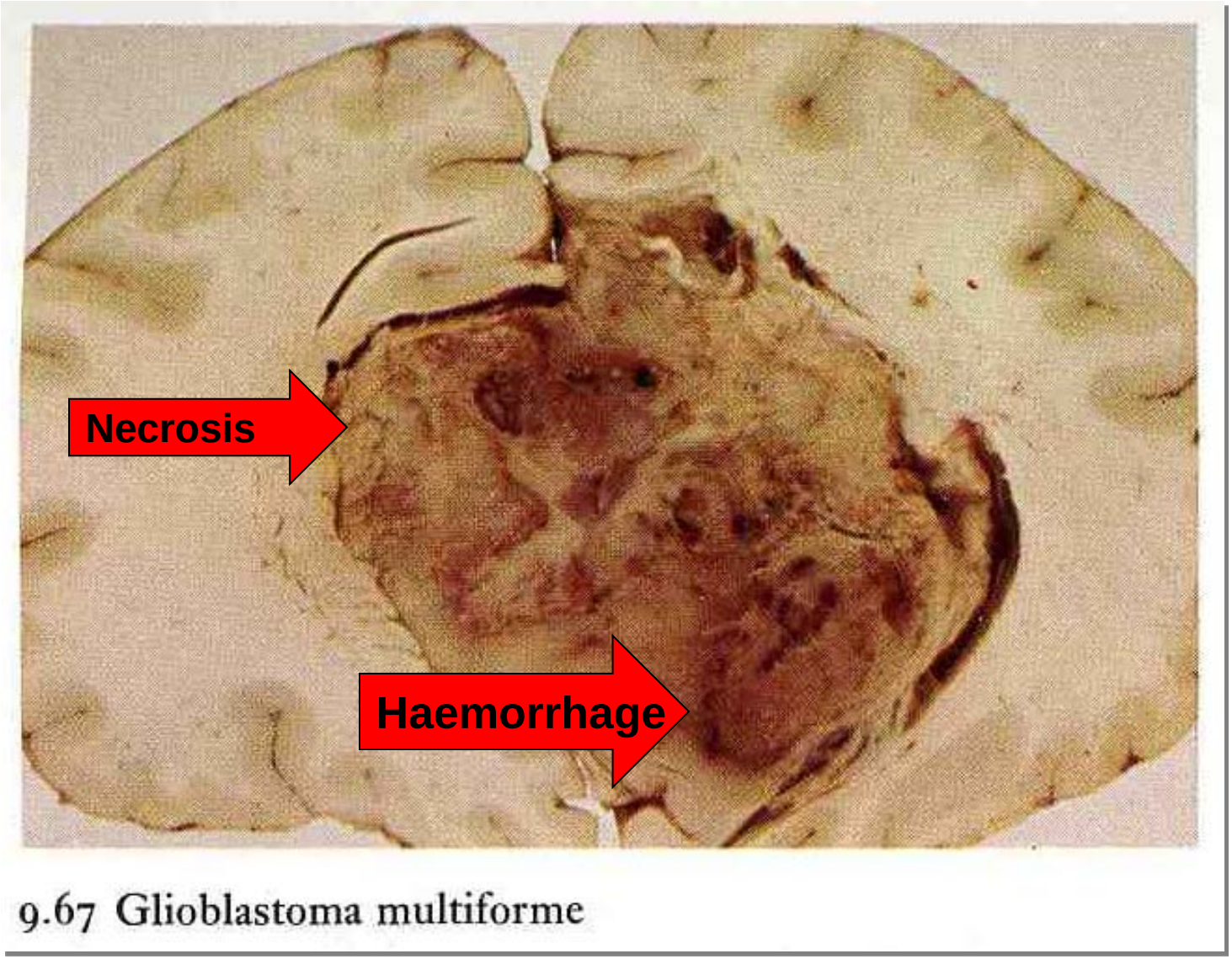






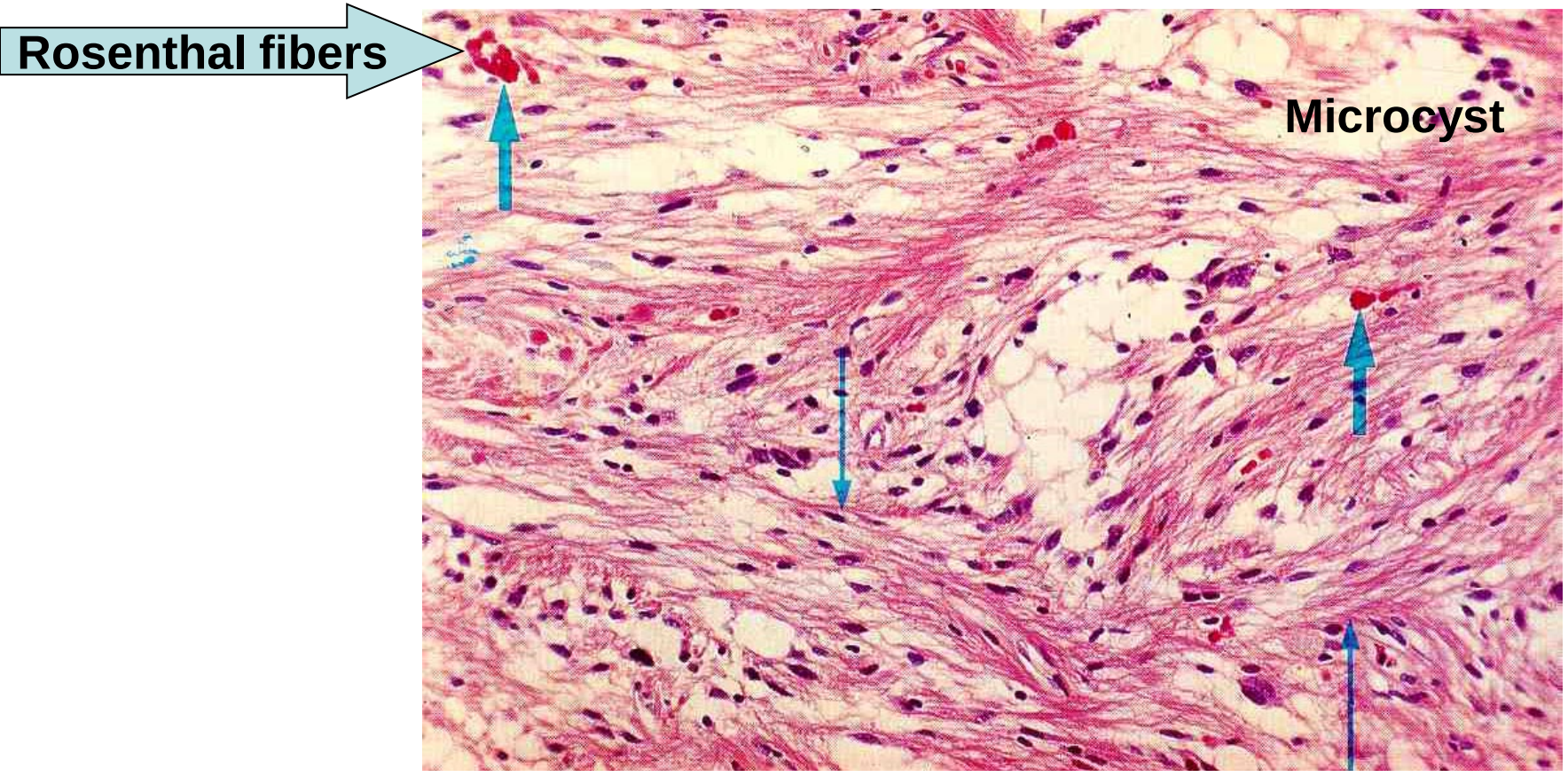
F23-22: **A, Low-grade astrocytoma** is seen as expanded white matter of the left cerebral hemisphere & thickened corpus callosum & fornices.
Glioblastoma: B, Necrotic, hemorrhagic, infiltrating **T;** histologically **C,** show (1) high cellularity + (2) pseudo-palisading of **T** cell nuclei around necrosis.

F 9-67:**Glioblastoma multiforme.** Massive tumor infiltrating the corpus callosum & both cerebral hemispheres; showing yellow-white (necrotic) & reddish-brown (hemorrhagic) areas.



◘ 4.31: **Astrocytoma (Fibrillary): brain X 200.**

Consist of mature-looking neoplastic astrocytes with ill-defined cytoplasmic boundaries & pleomorphic ovoid/elongated basophilic nuclei. Their **neurofibrillary processes** are well-developed & abundant & arranged in large eosiniphilic bundles (thin A), within which there are collections of fluid (**microcysts**). The dens red bodies (thick A) are **Rosenthal fibers.**



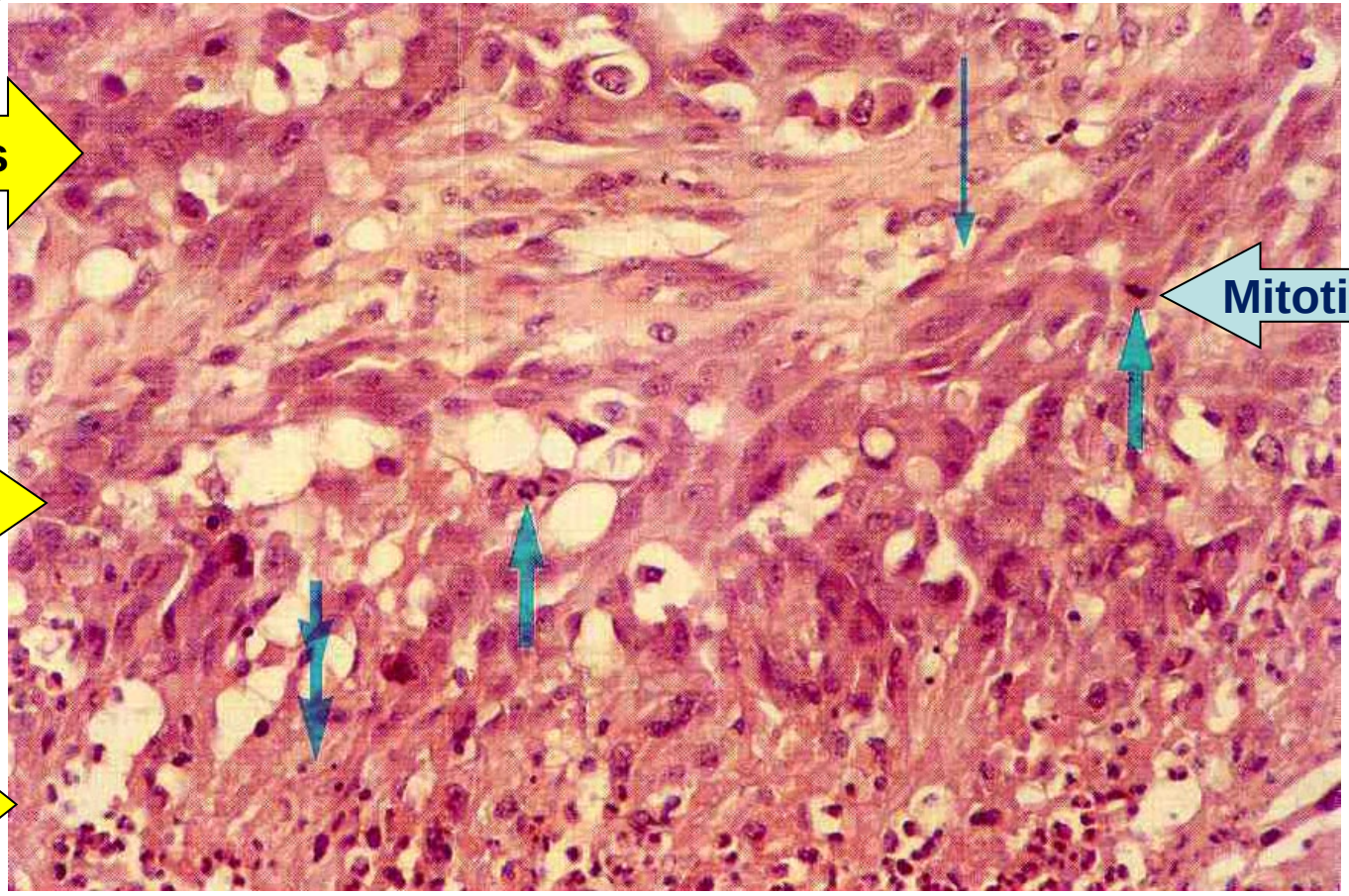
• The highest grade **T** , known as **glioblastoma**, has a histologic appearance similar to anaplastic astrocytoma with the additional features of (1) **palisading necrosis (◘** 4.35), **(2) pseudo-palisading nuclei** (F23-22C) & **(3) vascular or endothelial cell proliferation (◘**4.36).

Pilocytic Astrocytoma (F9-59)

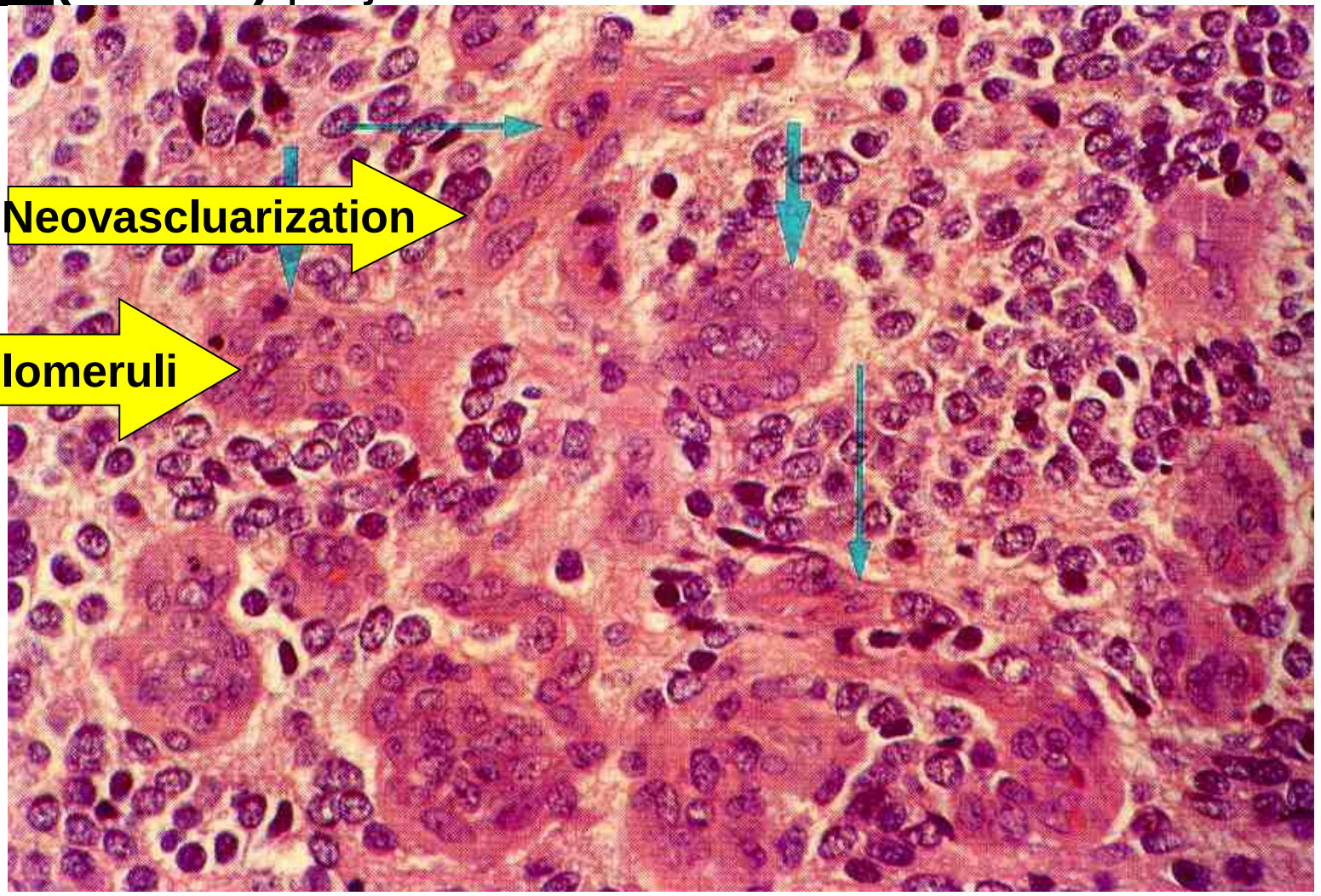
★Pilocytic astrocytomas are **relatively** • **benign T**, often • **cystic**, that typically occurs in • **children & young adults** & are usually located in the • **cerebellum** but may also appear in the floor & walls of the third ventricle, the optic nerves, & occasionally the cerebral hemispheres.
☺ Symptomatic recurrence from incompletely resected lesions is often associated with cyst enlargement rather than growth of the solid component.

►**Grossly**, pilocytic astrocytoma is often **cystic,** with a **mural nodule in the wall of the cyst**; if **solid**, it is usually well circumscribed.
◘ H, it composed of areas with bipolar cells with long, thin "hairlike" processes that are GFAP positive; Rosenthal fibers, eosinophilic granular bodies, & microcysts are often present. **Necrosis & mitoses are absent**.

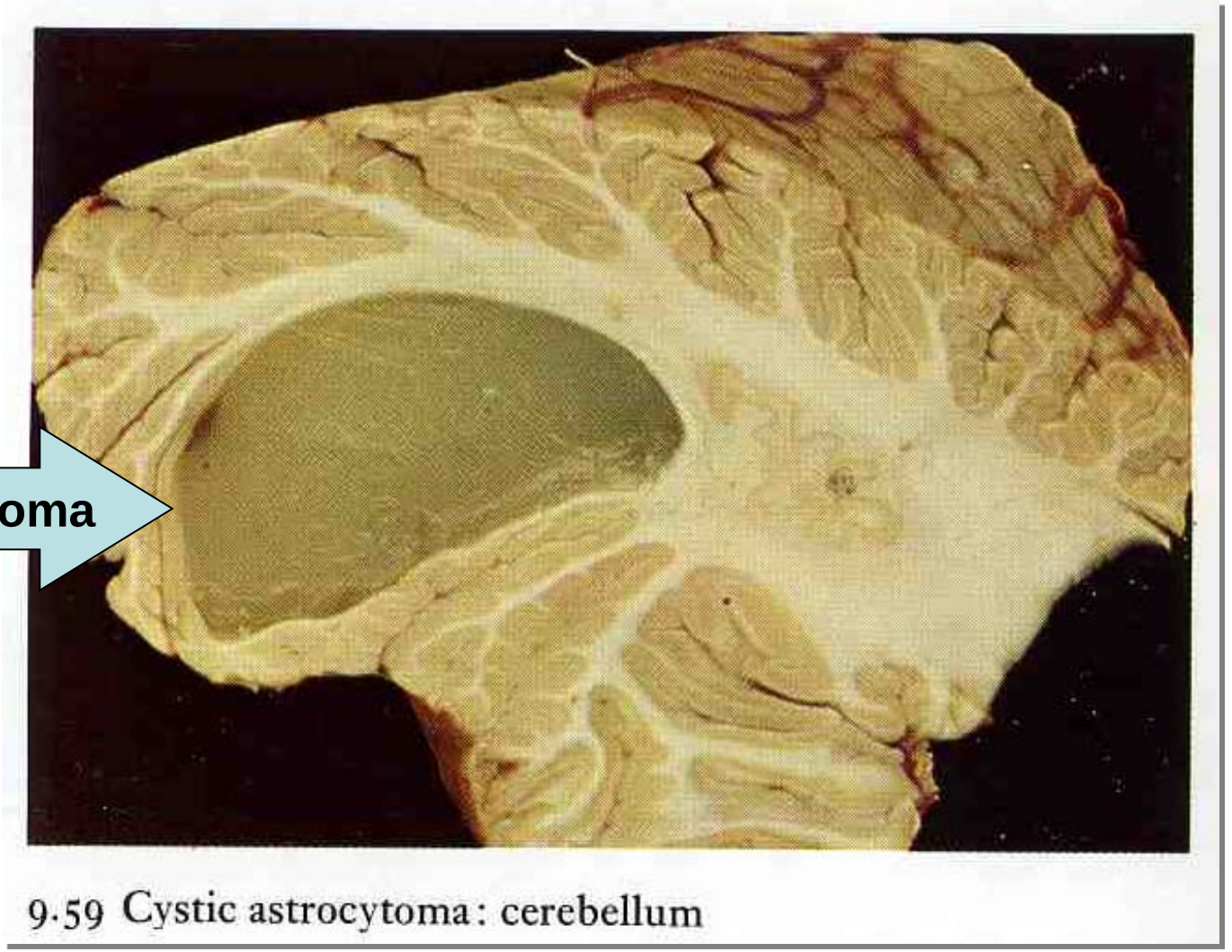
◘ 4.35: **Glioblastoma multiforme: brain.** Grade IV out of IV astrocytoma. Cells are (1) **very pleomorphic,** most are elongated (**thin A**), with long fibrillary processes, elongated nuclei with round blunt ends & many contain prominent **nucleoli** & (2) some are **multinucleated, &** many show (3) **mitotic** figures (**thick A**), some are abnormal; (4) **Necrosis** is marked (**double A**).



◘ 4.36:**Glioblastoma multiforme: Brain X360.** The tumor is very vascular, prominent (1) **neovascluarization (thin A)** lined by large plump EC with abundant cytoplasm. A prominent feature are ‘Buds’ of proliferating EC, resembling (2) **miniature glomeruli (thick A)** project from the surface of the BV.



F 9-59: **Pilocytic (cystic) astrocytoma: cerebellum.** Crescentic **cyst** cavity, filled with gelatinous pale green fluid occupying the lateral lobe of the **cerebellar** hemisphere. The tumor is slowly-growing & affects mainly **children & young adults**.



9·59 Cystic astrocytoma: cerebellum

Oligodendroglioma

★ Constitute 5% to 15% of all gliomas. • Most common in the 4th & 5th decades. •Found mostly in the cerebral hemispheres.

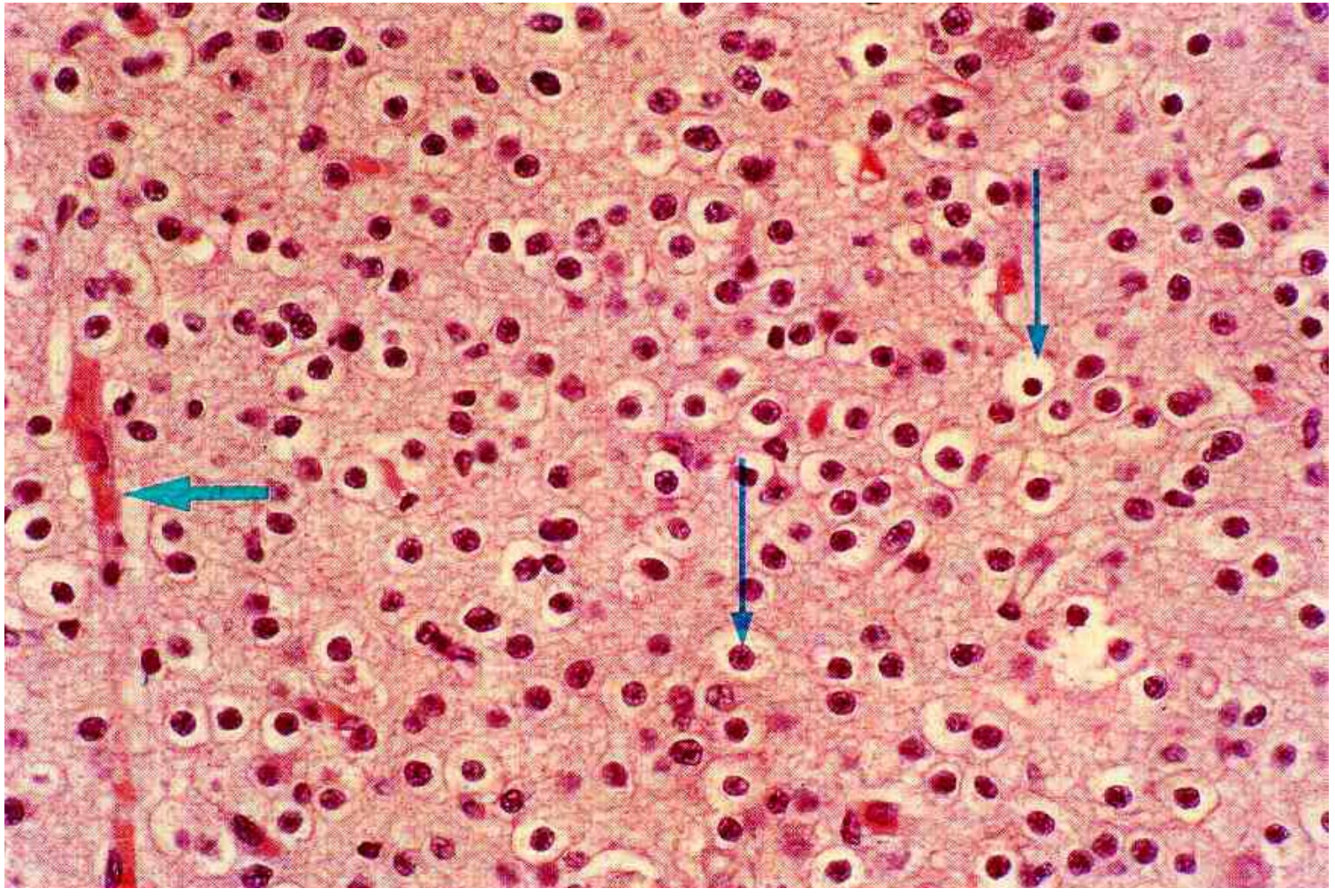
•The most common genetic findings are loss of heterozygosity for chromosomes 1p 7 19q. • Patients may have had neurologic complaints, including **seizures**.

►**Grossly**, **infiltrative** gelatinous, gray **T** & may show cysts, focal hemorrhage, while **calcification is present in 90% of T.**

◘ **T** cells are regular (similar to normal oligodendrocytes), with spherical nuclei, containing finely granular chromatin surrounded by a clear halo of cytoplasm (F23-23A & ◘ 4.31), with delicate network of anastomosing capillaries & very rare mitotic figures, **Calcification** present in 90% of **T**.
☹ Anaplastic oligodendroglioma shows ↑ cell density & mitotic activity, nuclear anaplasia, & necrosis.

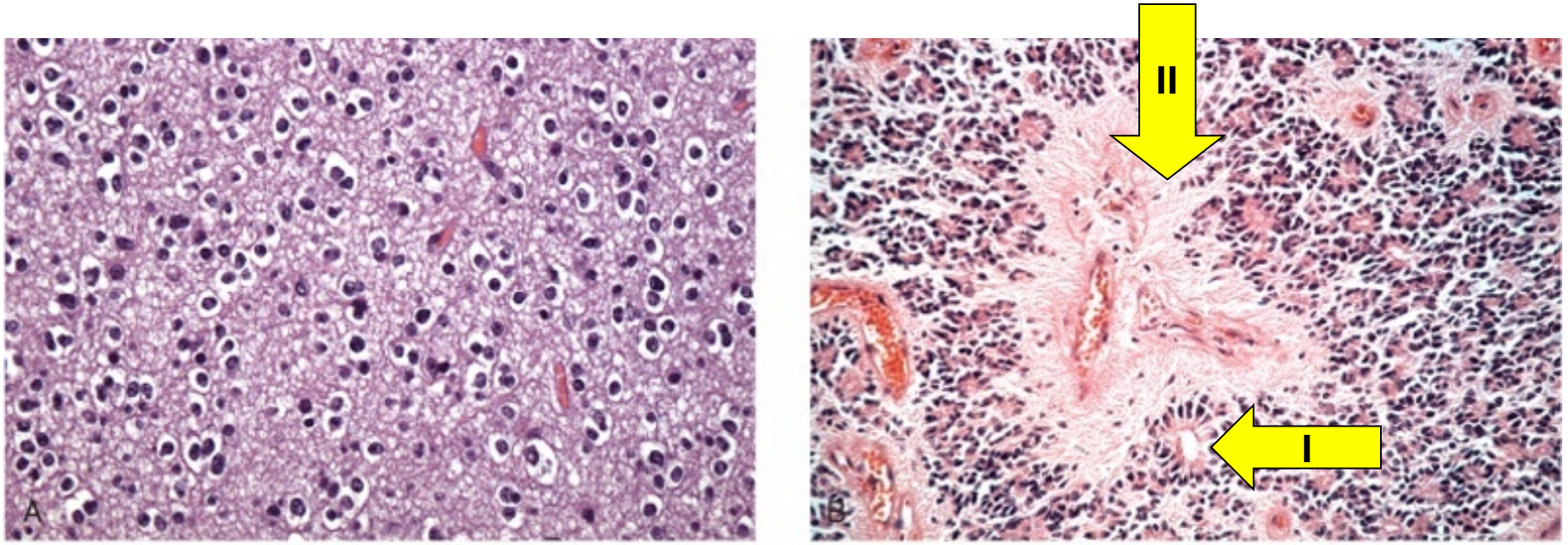
• **Prognosis** is better than that of astrocytomas.
Combine surgery, chemotherapy, & radiotherapy yields an average survival of 5 to 10 years.
☹ Anaplastic oligodendroglioma have worse prognosis.

◘ 4.31:**Oligodendroglioma: brain X360.** Highly cellular **T**, each cell has (I) a moderate amount of eosinophilic cytoplasm, bounded by a well-defined membrane & (II) a small rounded darkly basophilic nucleus, surrounded by a perinuclear, large clear halo (thin A), appearance called **‘ boxing’ of the nucleus**.



F23-23: **A, Oligodendroglioma.** Regular cells having round nuclei, with a cytoplasmic halo.

B, Ependymoma: (I) tumor cells form round or elongated structures (**rosettes**, canals) resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen & **(II) perivascular pseudo-rosettes,** with tumor cells arranged around vessels with an intervening zone consisting of thin ependymal processes directed toward the wall of the BV.



Ependymoma

★Mostly arise next to the ependyma-lined ventricular system, including the central canal of the spinal cord.

- In the **first two decades** of life, they constitute 5% to 10% of the primary brain **T** & they typically occur near the **4th ventricle**
- In **adults**, the spinal cord is their most common location; & in which they are particularly frequent in neurofibromatosis type 2.
- **Because ependymomas usually grow within the ventricles, CSF dissemination is a common occurrence.**

►**Grossly**, in the 4th ventricle, **T** are typically solid or papillary masses extending from the floor of the ventricle.

◘ H, **T** cells, with regular round to oval nuclei & abundant granular chromatin. Between the nuclei there is a variably dense fibrillary background. **T** cells may form:
(I) rosettes or canals (round or elongated structures that resemble the embryologic ependymal canal, with long, delicate processes extending into a lumen {F 23- 23B (I) }.

◘ **(II) perivascular pseudo-rosettes** are more frequently seen, in which **T** cells are arranged around vessels, with an intervening zone consisting of thin ependymal processes directed toward the wall of the vessel {F23- 23B (II) & ◘ 4.38).

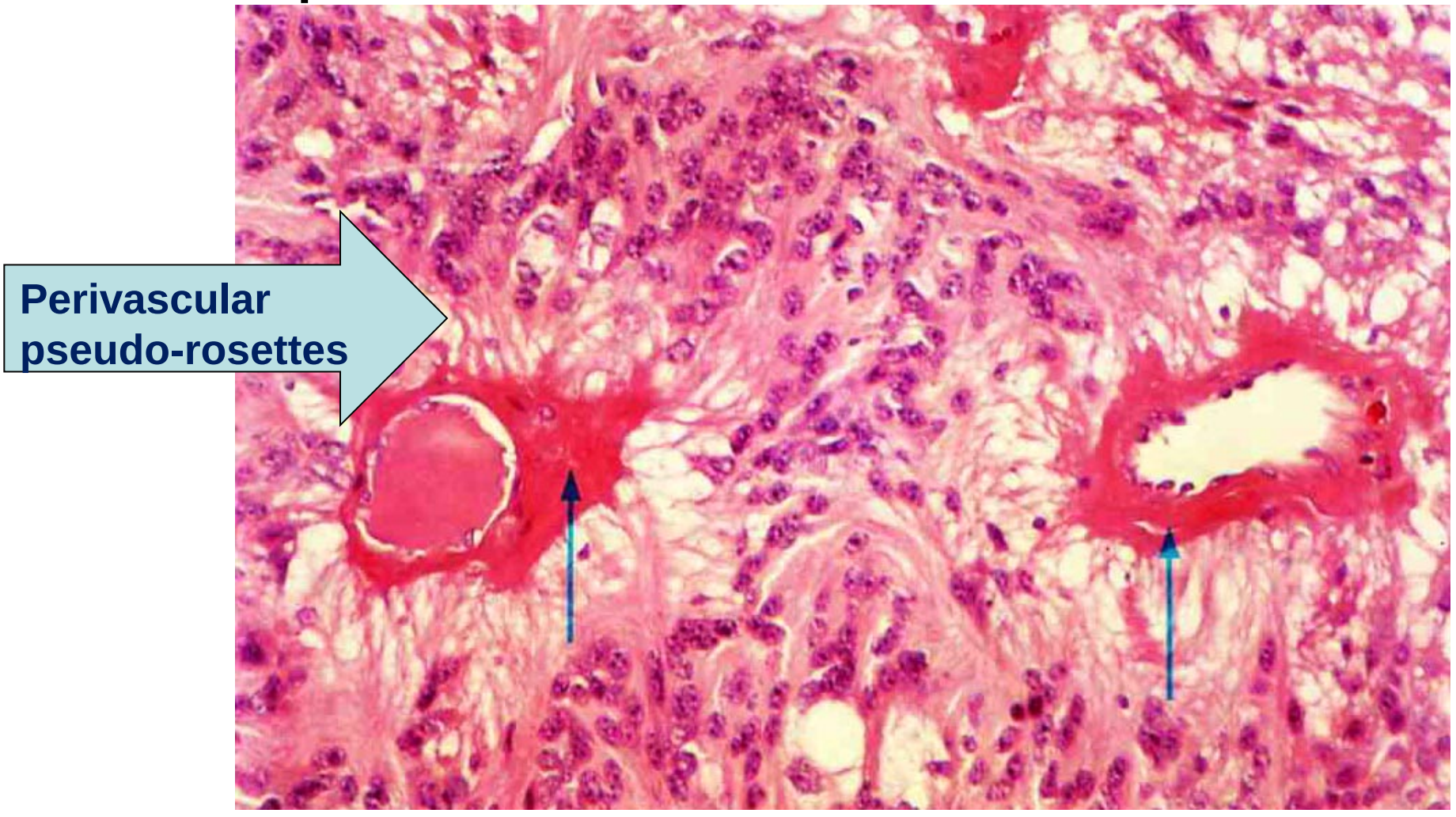
• **Anaplastic ependymomas** show ↑ cell density & mitotic rates, necrosis, & less evident ependymal differentiation.

Neuronal Tumors

★ ***Central neurocytoma*** is a low-grade neuronal **T** found within & adjacent to the ventricular system (most commonly the lateral or 3rd ventricles), characterized by evenly spaced, round, uniform nuclei & often islands of neuropil.

★ ***Ganglio-gliomas*** are **T** with a mixture of glial elements (looking like a low-grade astrocytoma) & mature-appearing neurons (ganglion like). Most of these **T** are **slow growing**, but the glial component occasionally becomes frankly anaplastic, & the disease then progresses rapidly. These lesions often **present with seizures**.

◘ 4.38: **Ependymoma: brain X 360.** Two dilated BV, with thick hyalinized deeply eosinophilic walls (arrows); surrounded by tumor cells arranged around & attach to the walls of BV by their elongated filamentous (& very vacuolated) bases, so-called **Perivascular pseudo-rosettes.**



★*Dysembryoplastic neuroepithelial tumor*

★A distinctive, low-grade **T** of childhood, showing slow growth & a relatively good prognosis after resection; it often **present with seizures**.

★These lesions are typically located in the superficial temporal lobe.

◘ **consist of small round cells with features of <u>neurons</u>** arranged in columns & around central cores of processes. These typically form multiple discrete **intracortical nodules** that have a myxoid background.

There are well-differentiated "floating neurons" that sit in the pools of mucopolysaccharide-rich fluid of the myxoid background.

Medulloblastoma

★Occurs mainly in • **children** (accounting for 20% of pediatric brain **T**) & exclusively **(ONLY)** in the • **cerebellum.** It is largely **undifferentiated T,** although it is of **neuroectodermal origin** & may express neuronal & glial markers.
It is • **highly malignant with poor prognosis** for untreated patients, however, it is very • **radiosensitive**. With total excision & radiation, the 5-year survival rate may be 75%.
• **T** of similar histology & poor degree of differentiation can be found elsewhere in the CNS (called CNS primitive neuroectodermal tumor or CNS PNET).

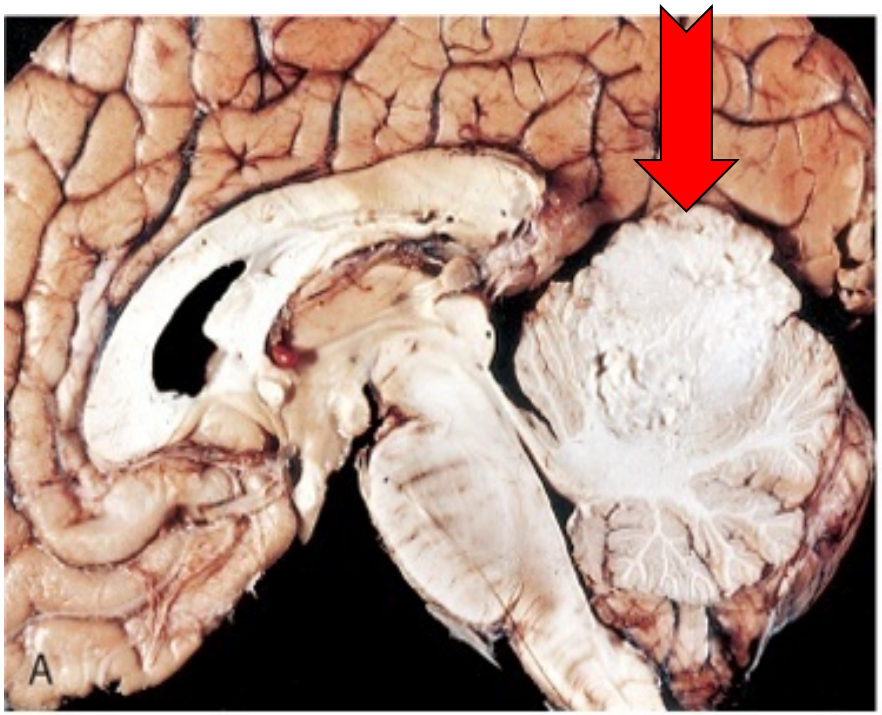
►**Grossly**, in children, medulloblastomas are located in the **midline of the cerebellum**; lateral **T** occur more often in adults. **T** is well **circumscribed, gray, & friable**, & may be seen extending to the surface of the cerebellar folia (F 9-72) & **involving the leptomeninges** (F23-24A).

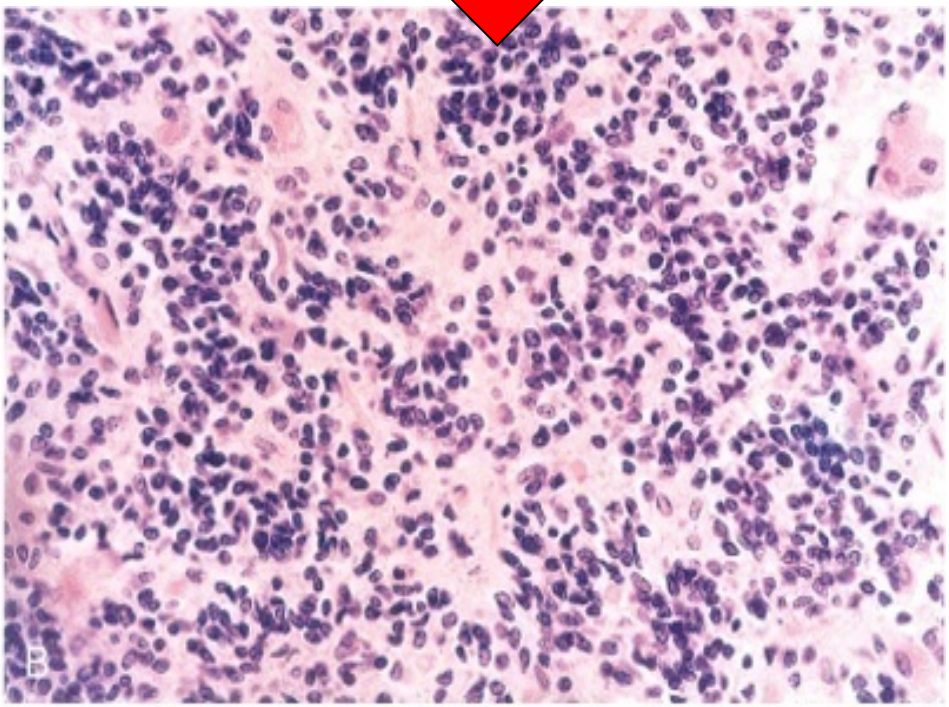
◘ **T** are extremely cellular, with sheets of anaplastic **("small blue") cells.** The Individual **T** cells are small, with little cytoplasm & hyperchromatic nuclei; mitoses are abundant (F23-24B). **T** cells spread by the CSF.

F23-24: **Medulloblastoma: Brain**

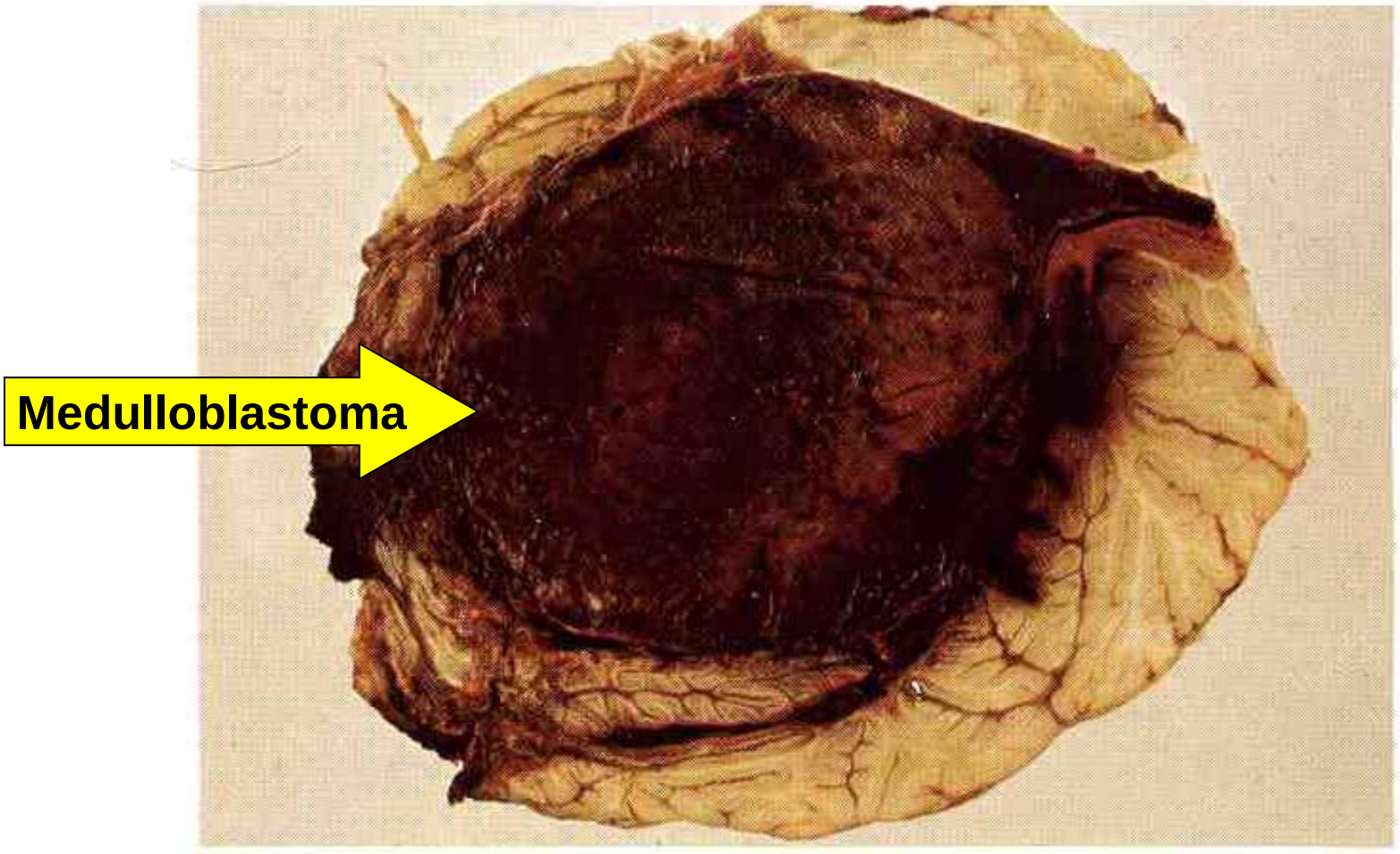
A, Sagittal section of brain showing medulloblastoma destroying the superior midline cerebellum.

B, ◘ H, An extremely cellular tumor, with sheets of anaplastic **("small blue ells").** The individual tumor cells are small, with little cytoplasm & hyperchromatic nuclei; mitoses are abundant.





F 9-72: **Medulloblastoma.** Large, rounded, friable, necrotic & hemorrhagic well-demarcated, tumor expanding cerebellar hemisphere; occuring predominantly in children (5 to 8 yr) tumor tend to spread through CSF allover the brain & spinal cord.



9.72 Medulloblastoma

Other Parenchymal Tumors

Primary Central Nervous System Lymphoma

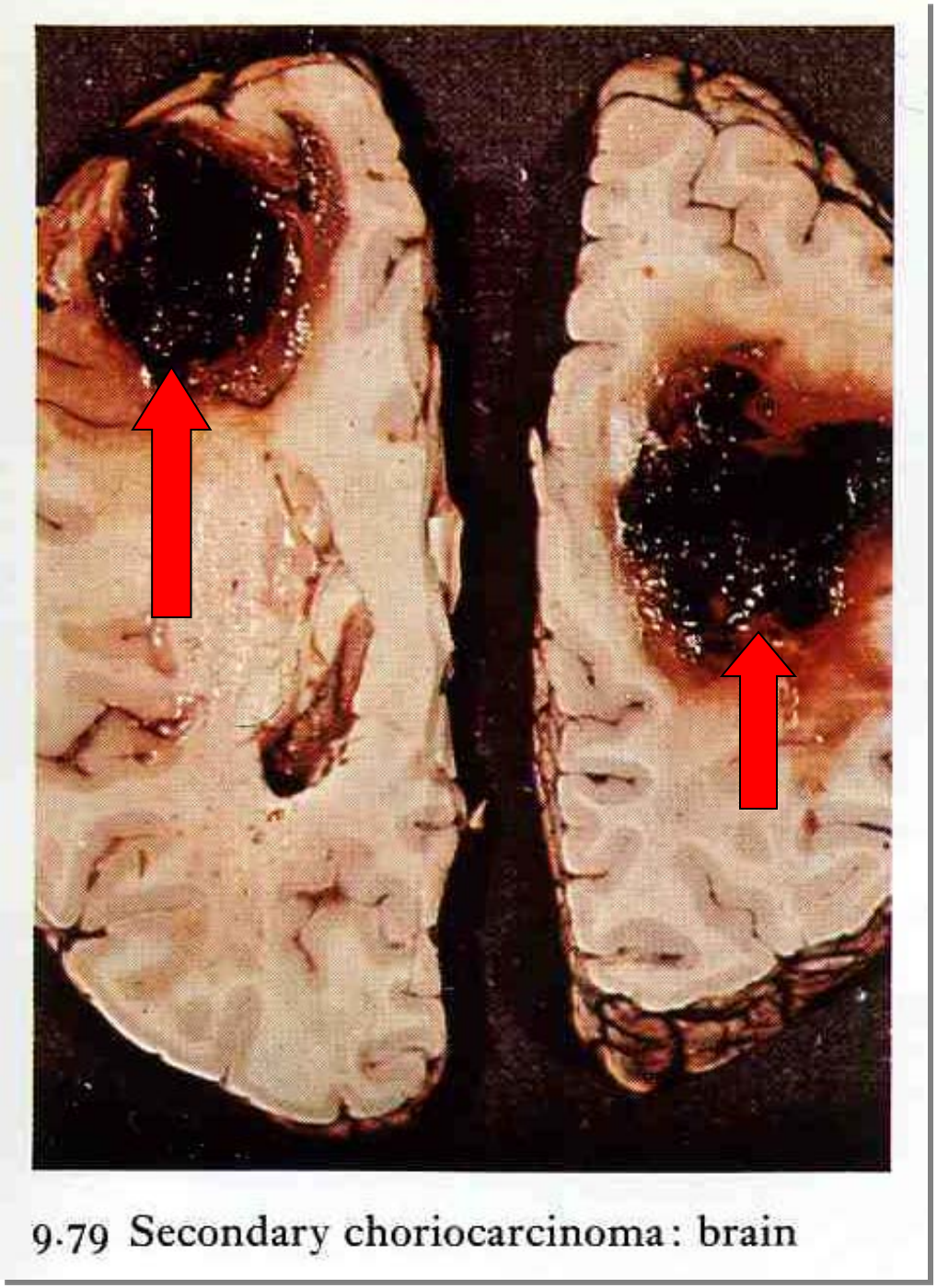
- accounts for 2% of extranodal lymphomas & 1% of intracranial tumors.
- The **most common CNS neoplasm in immunosuppressed** individuals (including transplant recipients & AIDS patients); in which lymphomas are nearly **all driven by Epstein-Barr virus.**
- In nonimmunosuppressed populations the incidence ↑ after 60 years of age; most of these **T** are **diffuse large B-cell lymphomas**.
- **All primary brain lymphomas are aggressive with relatively poor response** to chemotherapy as compared with peripheral lymphomas.

►**Grossly**, **T** often infiltrate all of the white, gray matter & cortex. Periventricular spread is common.
The **T** are **relatively well defined** as compared with glial neoplasms but are not as discrete as metastases.
◘ H, most commonly, they are large-cell lymphomas, showing extensive areas of **central necrosis;** infiltrating the parenchyma of the brain & accumulate around BV.

Germ-Cell Tumors

★ **Primary** brain germ-cell **T** occur **along the midline**, most **commonly in the pineal & the suprasellar regions.**

- They account up to 1% of brain **T** in people of European descent but as many as **10% of brain tumors in Japanese.**
- **90% occurs during the first two decades**. Germ-cell **T** in the pineal region show a strong male predominance.
- Germ-cell **T** in the brain share many of the features of their counterparts in the gonads. CNS **T** that is the counterpart to the **testicular seminoma** is called a **germinoma.**
- CNS involvement by a gonadal germ-cell **T** **secondareies** is not uncommon (F9-79).



9.79 Secondary choriocarcinoma: brain

F 9-79: **Secondary choriocarcinoma: Brain**.

☠ Two large hemorrhagic lesions are present (which resemble intracranial hemorrhages).
Histology reveals secondary choriocarcinoma in the brain

The patient was a 36 years old man with testicular choriocarcinoma.

Meningiomas (F23-25A & F 9-51)

★A predominantly • **benign T of adults**, **attached to the dura,** & • arising from the **meningothelial cell of the arachnoid.**

• May be found along any of the external surfaces of the brain as well as **within the ventricular** system, where they **arise from the stromal arachnoid cells of the choroid plexus.**

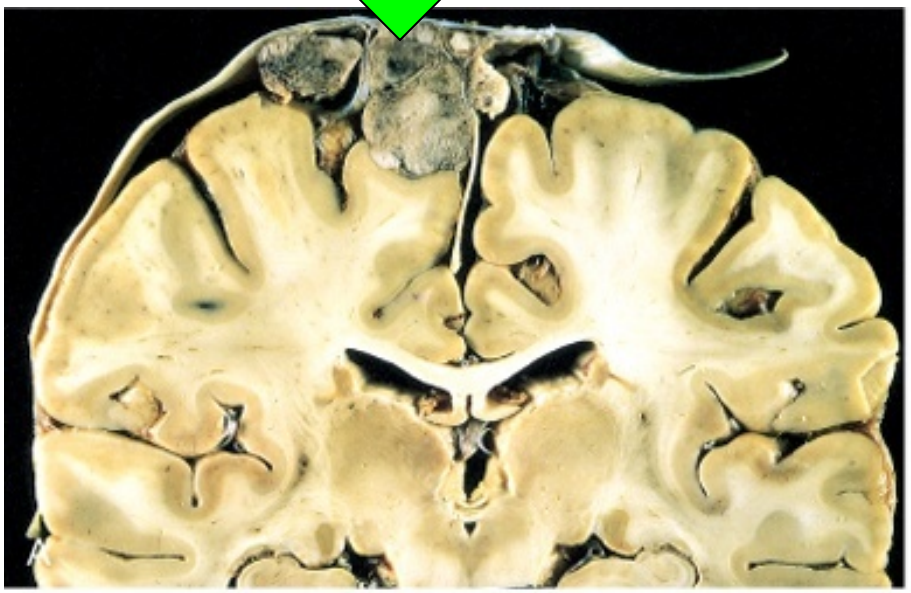
★They usually present with• **vague** nonlocalizing symptoms, or with • **focal findings** due to compression of underlying brain.

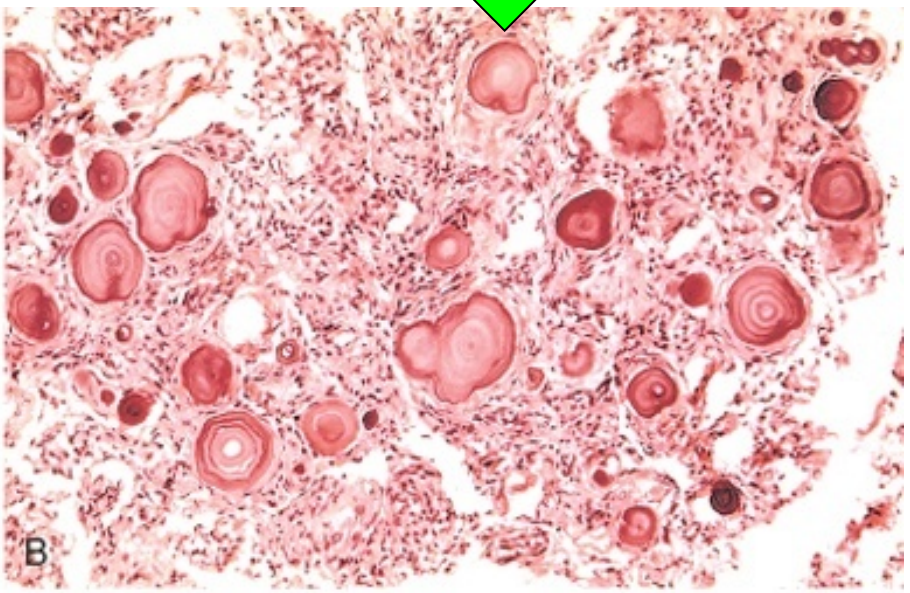
• When **multiple meningiomas** are present, especially in association with 8th nerve schwannomas or glial **T**, a possible diagnosis of **neurofibromatosis type 2** should be considered.

• 50% of meningiomas, not associated with NF2, still have mutations in the NF2 gene on the long arm of chromosome 22.

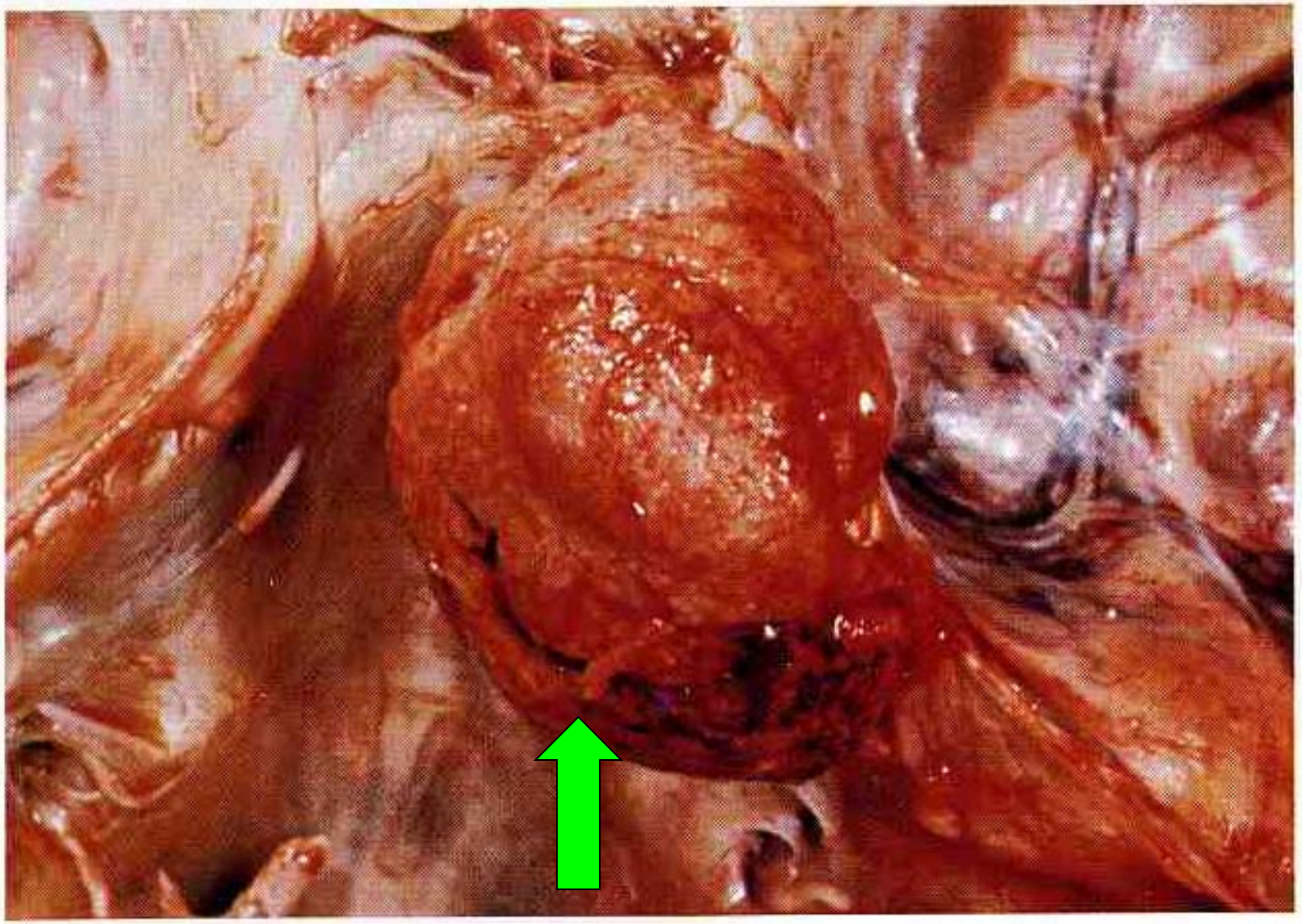
►**Grossly**, meningiomas grow as • **well-defined dural-based masses** that • **compress underlying brain** but are **easily separated from it** (F23-25A & F 9-51). Extension into the overlying bone may be present.

F23-25: **Meningioma.**
A, Parasagittal multilobular meningioma *attached* to the *dura* with *compression* of the underlying brain; but it is easily separated from it
B, ◘ H, Whorled pattern of cell growth & psammoma bodies.





F 9-51: **Meningioma.** A large smooth, lobulated, pink-red tumor situated posterior to the dorsum sellae (skull base).



9.51 Meningioma

◘ H, patterns: • **Syncytial,** with whorled clusters of cells that sit in tight groups without visible cell membranes; • **Fibroblastic,** with elongated cells & abundant collagen deposition between them; • **Transitional (◘** 4.30**),** which shares features of the syncytial & fibroblastic types; • **Secretory,** with PAS-positive intracytoplasmic droplets; • **Microcystic,** with a loose, spongy appearance, & • **psammomatous,** with numerous psammoma bodies (F23-25B).

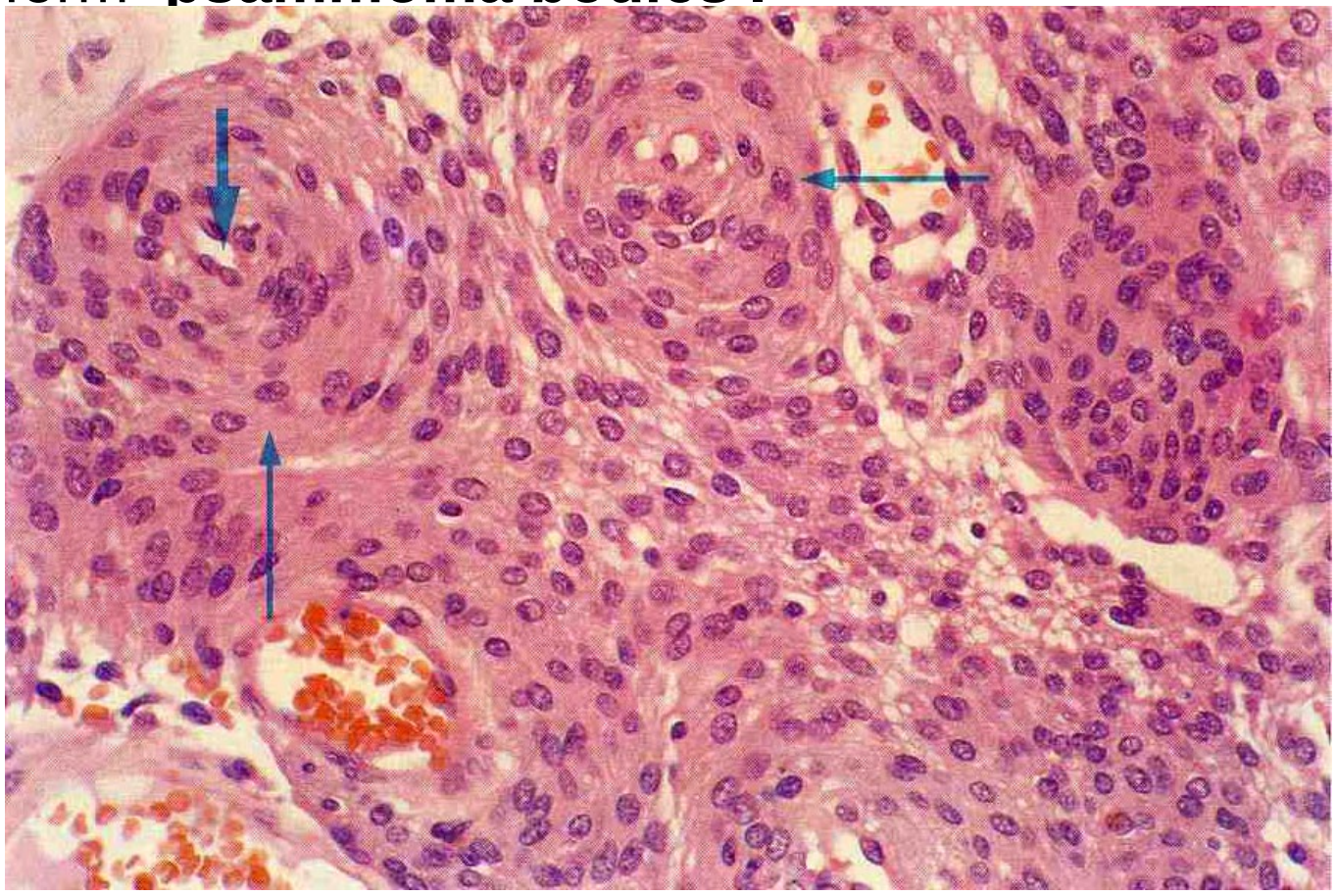
Atypical meningiomas

• **Are T** recognized by a ⇨higher mitotic rate**,** showing ⇨ more aggressive local growth, ⇨ higher rate of recurrence.
• **Anaplastic (malignant) meningiomas** are highly aggressive **T**, resemble high-grade **sarcoma,**

★ Most meningiomas are easily separable from underlying brain, but **some infiltrate the brain.** Brain invasion is associated with ↑ risk of meningioma **recurrence.**

• Prognosis of meningiomas is influenced by the *size* & *location* of the lesion, *surgical accessibility*, & *histologic grade.*

◘ 4.30: **Meningioma, Transitional type. X360.** 5 Compact **whorls** of uniform tumor cells (thin arrows), having abundant eosinophilic cytoplasm, & ill-defined boundaries. The nuclei are uniform ovoid & vesicular & their chromatin is pale & finely granular. A small cavity at the center of the whorls (thick A) is seen, & the central cells eventually become hyalinized & may calcify to form **‘psammoma bodies’.**



Metastatic Tumors in the CNS

★ 50% of intracranial (Brain & meninges) **Tumors** are metastatic & mostly are carcinomas.

★ The commonest 5 primary cancer sites, which account for about 80% of all metastases are: **lung (◘** 4.48**), breast (**F9-76 & ◘ 4.47**), skin melanoma** (F23-26)**, kidney, & GIT.**

►**GROSSLY,** In the brain, metastases may be single but often are **multiple**, form **sharply demarcated masses**, usually surrounded by a zone of **edema** (F23-26) & microscopically the **boundary** between **T** & brain parenchyma is well defined.

★***Paraneoplastic syndromes***

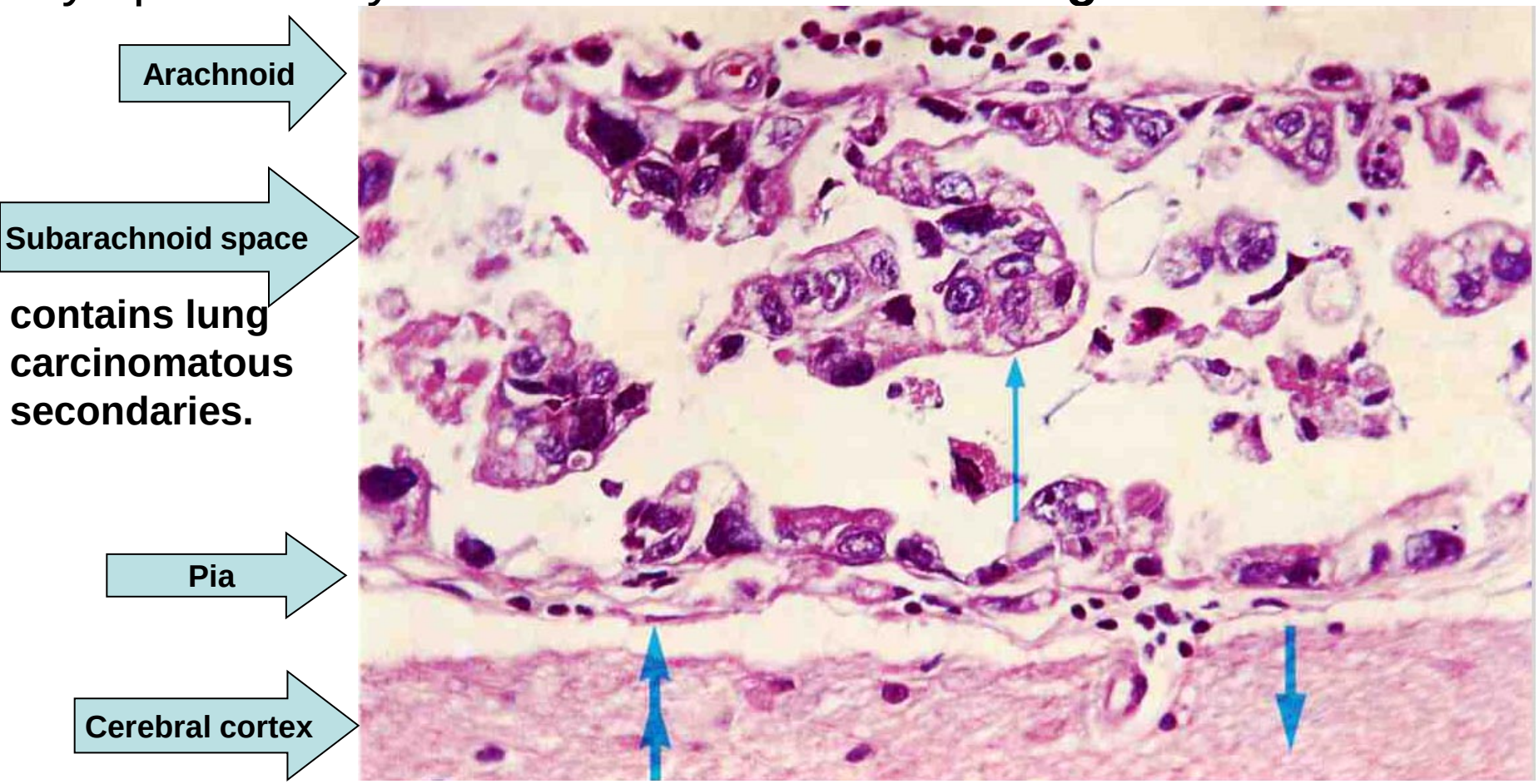
may involve the peripheral & CNS, sometimes, **even before** the clinical recognition of the malignant **T**. These syndromes are most **commonly** associated with **small-cell ca of the lung.**

★Characteristic paraneoplastic syndromes patterns include:

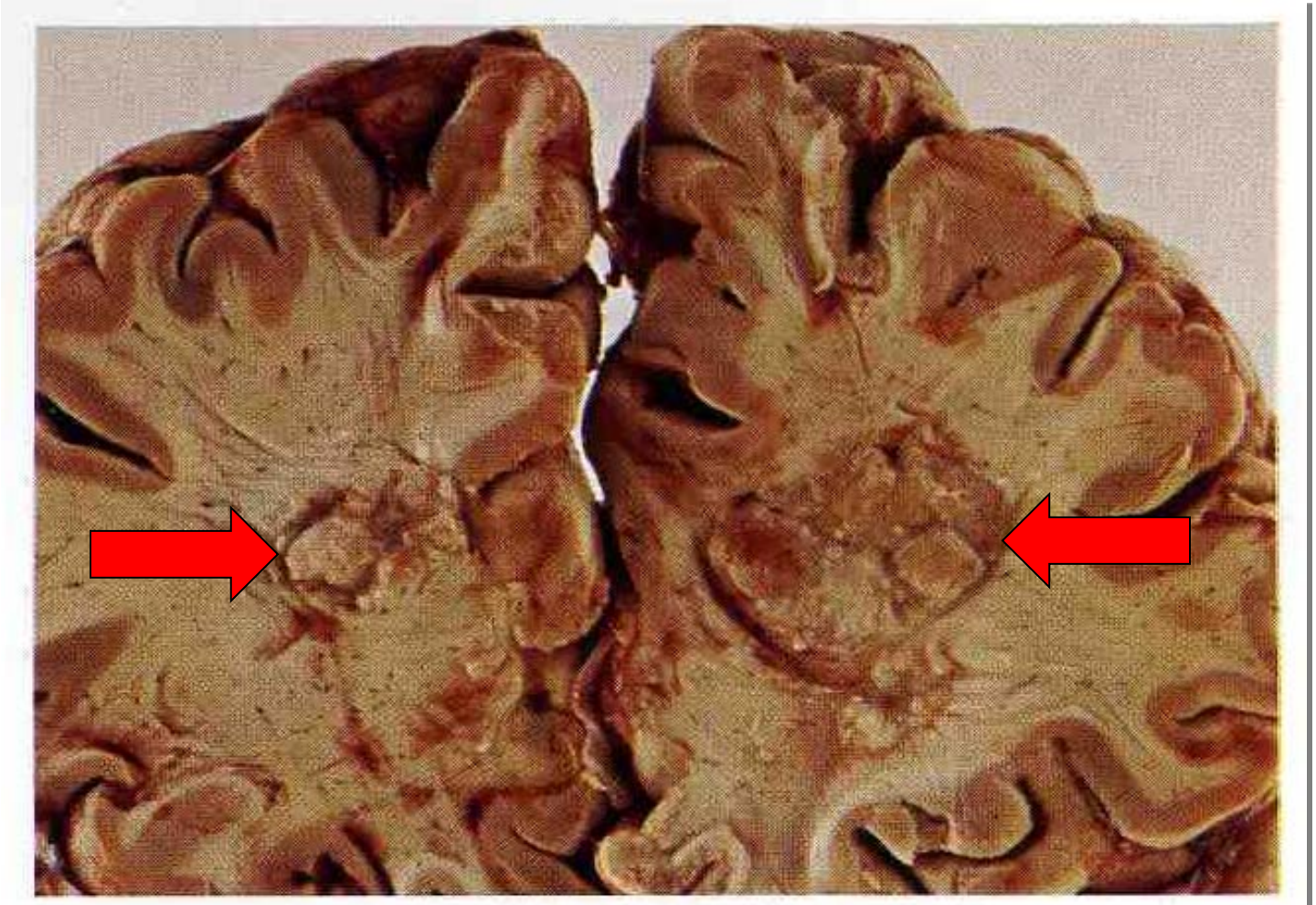
- ***Limbic encephalitis*** causing a subacute dementia,
- ***Subacute cerebellar degeneration*** resulting in ataxia, with destruction of Purkinje cells,
- **S*ubacute sensory neuropathy*** leading to altered pain sensation with loss of sensory neurons from dorsal root ganglia.

◘ 4.48: **Secondary carcinoma: brain X160.**

The **subarachnoid space** contains malignant • **carcinomatous cells secondaries** (thin A) from the **lung** with very pleomorphic, large pale vesicular nuclei & prominent nucleoli & vacuolated cytoplasm. Such lesion may give rise to clinical signs & symptoms very similar to • **bacterial meningitis.**

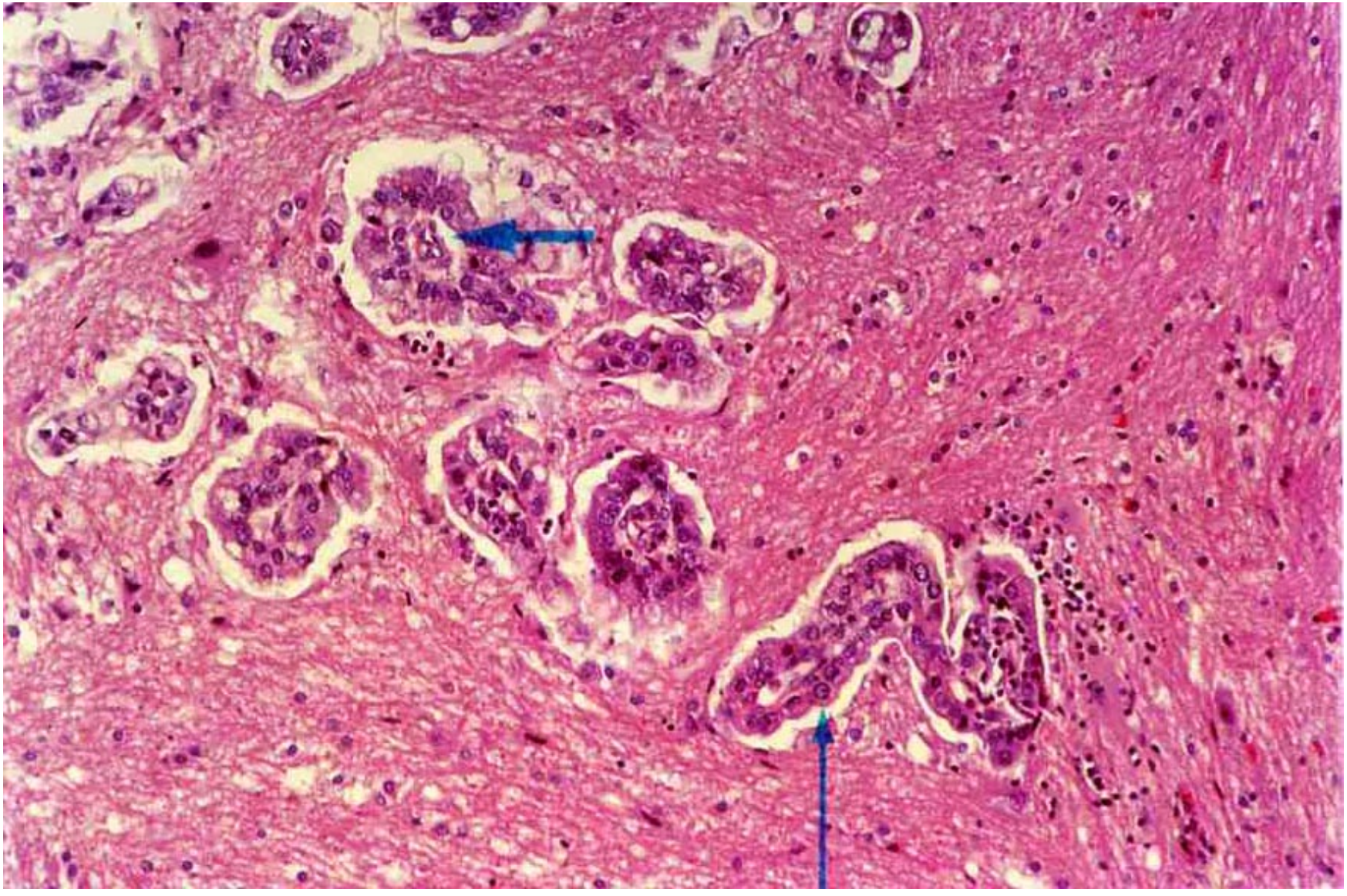


F 9-76: **Secondary carcinoma: brain.**
The patient had carcinoma of the **breast**. Frontal region section shows two large necrotic secondary deposits in the central white matter of both cerebral hemispheres.

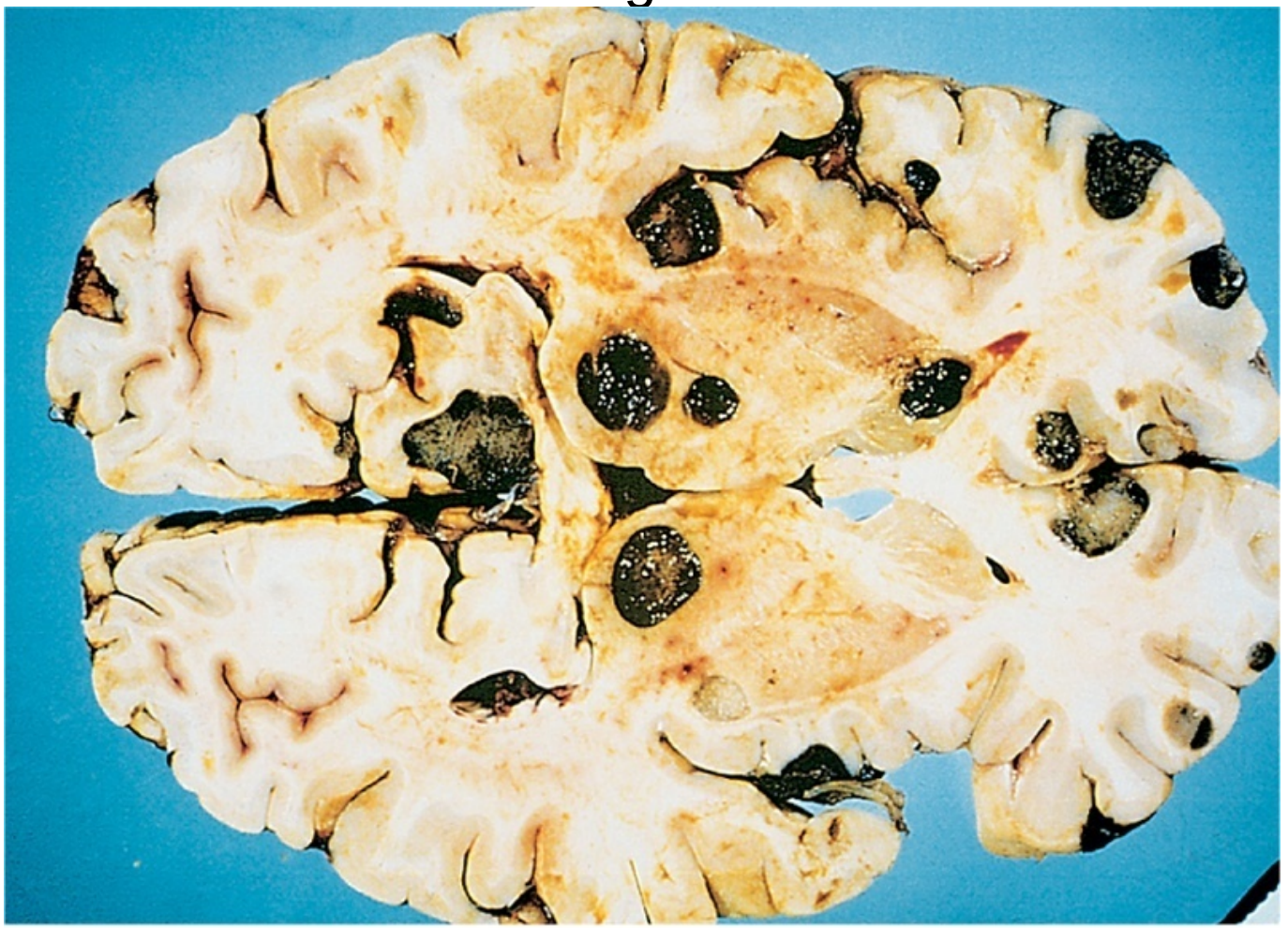


9.76 Secondary carcinoma: brain

◘ 4.47: **Breast carcinomatous secondaries in the brain.**
Well-differentiated , papillary adenocarcinomatous (thin arrow) tumor secondaries infiltrate the brain white matter.



F23-26: **Metastatic melanoma.** Metastatic tumors secondaries are **distinguished** grossly from most primary CNS tumors by their (1) ***multicentric*** **& their (2)** ***well-demarcated margins.***
☠The dark pigment in the **15** tumor secondaries in this brain section is characteristic of malignant melanoma.



PRIMARY DISEASES OF MYELIN

☺ **Normally,** within the CNS, axons are tightly ensheathed by **myelin**, which serves as an **electrical insulator** to allow rapid propagation of impulses.

★Myelin **consists** of multiple layers of the specialized plasma membrane of oligodendrocytes, with most of the cytoplasm excluded.

★These portions of the oligodenrocyte membrane contain **specialized proteins & lipids** that contribute to the orderly packing of the layers.

★ One oligodendrocyte cell extends processes toward many different axons & wraps a segment of roughly a few hundred microns of axon.

★ Each of these **segments** is called an ***internode,*** & the gaps between internodes are known as ***nodes of Ranvier.*** Although **myelinated axons** are present in all areas of the brain, they are the **dominant component in the *white matter***, therefore, *most diseases of myelin are primarily white matter disorders*.

☺ **Normally,** the myelin in peripheral nerves is similar to the myelin in the CNS but, has several important differences:

(1) Peripheral myelin is made by **Schwann cells,** not by oligodendrocytes;

(2) Each **Schwann cell** in the peripheral nerve contributes to only **one internode**, while in the CNS, many internodes comes from a single oligodendrocyte; &

(3) The **specialized proteins & lipids are also different**.

☺ Therefore, **Thank God**, most diseases of CNS myelin do not significantly involve the peripheral nerves, & vice versa

★**If the myelin along a set of axons is disrupted**, there are **changes in the ability of these axons to transmit signals**, & the symptoms **depends on the site (or sites**, since most diseases of myelin are multiple, affecting **many** regions of the brain at the same time) where demyelination occurs.

★The **natural history** of demyelinating diseases is determined, in part, by (1) **the limited capacity of the CNS to regenerate normal myelin** & by (2) **the degree of secondary damage to axons** that occurs as the disease runs its course.

Generally, diseases involving myelin are of 2 broad **groups**:

(I) ***Demyelinating diseases*** of the CNS: are **acquired** conditions, characterized by **damage to previously normal myelin**. The commonest diseases in this group result from (1) **immune-mediated injury**, such as multiple sclerosis **(MS)** & related disorders.

Other processes that can cause *demyelination* include (2) **viral infection of oligodendrocytes** as in progressive multifocal leukoencephalopathy {**PML,** discuss before}, & (3) injury caused by **drugs & other toxic agents.**

▼In contrast to *demyelinating diseases,*

(II) ***Leukodystrophy or dysmyelinating diseases, occur when the myelin is not formed properly or it has abnormal turnover kinetics;*** *&* are associated with **mutations affecting the proteins** required for formation of normal myelin, or mutations that affect the synthesis or degradation of myelin lipids.

Multiple Sclerosis (MS)

- **MS** is an **autoimmune demyelinating disorder** characterized by (1) *distinct **episodes** of neurologic deficits, separated in **time**, attributable to (2) white matter **plaques** that are separated in **space**.*
- **MS** is the **commonest demyelinating disorders**, having a prevalence of **1/1000 persons** in US & Europe=like Malignancy
- **MS** may affect **any age**, although onset in childhood or after age 50 years is relatively rare.
- **MS M/F ratio is 1:2**.
- **MS** shows **relapsing & remitting episodes** of neurologic deficits in most individuals. The frequency of relapses tends to ⬇ during the course of the illness, but there is a steady neurologic deterioration in a subset of patients.
- A transmissible **agent** has been proposed as a cause of **MS,** but **never** been conclusively identified!
- **MS,** like other autoimmune diseases, is believed to be caused by a combination of **genetic** & **environmental** factors that result in a **loss of tolerance to self proteins** (the myelin antigens in the case of **MS**).

• **MS risk of development is X15-fold higher** when the disease is present in a first-degree relative.

• **MS** concordance rate for **monozygotic twins** is **25%,** with a much lower rate for **dizygotic twins** indicates a strong, but not causative, role for genes. Genetic linkage of MS susceptibility to the HLA-DR2 extended haplotype is well established.

◘ Immune mechanisms that may be the cause of myelin destruction have been investigated because of **prominence of chronic inflammatory cells** within & around **MS** plaques,
➔ *Experimental allergic encephalomyelitis* is an **animal model** of **MS** in which **demyelination & inflammation occur after immunization with myelin, myelin proteins, or certain peptides from myelin proteins**.
➔In this model, the lesions are **caused by a T cell-mediated DHR (Type IV) to myelin** proteins, & the same immune mechanism is thought to be central to the pathogenesis of **MS**.

😐 While **MS** characterized by demyelination out of proportion to axonal loss, however some injury to axons does occur.

►**GROSSLY, MS** is a white matter disease, The affected areas show **multiple well-circumscribed plaques, glassy, gray-tan, slightly depressed irregular** lesions.

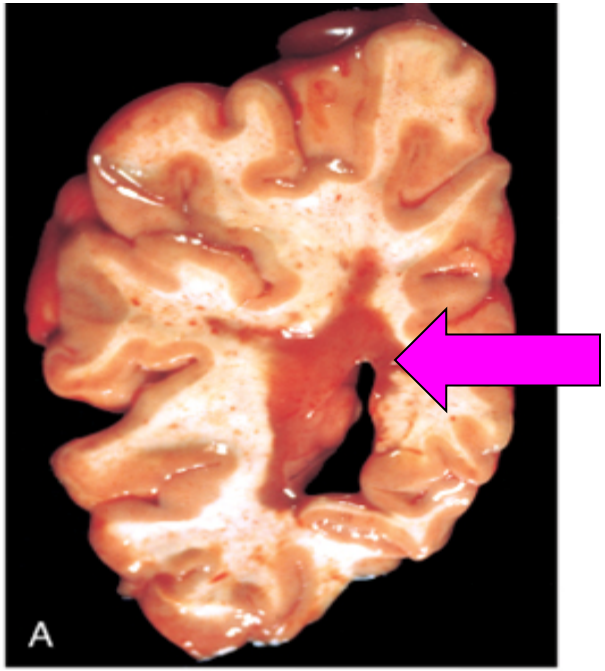
★ **Plaques** commonly occur **beside the ventricles, & are** frequent in the optic nerves & chiasm, brain stem, ascending & descending fiber tracts, cerebellum, & spinal cord (F23-27A & 9-26 & 27),
◘ H, the lesions have **sharply** defined borders {F23-27B & ◘ 4.21&23},

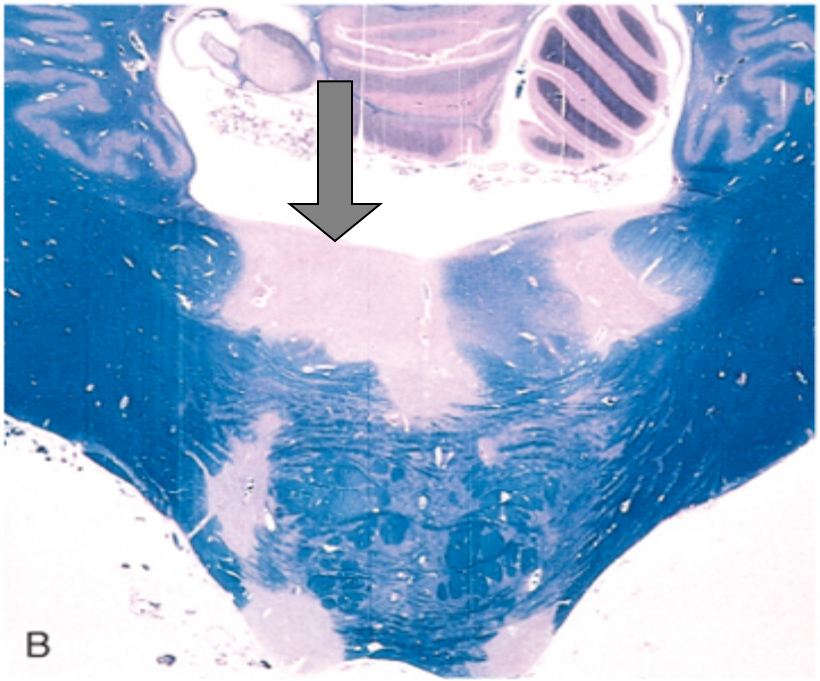
★In an **active plaque** there is evidence of ongoing:

(1) **Perivascular cuff of** l**ymphocytes & monocytes**

(2) **Abundant macrophages containing myelin debris**.
(3) **Myelin breakdown,** with

(4) Small active plaques are often **centered** on small veins, &
(5) **Axons are relatively preserved**, although they may be reduced in number.

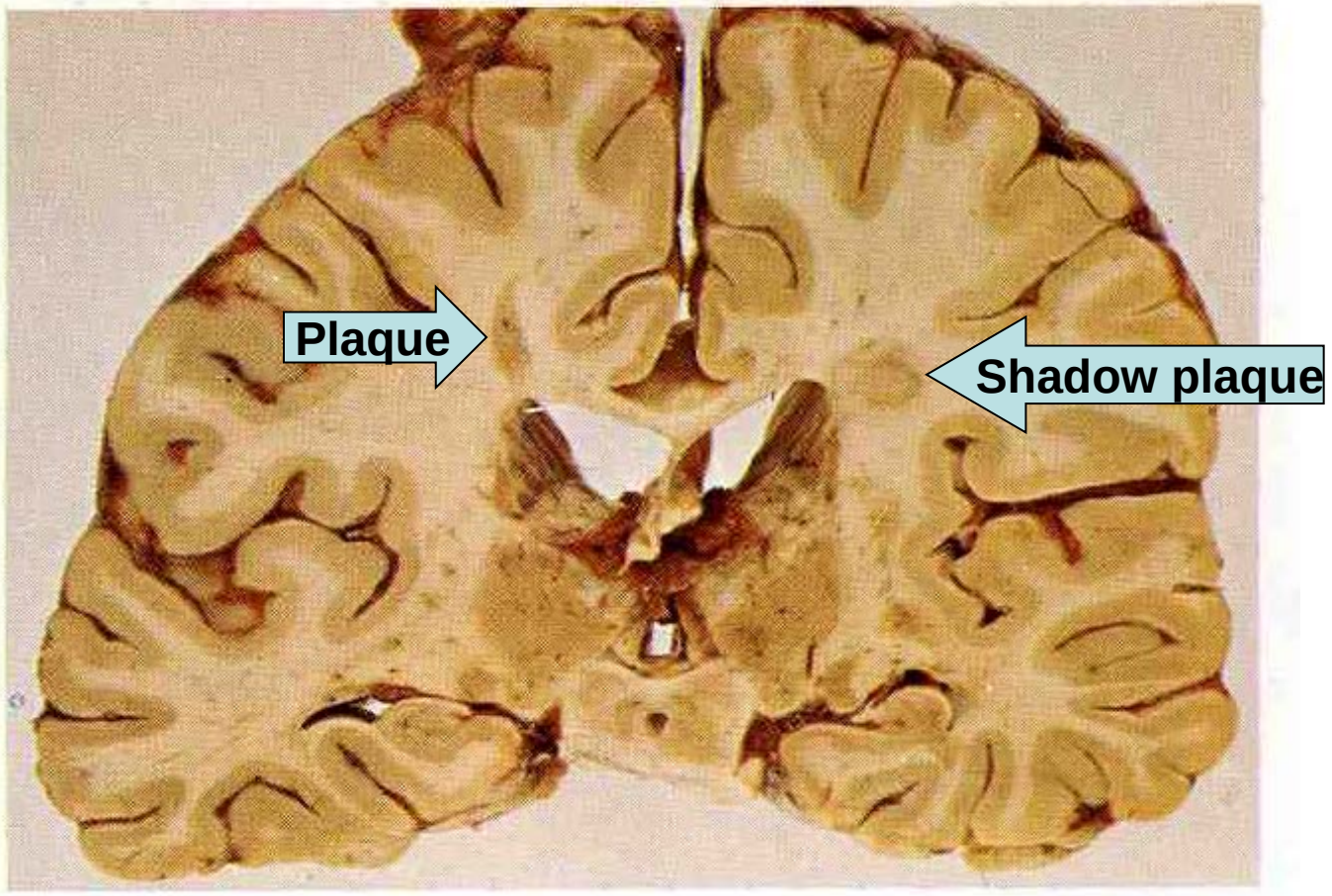




F23-27: **Multiple sclerosis**
A, Fresh brain section showing a well-circumscribed, slightly depressed, gray-tan, irregularly shaped plaque around occipital horn of the lateral ventricle.

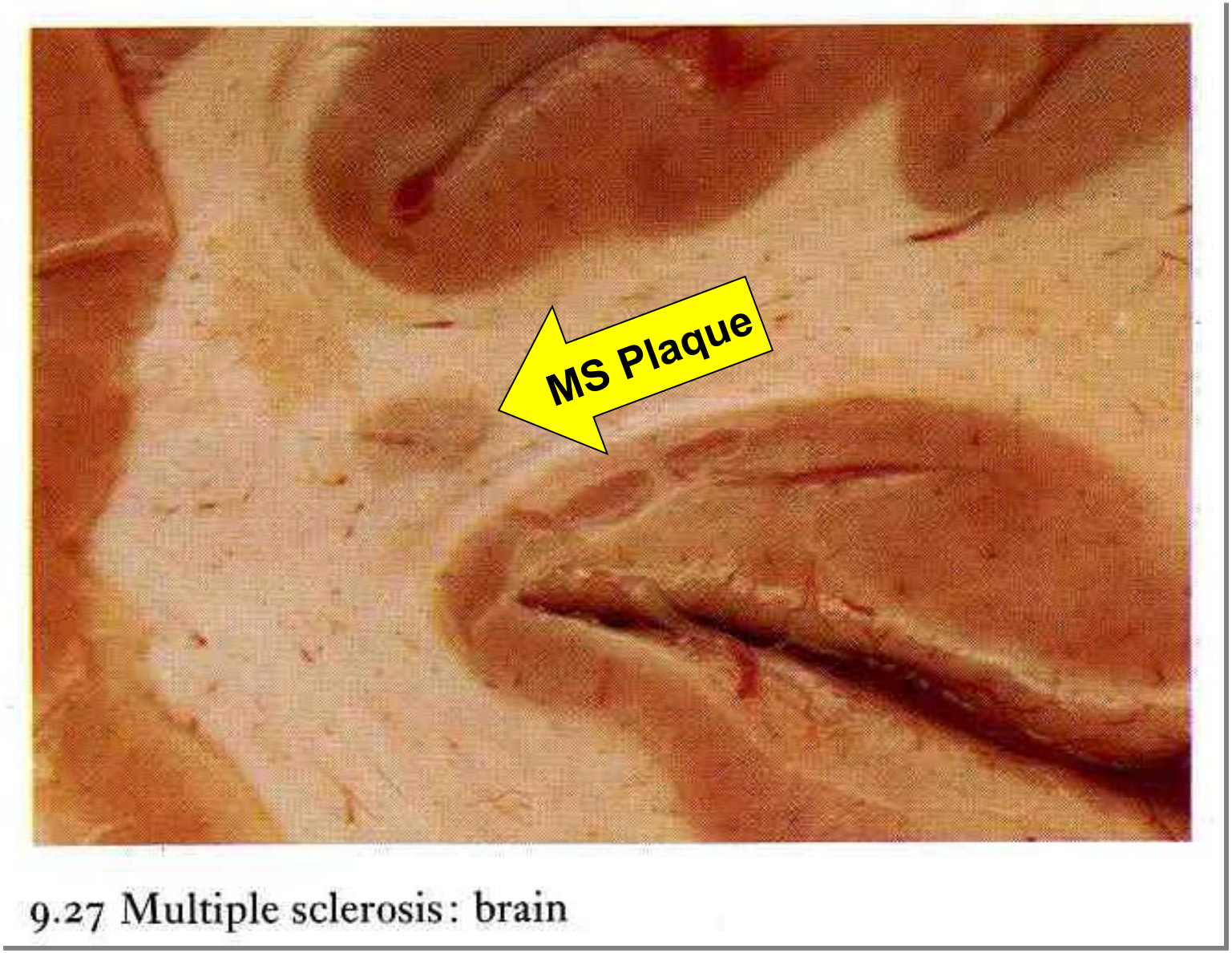
B, Unstained region of demyelination (**MS plaque**) around the fourth ventricle. (Luxol fast blue-PAS stain for myelin.)

F 9-26: **Multiple sclerosis: brain.** Coronal section of the brain showing well-defined greyish-brown chronic plaques of demyelination at the upper angles of both lateral ventricles within the white matter of the centrum semiovale. The right plaque shows features of **‘shadow plaque’.**



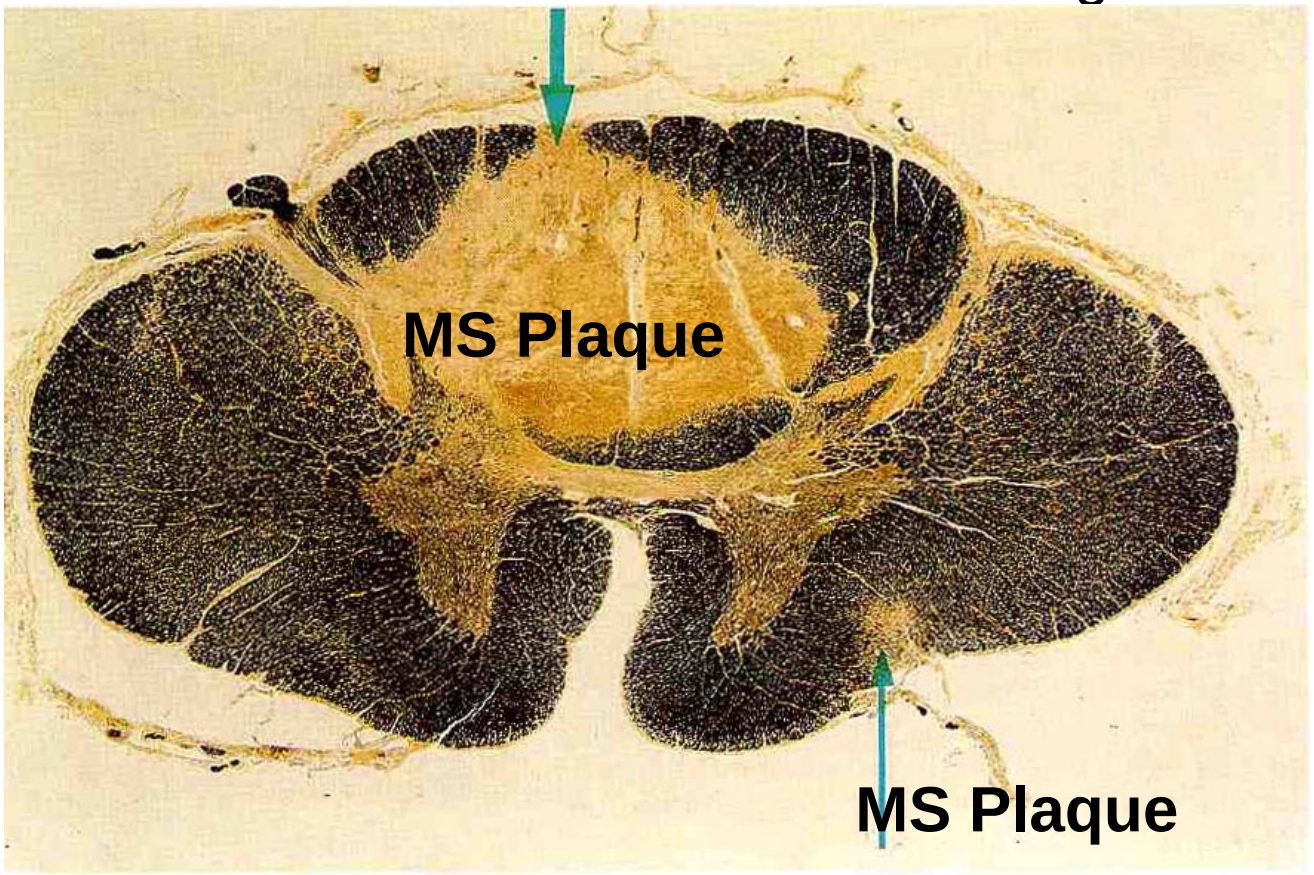
9.26 Multiple sclerosis: brain

F 9-27: **Multiple sclerosis (MS) : brain.** Close-up view. A recently-formed oval, pinkish-grey plaque is present in the white matter beneath the cortical ribbon. This is a characteristic site.

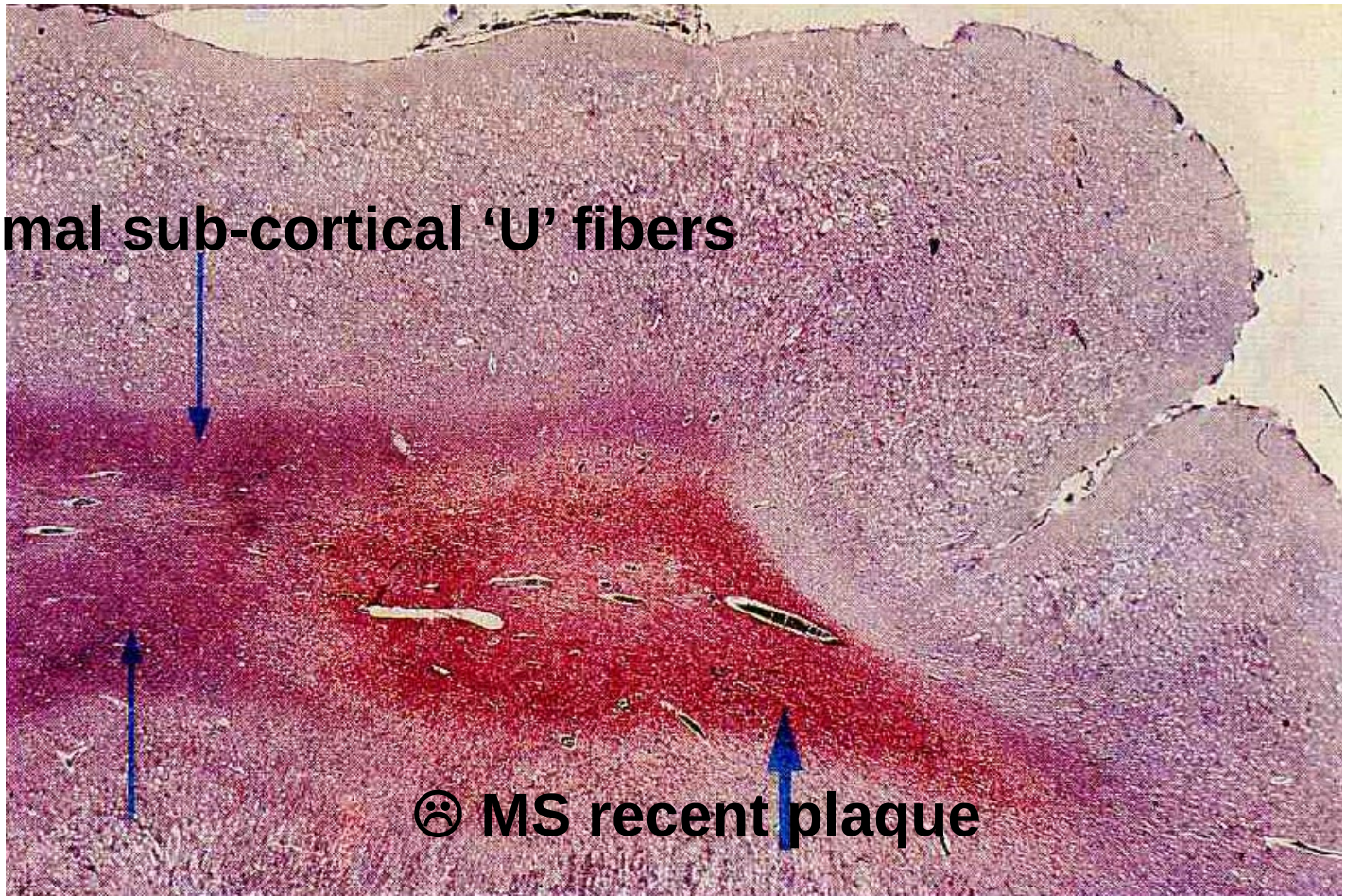


9.27 Multiple sclerosis: brain

◘ 4.21: **Multiple sclerosis (MS) X9.** Cervical spinal cord section, stained by the Weigert-Pal method, which colors the myelin black, **showing 2** plaques of demyelination: (1) a small round one in the ventrolateral part of the cord (thin A), (2) much larger, **irregular** shaped one (thick A) which affects most of the posterior columns, with **complete loss of the myelin** & **sharp line of demarcation** between it & the surrounding tissues.



◘ 4.23: **Multiple sclerosis (MS): Brain, Sudan IV X11.** Frozen section of cerebellar recent plaque, stained with **Sudan IV** to show **fat** (**orange-red color**, thick A) from the presence of much stainable fat which comes from the breakdown of myelin lipids. Above & to the left of the plaque there is purplish-blue sheet of normal, unaffected sub-cortical ‘U’ fibers (thin A).



◘ **Inactive plaques MS** (when plaques become quiescent),
(1) **Disappearance of inflammation,** leaving behind little or
(2) **No myelin**. Instead, there is

(3) **Gliosis** & prominent astrocytic proliferation &
(4) **Shadow plaques may be seen (F 9-26),** where the border between normal & affected white matter is not sharply circumscribed. Here, thinned-out myelin sheaths can be demonstrated, especially at the outer edges, suggesting that this border region represents either (1) incomplete myelin loss or (2) partial remyelination.

►***Clinically,*** **commonly,** there are multiple episodes of injury (***relapses)*** followed by episodes of recovery (***remissions)*****;** typically, the recovery is not complete, with **gradual**, **often stepwise, accumulation** of ↑ neurologic deficits.

★ **Unilateral visual impairment,** occurring over the course of a few days is a frequent initial symptom of MS due to optic nerve involvement **(*optic neuritis, retrobulbar neuritis*).**

★Involvement of the **brain stem** produces cranial **nerve signs & ataxia**, & can disrupt conjugate eye movements.

★ **Spinal cord** lesions give rise to **motor & sensory impairment of trunk & limbs,** spasticity, & difficulties with the voluntary control of bladder function.

☹ **In any individual patient, it is hard to predict when the next relapse will occur!**

▼**CSF** shows (1) in 1/3 of cases there is moderate pleiocytosis.

(2) A mildly elevated protein level with an ↑ **proportion of γ-globulin**, which when examined further, show ***oligoclonal bands,*** representing **antibodies directed against a variety of antigenic targets.**

➔ Although these antibodies constitute a **marker for disease activity**, it is not clear if they are a critical part of the disease mechanism.

▼ **MRI can show the distribution of lesions across the CNS during active disease.** From this, it has become clear that there are often **more lesions** in the brains of MS patients **than might be expected by clinical examination** & that lesions can come & go much more often than was previously suspected!

Other Acquired Demyelinating Diseases

☹ Immune-mediated demyelination can occur after a number of systemic infectious, including relatively **mild viral diseases**, which are not thought to be related to direct spread of the infectious agents to the nervous system, rather…

➔ it is believed that the **immune response to pathogen-associated antigens cross-reacts with myelin antigens,** & resulting in myelin damage (Cytotoxic reaction, Type II)

★ Two patterns of post-infectious, immune-mediated demyelination recognized, both, unlike MS, are
• **monophasic illnesses with relatively • abrupt onset:**

(I) ➔*Acute disseminated encephalomyelitis*, symptoms typically develop • a week or two after the antecedent infection & suggest • diffuse brain involvement (rather than the focal findings typical of MS) with headache, lethargy, & coma, which progress rapidly, to a **fatal outcome in about 20% of cases**; in the remaining patients there is complete recovery.

(II) ➔*Acute necrotizing hemorrhagic encephalomyelitis* is a more devastating, typically affects young adults & children.

Central pontine myelinolysis

★Is **nonimmune process** characterized by **loss of myelin involving the center of the pons, most often after rapid correction of hyponatremia.**

►It occurs in a variety of clinical settings including **severe electrolyte or osmolar imbalance & alcoholism .**

☹ Most characteristic lesion occurs in the pons fibers, which carry signals to motor neurons in the spinal cord, resulting in rapid **quadriplegia**.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease that occurs following reactivation of JC virus in immunosuppressed patients (See CNS infection).

Leukodystrophies

★ Are **inherited dysmyelinating diseases** in which the clinical symptoms derive from either **abnormal myelin synthesis or turnover.** Some disorders involve lysosomal enzymes, while others involve peroxisomal enzymes; a few are associated with mutations in myelin proteins. **Most are autosomal recessive, although X-linked diseases** occur (Table 23-2).

►**GROSSLY,** lesions of leukodystrophies are found in the **white matter,** in some diseases, there may be **early patchy** involvement**;** however, in the **end,** nearly all leukodystrophies **show diffusely affected abnormal white matter: (I)** in color (gray & translucent) & (II) in volume (decreased).

★With the loss of white matter, the brain becomes **atrophic,** the ventricles enlarge, & secondary changes can be found in the gray matter.

◘ H, myelin loss is common, with macrophages stuffed with lipid. Some leukodystrophies also show specific inclusions, due to accumulation of particular lipids.

◤ *Clinically,* Each disorder of the various leukodystrophies has a characteristic **clinical presentation**, & most can be **diagnosed by genetic or biochemical methods.**

☺ Affected children are normal at birth, ☹ but begin to miss developmental milestones during infancy & childhood.

Diffuse involvement of white matter leads to deterioration in motor skills, spasticity, hypotonia, or ataxia.

DEGENERATIVE DISEASES & DEMENTIAS

★ **Dementia** is the **development of memory impairment & other cognitive (recognition) deficits, with preservation of a normal level of consciousness**.

✱ It is emerging as one of the most important public health issues in the industrialized world. There are many causes of dementia (Table 23-3); BUT, regardless of etiology; the

★ **Rule: Dementia is not part of normal aging & always represents a pathologic process.**

Table 23-3 Major Causes of Dementia

★Primary Neurodegenerative Disorders

Alzheimer AD, **Huntington** D, **Motor neuron** D, **Parkinson D** & diffuse Lewy body disease ; **Pick** D & other frontotemporal degenerations, Progressive supranuclear palsy,

★ Infections

Prion-associated D: Creutzfeldt-Jakob D, fatal familial insomnia, & others.

(**AIDS** dementia) Human immunodeficiency virus encephalopathy

Progressive multifocal leukoencephalopathy **(PML)**

Miscellaneous forms of viral encephalitis, **Neurosyphilis**, Chronic meningitis

★ Vascular & Traumatic Diseases

Multi-infarct dementia & other chronic vascular disorders

Global hypoxic-ischemic brain injury,
Chronic subdural hematomas

★ **Nutritional & Metabolic Diseases**

Thiamine deficiency (Wernicke-Korsakoff syndrome), Vitamin **B12** deficiency, **Niacin** (pellagra) & Endocrine diseases.

★ **Miscellaneous**

Brain **tumors**, Neuronal **storage** diseases, **Toxic injury** (including mercury, lead, manganese, bromides)

★ While the diseases to be discussed in this section are considered as "degenerative" i.e., reflecting an underlying cellular degeneration of neurons in the brain, …

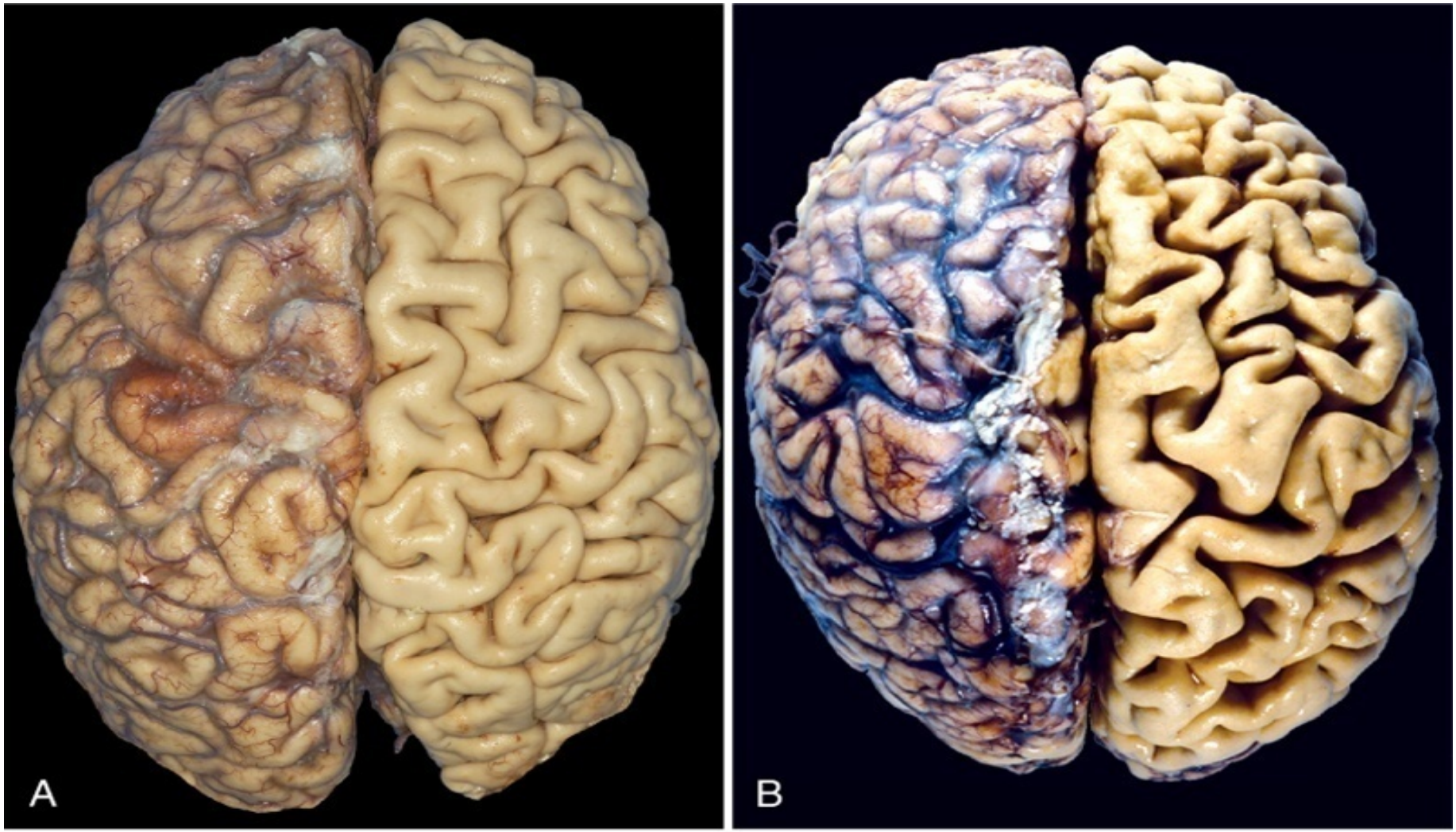
Not all forms of dementia is degenerative.

★Vascular disorders are an important cause of dementia. Patients who suffer multiple, bilateral, gray & white matter (centrum semiovale) infarcts during months or years develop dementia, called ***vascular (multi-infarct) dementia*****.**

★ When the pattern of injury preferentially involves large areas of the subcortical white matter with myelin & axon loss, the disorder is referred to as ***Binswanger disease (F1-4)*****.**

★Herewith, we will discuss the main causes of dementia, including Alzheimer, Parkinson, & Huntington diseases.

F1-4: **A, Normal** young adult brain., **B, Atrophy** of the brain in an 82 years-old male with atherosclerotic disease. Note that the loss of the brain substance (due to **aging** & **reduced blood supply**) narrows the gyri & widens the sulci.



Alzheimer Disease (AD)

★ **AD is the most common cause of dementia in the elderly.** The disease usually becomes clinically apparent as insidious impairment of higher intellectual function, with alterations in mood & behavior. Later, progressive disorientation, memory loss, & aphasia indicate severe cortical dysfunction, & over the next 5 to 10 years, the patient becomes profoundly disabled, mute, & immobile.

☠ Death usually occurs from **intercurrent infections.**

★ **AD** incidence is: **3%** (in 65-74 years age group),**19%** (75-84 y), & **47%** (85 years or more).
★ This ↑ incidence with age has given rise to **major medical, social, & economic problems** in some countries.

★Although **pathologic examination** of brain tissue remains necessary for the **definitive diagnosis of AD**, the combination of **clinical** assessment & modern **radiologic methods** allows accurate diagnosis in 80% to 90% of cases.
★ Most **AD** cases are sporadic, 5% -10% are familial.

★ **AD** patients rarely become symptomatic before 50 years of age, but early onset is seen with some of the heritable forms.

★ Evidence from familial forms of the AD disease indicates that ➔ the **accumulation of a peptide (myloid β, or Aβ) in the brain initiates a chain of events** that result in the morphologic changes of AD & dementia. This peptide is derived from a larger membrane protein known as amyloid precursor protein (APP), which is processed in one of two ways **(F 23-28)**

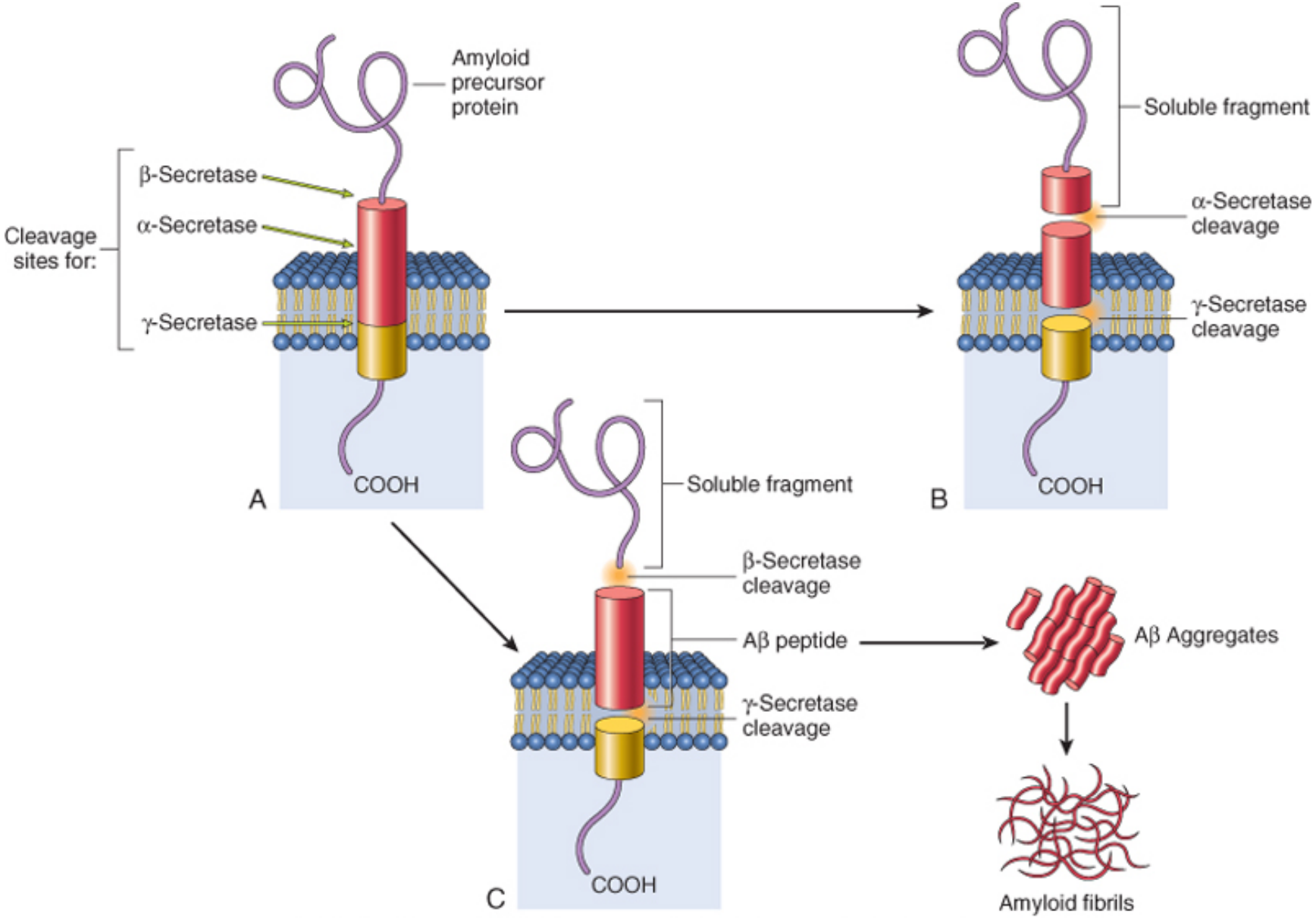
★ **AD** occurs in all patients with trisomy 21(Down syndrome)- where the gene encoding APP is located - who **survive** beyond 45 years.

☹ Accumulation of **Aβ has several effects:**

• Small Aβ aggregates can alter neurotransmission, & can be → **toxic to neurons** & **synaptic endings**.

• Larger Aβ deposits, in the form of plaques, lead to → **neuronal death, eliciting a → local inflammatory response that can result in further cell injury,** & may cause altered region-to-region communication, through mechanical effects on axons & dendrites.

F23-28: **Accumulation of the peptide (β amyloid, or Aβ) in the brain in Alzheimer disease.**



►**GROSSLY,** the brain is small (often less than 1000g) shows a variable degree of **cortical atrophy,** with **widening of the cerebral sulci** in the frontal, temporal, & parietal lobes & **compensatory ventricular enlargement.**

◘ **AD** is diagnosed histologically by the presence of **neuritic plaques** (an extracellular lesion); & **neurofibrillary tangles** (an intracellular lesion) **(F 23-29);** both of which are **not specific** because they may also be present to a lesser extent in the brains of elderly nondemented individuals.

▼The current criteria for a diagnosis of AD are based on a combination of clinical & pathologic features.

★ There is a fairly **constant pattern of progression** of involvement of brain regions: pathologic changes (specifically plaques, tangles, & the associated neuronal loss & glial reaction) are evident ⇨earliest in the entorhinal cortex, then ⇨ spread through the hippocampal formation & isocortex, & then ⇨ extend into the neocortex.

Silver staining or immunohistochemistry are extremely helpful in assessing the true burden of these changes in a brain.

★ **Neuritic plaques** are 20 to 200 μm in ∅ with microglial cells & reactive astrocytes, consist of a:

☹ **Neuritic plaques = amyloid core +** Surrounding **dystrophic neurites; i.e.,**

(I) *Central* ***amyloid core*** (contains **accumulation of a peptide (β amyloid, or Aβ,** F 23-29B),

(II) Surrounded by **dystrophic neurites (**F23 -29 & ◘ 4.18) a focal, spherical collections of dilated, tortuous, silver-staining (argyrophilic) neuritic processes present at their periphery.

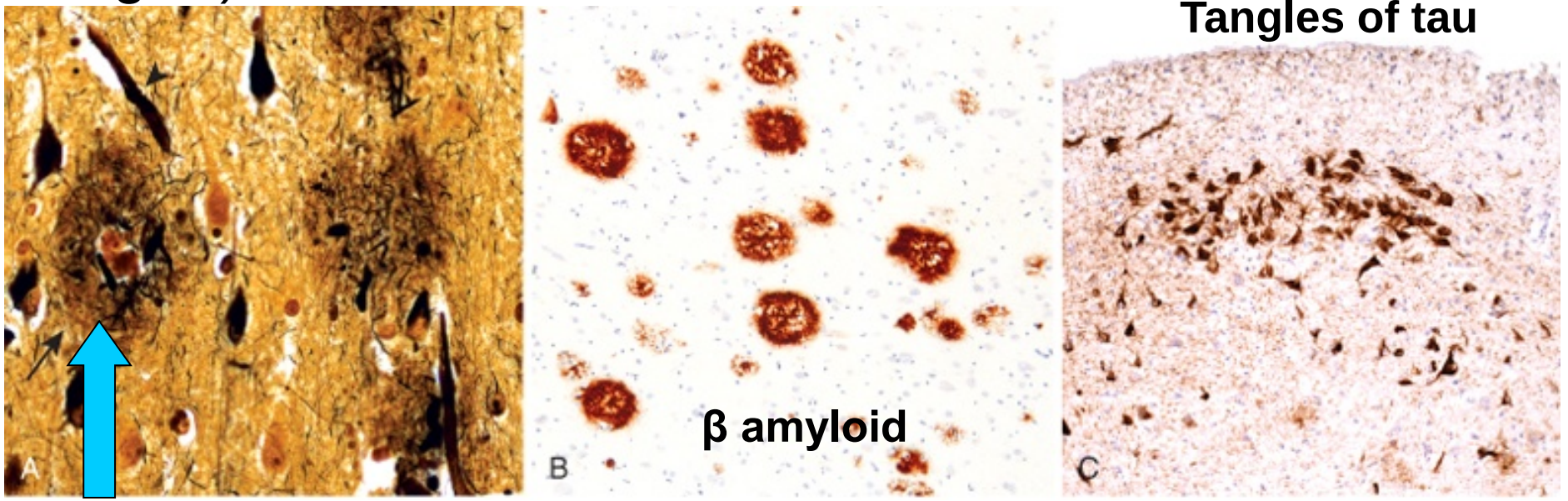
★ **Neuritic plaques** can be found in the hippocampus & amygdala as well as in the neocortex, although there is usually relative sparing of primary motor & sensory cortices until late in the course of the disease.

★ **Diffuse plaques are Aβ** deposits which can also be found that **lack** any surrounding neuritic reaction these are typically found in superficial portions of cerebral cortex as well as in basal ganglia & cerebellar cortex & may represent an **early stage of plaque development**

F23-29: **Alzheimer disease. A, Neuritic plaque {**Bielschowsky stain, arrow} is 20 to 200 μm in ∅, focal spherical collections of dilated, tortuous, silver-staining dystrophic neurites & tangles which are filamentous extracellular inclusions, surrounding a central amyloid core,

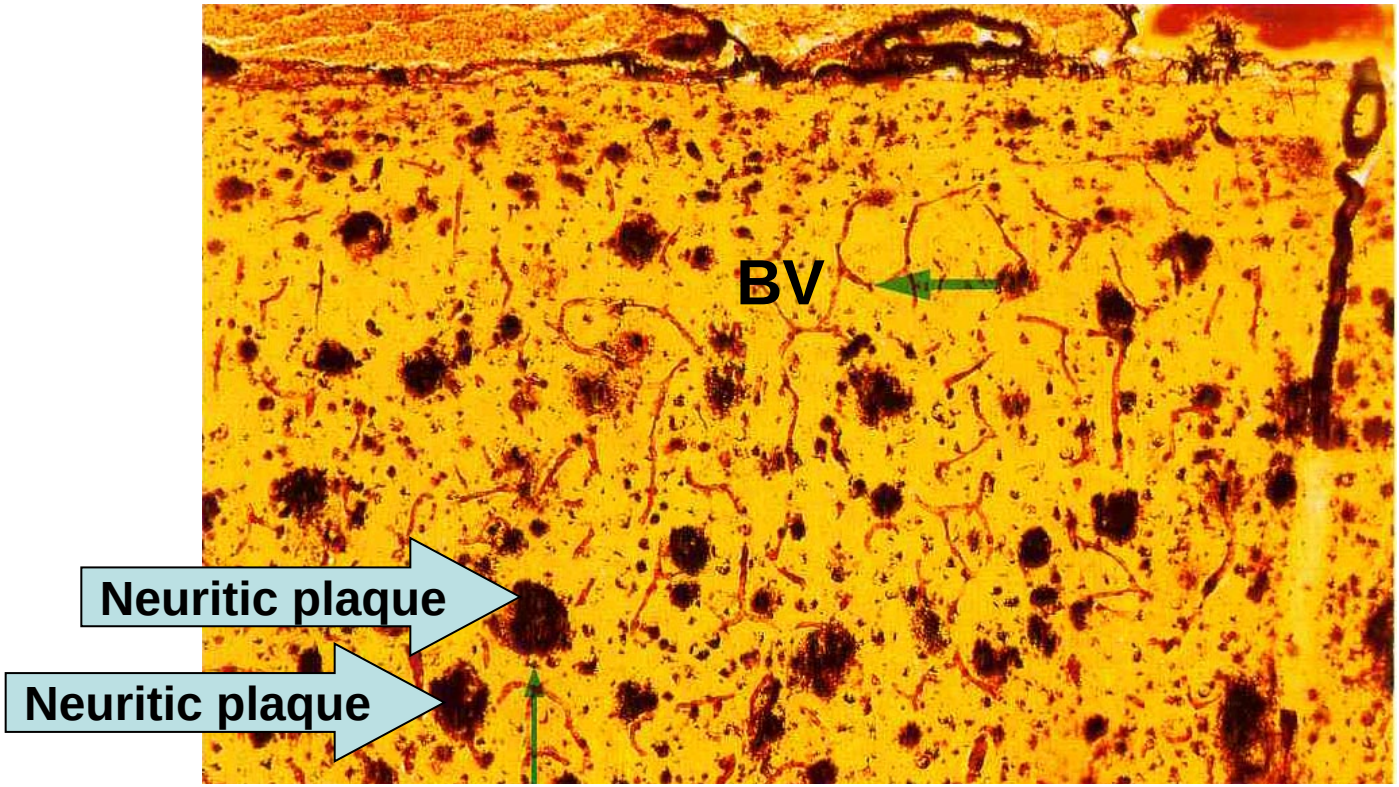
B, Immunohistochemistry against **Aβ (β amyloid)** shows that the **Aβ** peptide is present in the core of the neuritic plaques & in the surrounding region.

C, Immuno stain for **tau** protein showing neurons containing **tangles**).



◘ 4.18: **Alzheimer disease: Brain X90.** Biopsy specimen from the cortex of a man of 63 stained by periodic acid silver method.

- The subarachnoid space & cortex surface are at top.
- Many rounded & dark **neuritic plaques** (thin A) consisting of (I) *Central amyloid core* (contains **accumulated β amyloid),** (II) Surrounded by **Dystrophic neurites,** spherical collections of extracellular dilated, tortuous, silver-stained (argyrophilic) degenerated neuritic processes



★**Neurofibrillary tangles;**

Are bundles of paired helical filaments visible as basophilic fibrillary **intracytoplasmic** structures of the neurons, that displace or encircle the nucleus (F23-29C);

Tangles can remain after neurons die, then becoming a form of extracellular pathology.

They are commonly found in cortical neurons, especially in the entorhinal cortex, as well as in other sites such as pyramidal cells of the hippocampus, the amygdala, the basal forebrain, & the raphe nuclei.

A major component of paired helical filaments is abnormally hyperphosphorylated forms of the protein **tau** (F23-29C).

Tangles are not specific to AD, being found in other degenerative diseases as well.

Frontotemporal Dementia

★**Is** another **major** category of disease that results in dementia, some of these dementias are caused by mutations in the gene encoding **tau,** the protein found in tangles.

☹ They shares clinical features **(progressive language deterioration & personality changes**) corresponding to degeneration & atrophy of temporal & frontal lobes. **These symptoms often occur before memory disturbance, &** this difference in presentation can assist in their separation from cases of AD on clinical grounds.

►**GROSSLY,** the basic finding is **frontal & temporal lobes atrophy.** Different subgroups characterized by specific inclusions, which in some consist of **abnormal** accumulations of **tau.**

Parkinsonism

★Is a clinical syndrome characterized by diminished facial expression **(masked facies), stooped (bended) posture, slowness of voluntary movement, festinating gait** (progressively shortened, accelerated steps), **rigidity,** & a "pill-rolling" **tremor.**

★This **syndrome** of motor disturbance is seen in a number of conditions that share **damage to dopaminergic neurons of the substantia nigra** or to their projection to the striatum, including **post-encephalitic Parkinsonism** (associated with the influenza pandemic), multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, & some cases of HD.

★**Parkinsonism can be induced** by drugs that affect these neurons, particularly **dopamine antagonists & toxins**; one toxin, **MPTP,** has now become an important tool in **animal models** to develop & test new therapies.

Idiopathic Parkinson disease

Is the most common neurodegenerative disease associated with Parkinsonism. Its ▼ **Diagnosis** is made in patients with progressive Parkinsonism in the **absence of a toxic or other known underlying etiology & if they show clinical response to l-dihydroxyphenylalanine (l-DOPA) treatment.**

★Most Parkinson disease cases are sporadic;

★However, there are both autosomal dominant & recessive forms of the Parkinson disease.

★ Genetic analysis has identified specific causal mutations, e.g.; **α-synuclein mutations cause autosomal dominant Parkinson disease,** as can gene duplications & triplications.

★ Even in cases of Parkinson disease not caused by mutations in this gene, the **diagnostic feature of the disease-the Lewy body-is an inclusion containing α-synuclein.** This is a widely expressed neuronal protein that is involved in synaptic transmission & other cellular processes.

★ **The presence of α-synuclein in the Lewy bodies** has *suggested that defective degradation of the protein in the proteasome might play a role.*

►**Grossly,** typically there is **pallor of the substantia nigra (F23-30A & B) & locus ceruleus**.

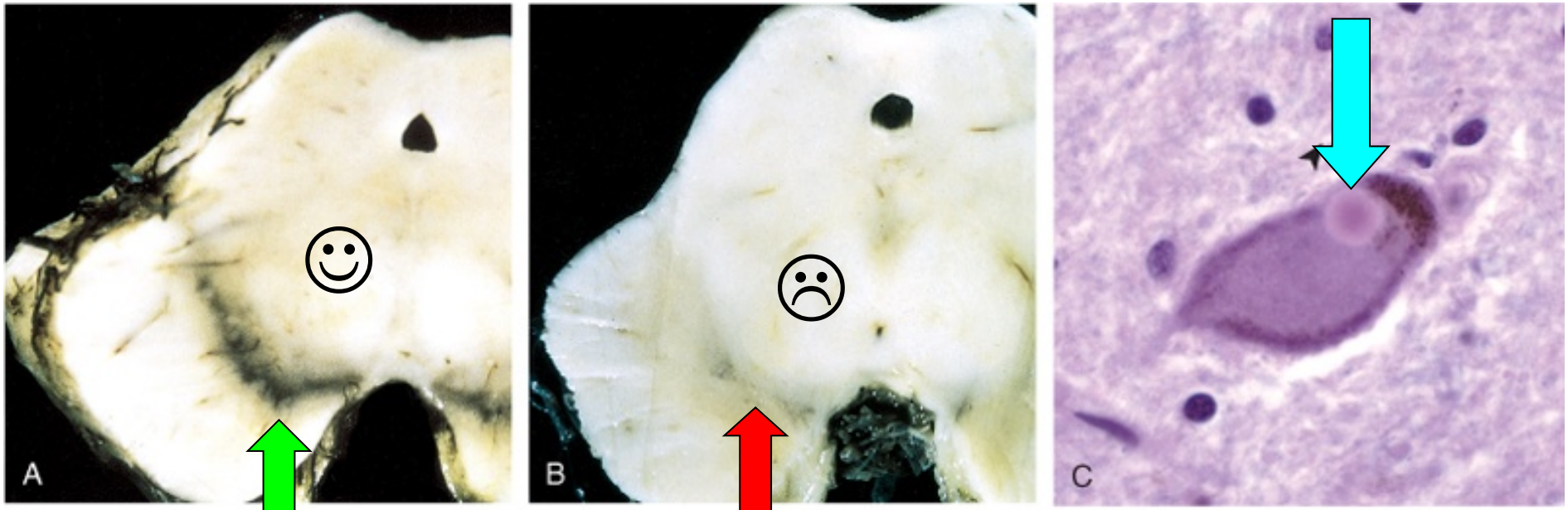
◘ H, there is (1) loss of the pigmented, catecholaminergic neurons in these regions with gliosis; & (2) **Lewy bodies (F23-30C**) may be found in some of the remaining neurons.

◘ **Lewy bodies** are **single or multiple, round or elongated, eosinophilic intracytoplasmic inclusions that often have a dense core surrounded by a pale halo**.

◘ ◘ Ultrastructurally, Lewy bodies are composed of fine filaments, densely packed in the core but loose at the rim. These filaments are **composed of α-synuclein,** along with other proteins including **neurofilament & ubiquitin.** Lewy bodies may also be found in the cholinergic cells of the basal nucleus of Meynert, & in other brain-stem nuclei.

◘ The presence of **Lewy bodies** in limbic & neocortical structures is associated with cognitive impairment-the disorder recognized as **[Dementia with Lewy bodies]**.

F23-30: **Parkinson disease.**
A, ☺ *Normal substantia nigra.*
B, ☹ ***Depigmented*** substantia nigra in idiopathic Parkinson disease.
C, ***Lewy body*** (arrow) in a neuron from the substantia nigra stains pink. An eosinophilic, round intracytoplasmic inclusion having dense core surrounded by a pale halo.



Clinically, ☺ **l-DOPA therapy is often extremely effective in symptomatic treatment,** but it does not significantly alter the progressive nature of the disease.
☹ **Over time, l-DOPA becomes less effective** at providing the patient with symptomatic relief & begins to cause fluctuations in motor function on its own.

▼The disease usually progresses over 10 to 15 years, with eventual severe motor slowing to the point of **near immobility**.

☠ Death is usually the result of:
(1) **intercurrent infection** or
(2) **trauma from frequent falls caused by postural instability**

☹ About **10% to 15%** of Parkinson patients develop **dementia**, with the incidence 🡅 with advancing age. While many affected individuals also have pathologic evidence of AD, the **dementia in other Parkinson disease patients is attributed to widely disseminated Lewy bodies in the cerebral cortex.**

Huntington Disease (HD)

★**HD** is an **inherited autosomal <u>dominant</u>** disease characterized clinically by **progressive movement disorders (I) <u>chorea</u> & (II) <u>dementia</u>, with degeneration of the striatum (caudate & putamen).**
Chorea consist of jerky, hyperkinetic & involuntary movements **affecting all parts of the body;** patients may develop Parkinsonism with bradykinesia & rigidity. **HD** is relentless & progressive, resulting in ☠ **death** after an average of 15 years.

►**All individuals with *HD have the same type of mutation-a <u>trinucleotide repeat expansion</u>* in a gene located on 4p16.3 that encodes a large protein (huntingtin).**

There is a polymorphic CAG trinucleotide repeat in the gene, encoding a polyglutamine tract in the protein.

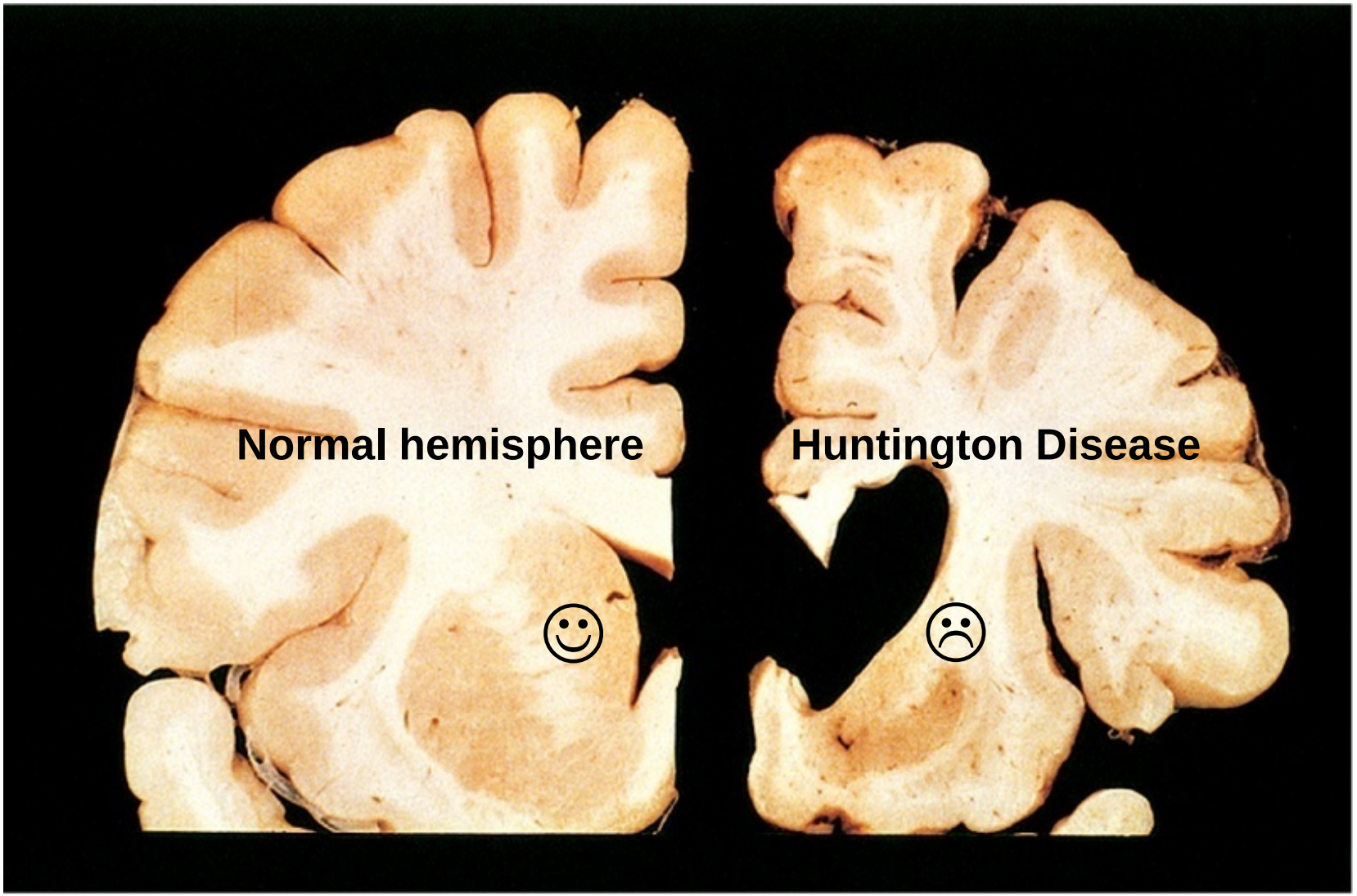
☺ **Normal alleles contain 11 to 34 copies of the repeat;**
☹ In **HD** disease-causing alleles, the number of repeats is ↑, sometimes **into the hundreds**.
There is strong genotype-phenotype correlation, i.e., the larger the number of repeats, the earlier the onset of the disease.

😐 **Pathogenesis: although** not formally proved, it is possible that the **abnormal protein fails to fold properly**, & accumulation of misfolded protein triggers apoptosis in some neurons.

►**Grossly, the HD brain is small & shows • striking atrophy of the caudate nucleus &, sometimes less dramatically, the putamen (F23-31).** Pathologic changes develop over the course of the illness in a medial to lateral direction in the caudate & from dorsal to ventral in the putamen. The globus pallidus may be atrophied secondarily, & the lateral & third ventricles are dilated. • **Atrophy** is frequent in the **frontal lobe,** less often in the **parietal** & occasionally in the entire cortex.

◘H, there is **(I) severe loss of neurons from these regions of the striatum,** with extensive fibrillary gliosis, &
(II) in the remaining striatal neurons & in the cortex, there are **intranuclear inclusions that contain aggregates of ubiquitinated huntingtin protein.**

F23-31: **Huntington disease.** Normal hemisphere on the left compared with the hemisphere with Huntington disease on the right showing atrophy of the striatum & ventricular dilation



Clinically, HD onset is commonly in the 4th & 5th decades & is related to the length of the CAG repeat. **When repeat lengths exceed 70 copies**, the disease can present in adolescence or even earlier (**juvenile HD).** There is:

(I) motor symptoms **choreiform ↑** involuntary jerky movements of all parts of the body with writhing (Tangling) movements of the extremities; often precede the (II) symptoms of higher cortical dysfunction which may progress to a severe **dementia.** ☠ HD patients have an **↑ risk of <u>suicide</u>**; **<u>intercurrent infection</u>** is the common natural cause of death.

Spinocerebellar ataxia (*Friedreich ataxia)*

★**Autosomal recessive progressive** illness that affect the **cerebellum ,** begin in the **1st decade** of life with **gait ataxia**, followed by **hand clumsiness & dysarthria.** There are ↓ or absent deep tendon reflexes; positive Babinski sign; impaired joint position & vibratory sense; & loss of pain, temperature sensation, & light touch. ☹ There is a **high incidence of cardiac disease & diabetes**. Most patients become wheelchair bound within 5 years of onset. ☠The cause of death is **intercurrent pulmonary infections & cardiac disease.**

Diseases of Motor Neurons

★These are a numbers of diseases that affect the:
(I) **lower** motor neurons in the spinal cord (**SC**) & in the brain stem, loss of which results in denervation of muscles, with resulting **muscular atrophy, weakness, & fasciculations;** & (II) **upper** motor neurons (Betz cells) in the motor cortex, the loss of the projection of upper motor neurons onto the lower motor neurons results in **paresis, hyperreflexia, spasticity, & positive Babinski sign.** Sensory systems & cognitive functions are usually unaffected, but types with dementia do occur.

Amyotrophic Lateral Sclerosis (Motor Neuron Disease)

- **ALS is the most common form of neurodegeneration affecting the motor system**; (1) "lateral sclerosis" refers to the degeneration of the corticospinal tracts in the lateral portion of the **SC** (◘ 4.25) as a result of loss of upper motor neurons, resulting in **Hyper-reflexia; while (2) the muscle atrophy** ("amyotrophy") **result from** loss of lower motor neurons.

- **ALS** affect men slightly more frequent than women.

- **ALS** manifest clinically in the 5th decade or later.
- 90% of **ALS** cases are **sporadic**.
- 10% of **ALS** are **familial, mostly autosomal dominant**, develop symptoms earlier; but the clinical course is comparable with the sporadic with a 50% 5-year survival.
- **ALS** disease locus is on chromosome 21, involving the **gene encoding a form of superoxide dismutase, SOD1.** Mutations in this gene cause 50% of the familial cases of **ALS**, & as with huntingtin, the **mutation may cause misfolding of the protein**, **leading to apoptosis**.

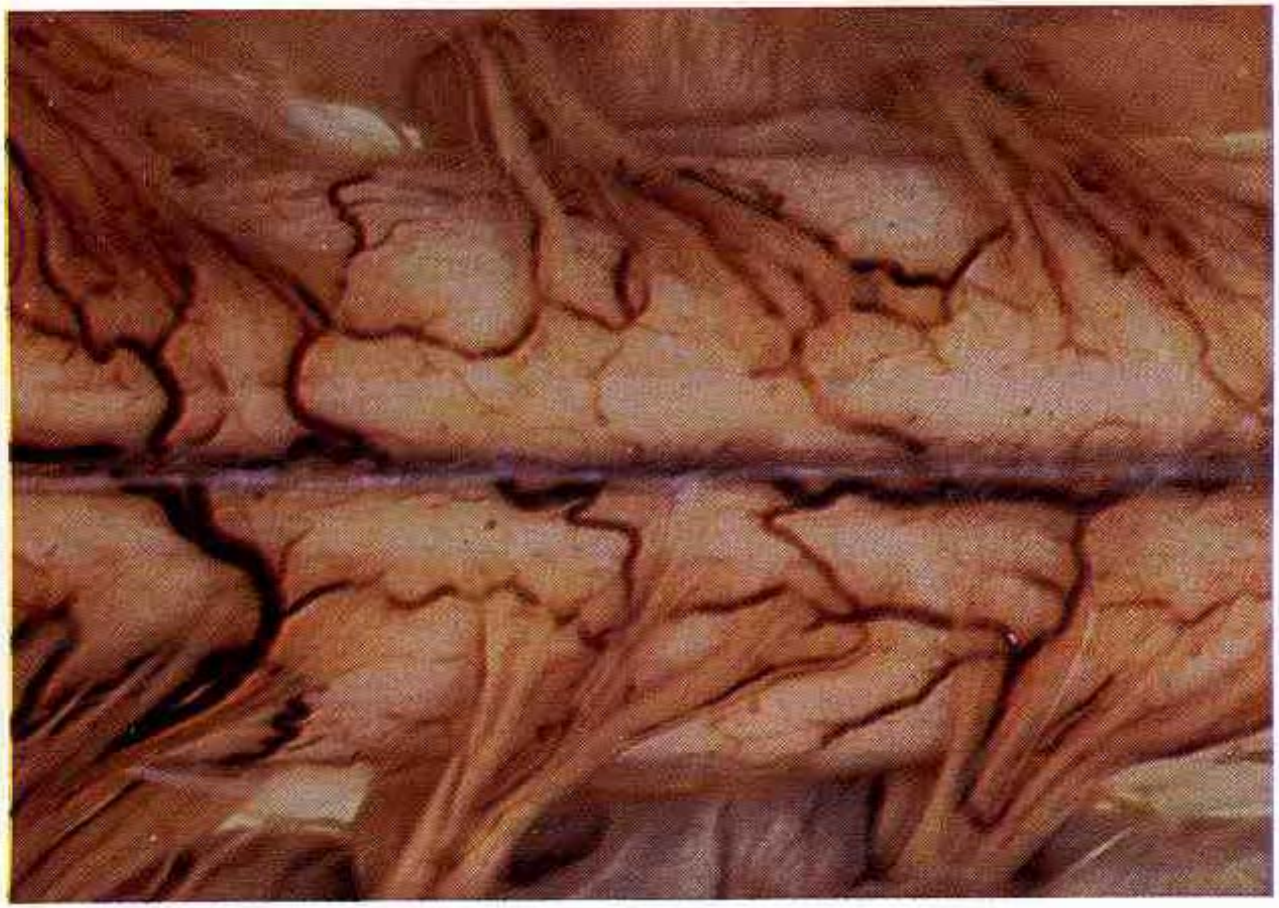
►**Grossly**, **ALS** most evident changes are found in:
(1) **anterior roots of the SC, which are thin & gray (rather than white, F9-25) &,** in especially severe cases, the
(2) **motor cortex (**precentral gyrus) **may be atrophic.**

◘H, there is a **reduction in the number of anterior horn cell throughout** the length of the **SC** with **loss of anterior root myelinated fibers (**◘ 4.25 & 26) & reactive gliosis**.**

◘ **Similar** findings are found with involvement of motor cranial nerve nuclei, always sparing those of the extraocular muscles.

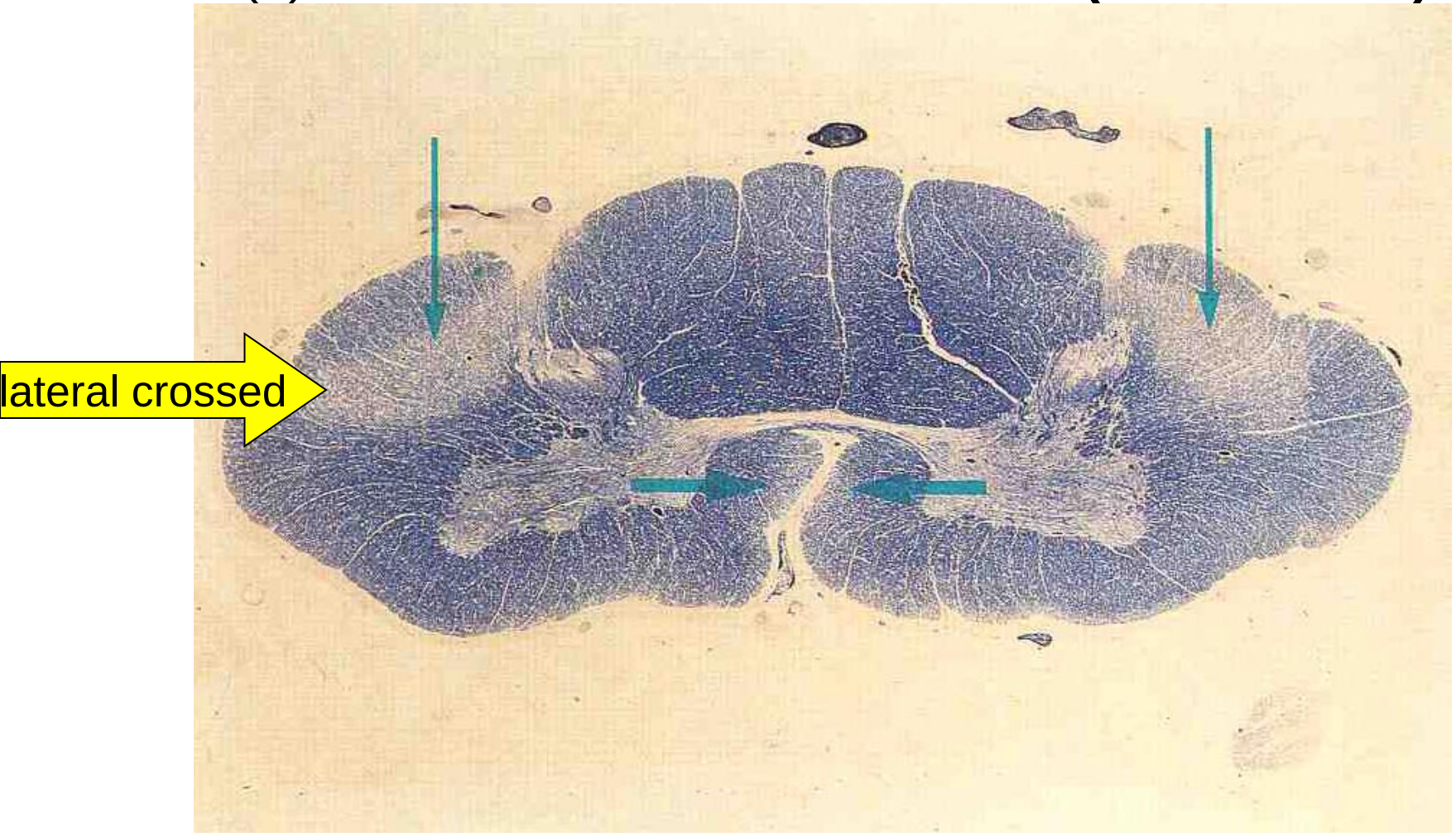
F9-25: **Motor neuron disease: Ventral surface of spinal cord**

☹ The anterior spinal nerve roots are *atrophic & thin* due to **reduction in the number of anterior horn cell neurons** throughout the length of the SC, with loss of anterior root myelinated fibers & reactive gliosis.

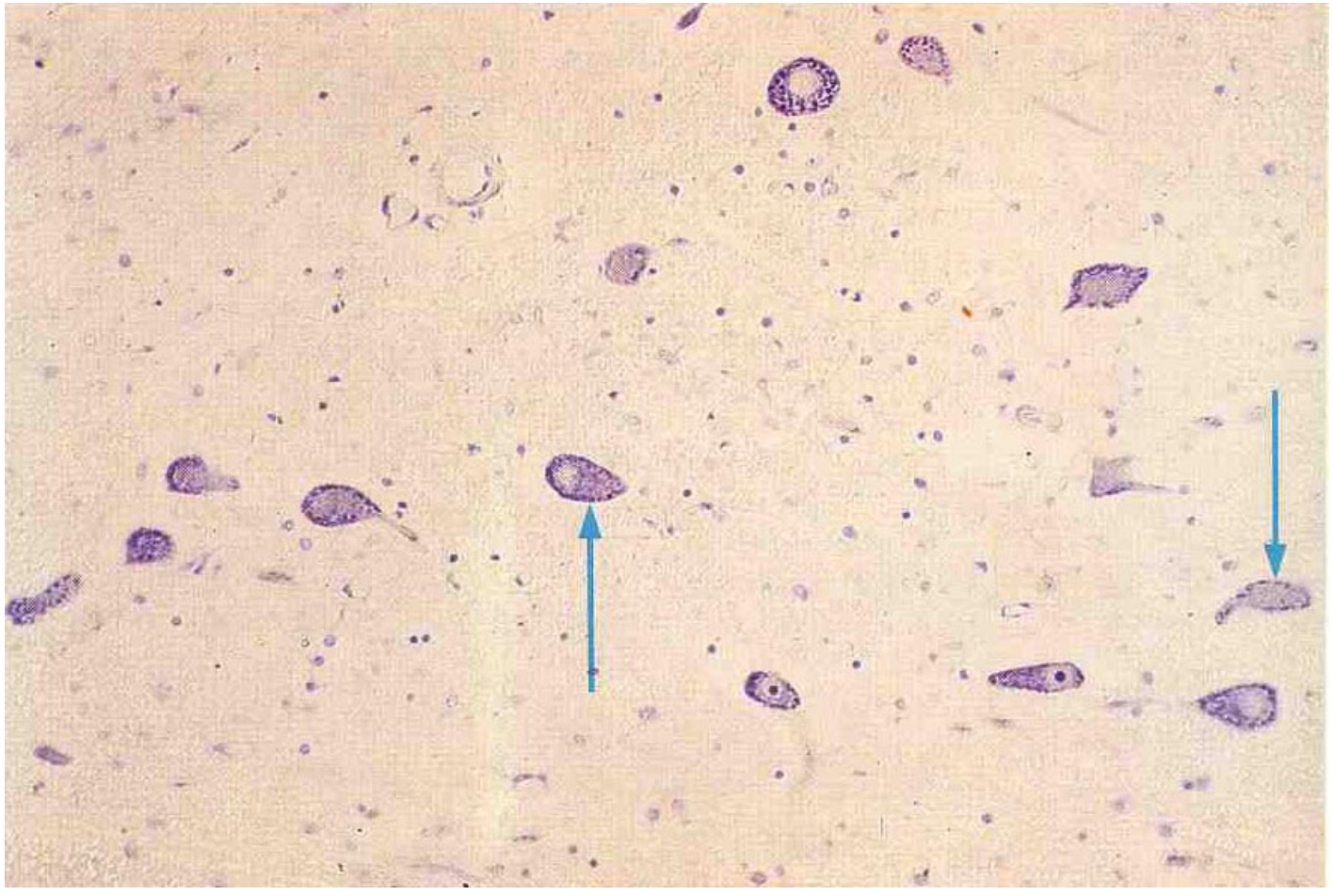


9.25 Motor neuron disease: spinal cord

◘ 4.25: **Motor neuron disease (ALS): Spinal cord** section stained deep blue for myelin. There is loss of staining (demyelination with pallor) affecting both the **(I) lateral crossed cerebrospinal tracts (thin arrows),** which is more pronounced than the (II) **anterior columns direct tracts (thick arrows)**



◘ 4.26: **Motor neuron disease (ALS): Spinal cord** section, showing anterior horn from a patient, who had progressive muscular atrophy, stained with thionin to demonstrate the motor neurons selectively. The number of motor neurons is much less than normal & the few which remain are degenerated, shrunken (arrows) showing chromatolysis & karyolysis.



In ALS (I) Death of **upper** motor neurons, causes degeneration of the descending corticospinal tracts, **easily seen** in the **SC**, **& (II)** Death of anterior horn cells [**lower** motor neurons] with loss of innervation causes **neurogenic atrophy** of skeletal muscles.

▲ ***Clinically,*** *early* symptoms include **asymmetric weakness of the hands,** manifested by **dropping objects** & difficulty performing fine motor tasks.
Later, muscle strength & bulk diminish and ***fasciculations*** {involuntary contractions of individual motor units) occur.

☠ Eventual, **respiratory muscles weakness** cause recurrent pulmonary infection, which is the usual cause of ☠ **death**.

★In some patients, degeneration of the **lower brain stem cranial motor nuclei** occurs early & progresses rapidly, a pattern of disease referred to as ***bulbar*** **ALS**, in which, abnormalities of swallowing & speaking dominate.

Bulbospinal Atrophy (Kennedy Disease)

★This X-linked, adult-onset disease, affecting **lower motor neurons; is characterized by distal limb amyotrophy** & bulbar signs such as dysphagia & atrophy & fasciculations of the tongue. Affected individuals manifest **androgen insensitivity** with **gynecomastia, testicular atrophy & oligospermia**.

😐 This is a trinucleotide-repeat disorder, similar to Huntington disease; in this case, the polyglutamine repeat is in the **androgen receptor**.

Spinal Muscular Atrophy

★These are a distinctive group of autosomal recessive motor neuron diseases that begin in childhood or adolescence. There is loss of lower motor neurons, muscle atrophy & weakness, often involves entire fascicles (panfascicular atrophy)

The most common form is **Spinal Muscular Atrophy (SMA1)** (Werdnig-Hoffmann disease), has its onset at birth or within the first 4 months of life & usually leads to death within the first 3 years of life. All forms of the disease are associated with mutations in the same gene (*SMN*) on chromosome 5.

SUMMARY

Degenerative Diseases: Neurodegenerative diseases cause symptoms depend on the pattern of involvement of the brain.

- Diseases that affect primarily the cerebral cortex (e.g., **Alzheimer** disease) are more likely to cause cognitive change, alterations in personality, & memory disturbance. Accumulation of the Aβ petide, derived from amyloid precursor protein (APP) is central to the pathogenesis of Alzheimer disease.

- Diseases that affect basal ganglia (e.g., **Huntington or Parkinson disease**) have motor symptoms as prominent clinical features. Parkinson disease is caused by loss of dopaminergic neurons, & Huntington disease is caused by trinucleotide repeat expansions in the gene encoding huntingtin protein , resulting in **disease-causing gain of function**.

- Diseases that affect the cerebellum (e.g., spinocerebellar ataxia) manifest as ataxia, along with other symptoms.
- Diseases that affect upper & lower motor neurons (e.g., amyotrophic lateral sclerosis) present with weakness as a dominant feature.
- Many of these diseases are associated with abnormal aggregation of proteins, which may lead to loss of function or may trigger apoptosis.
- Familial forms of these diseases are associated with mutations in the genes encoding these proteins.

DISEASES OF THE PERIPHERAL NERVOUS SYSTEM (NS)

★**The peripheral NS begins few mms from the pial surface of the brain & SC,** where **Schwann** cell processes replace oligodendroglial processes as source of **myelin.**

★ Peripheral NS myelin shares some structural similarities with CNS myelin, but also contains several proteins that are unique to the periphery. Abnormalities in some of these structural proteins have been implicated in the development of certain **hereditary peripheral neuropathies.**

☺ Normally, **myelinated axons** in the peripheral nerves are invested by concentric laminations of Schwann cell cytoplasm. The myelin sheath contributed by each Schwann cell is termed a ***myelin internode****,* & the space between adjacent internodes is termed the ***node of Ranvier*****.** Therefore, **each myelin internode is formed by a single, dedicated Schwann cell.**

★ The normal peripheral nerve also contains many smaller-diameter, **unmyelinated axons**, which lie in small groups **within** the cytoplasm of a single Schwann cell.

★ Groups of myelinated & unmyelinated axons, in turn, are compartmentalized into discrete fascicles by concentrically arranged ***perineurial cells.***

★ Similar to the blood-brain barrier, the axons are insulated from the interstitial fluids of the body by a "blood-nerve" barrier, formed by ⇨ tight junctions between EC of small peripheral nerve BV & tight junctions between adjacent **perineurial cells**.

★Peripheral NS disorders include peripheral **neuropathies & tumors** arising from Schwann & other nerve sheath cells.

Patterns of Nerve Injury

A variety of diseases can affect nerves (see Table 23-4).

★ In general, there are two main patterns of response of peripheral nerve to injury based on the target of the insult & whether it is the Schwann cell? or the axon?

★ **Diseases that affect primarily the Schwann cell** lead to a loss of myelin, referred to as *segmental demyelination.*

★ In contrast, **primary involvement of the neuron & its axon leads** to axonal degeneration. In some diseases, axonal degeneration may be followed by ***axonal regeneration.***

Segmental Demyelination.

★ Segmental demyelination occurs when there is either
(1) dysfunction or death of the Schwann cell, or
(2) damage to the myelin sheath;

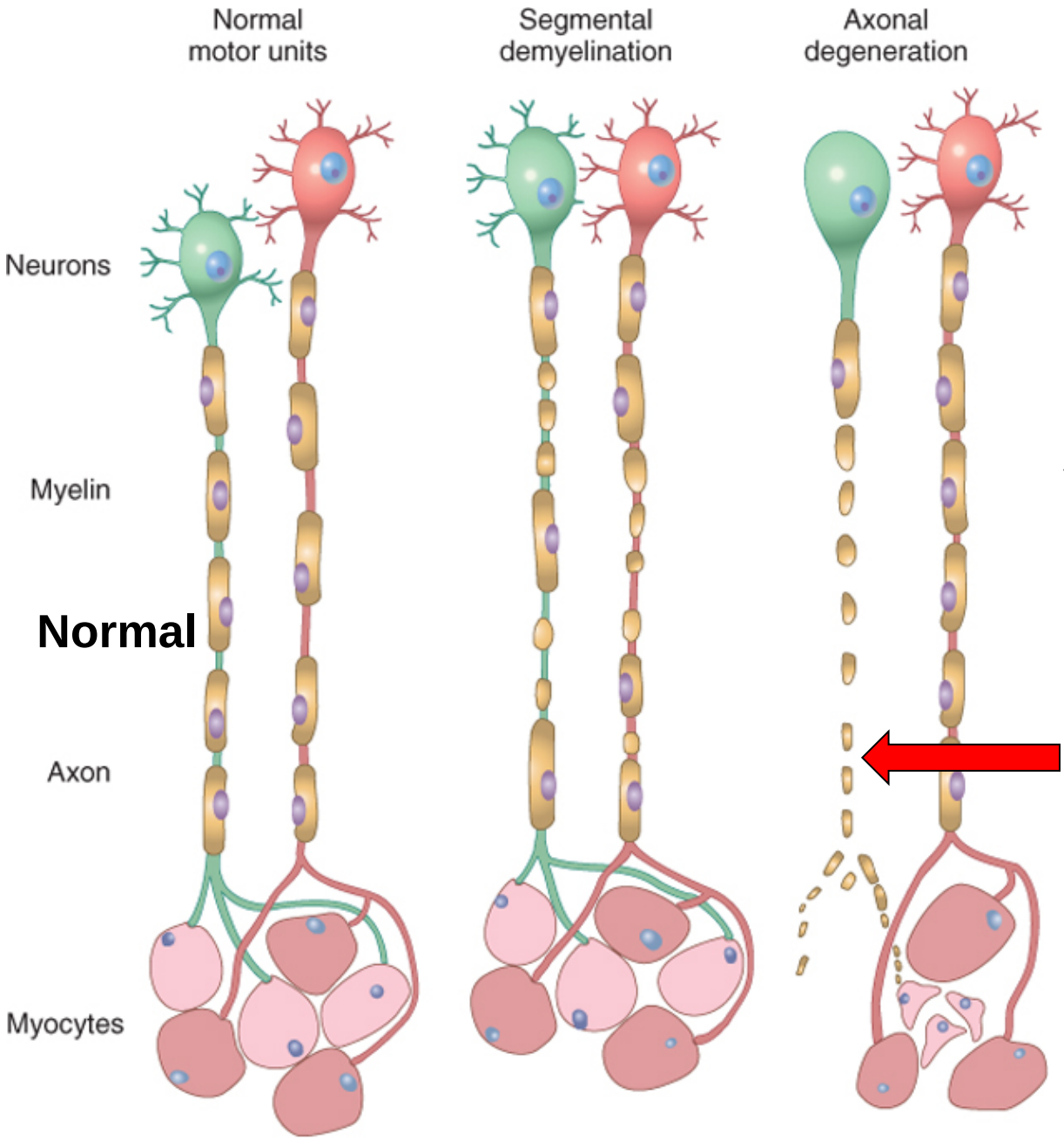
☺ **there is no primary abnormality of the axon.**

★ The process affects some Schwann cells & their corresponding internodes, while sparing others (F 23-32).

★The disintegrating myelin (◘ 4.28) is engulfed initially by Schwann cells & later by macrophages.

★The **denuded axon provides a stimulus for remyelination**, with a population of cells within the **endoneurium differentiating to replace injured Schwann cells.**
☺ These cells proliferate & encircle the axon &, in time, remyelinate the denuded portion.

★**Remyelinated internodes** are (1) **shorter than normal** & several are required to bridge the demyelinated region(F23-32), & (2) have **thinner** myelin in proportion to the diameter of the axon than normal internodes.

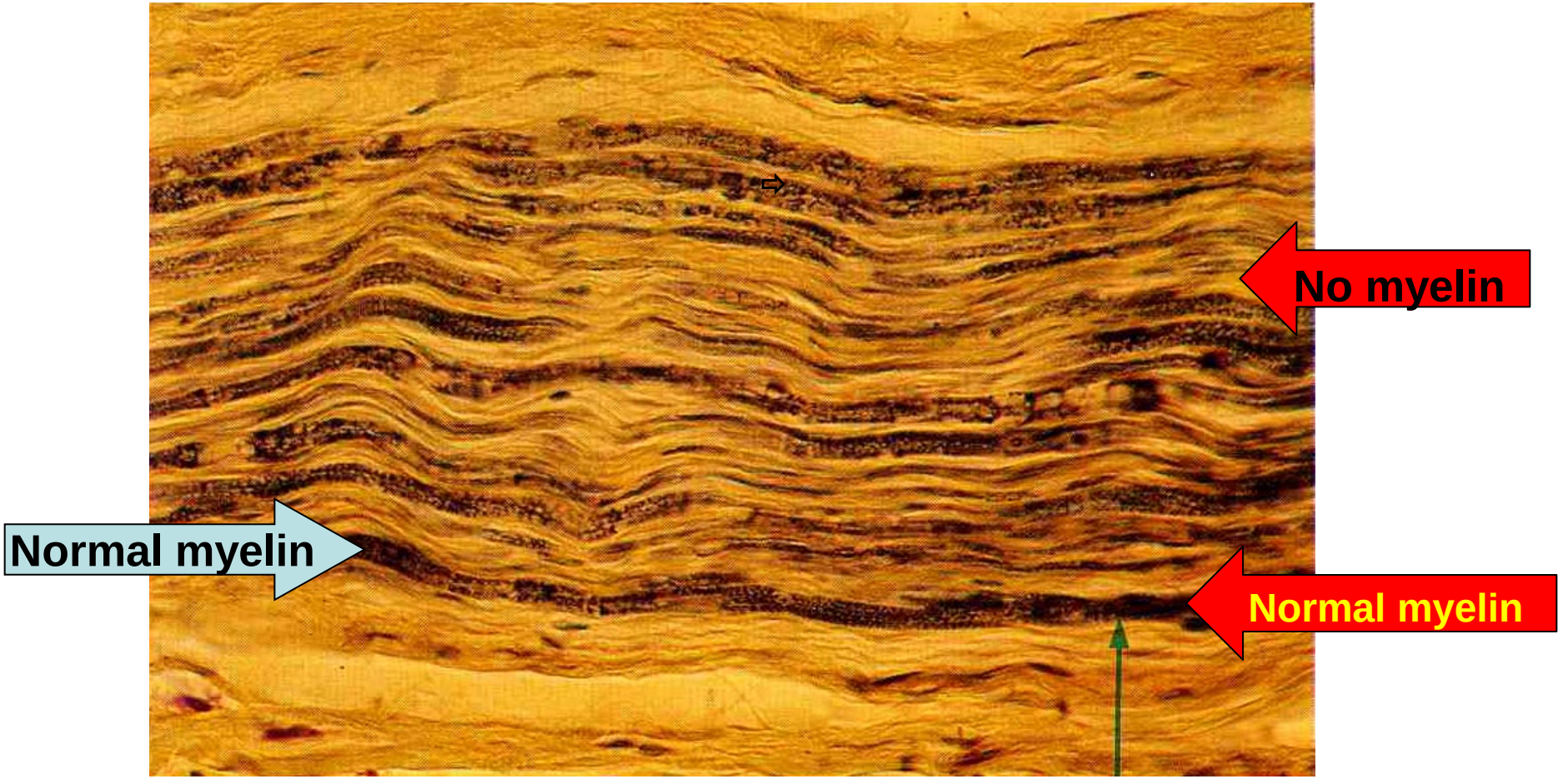


F23-32: ★**Two adjacent Normal motor units**.

★ **Segmental demyelination:** Random internodes of myelin are injured & are remyelinated by multiple Schwann cells, while the axon & myocytes remain intact.

★**Axonal degeneration:** The axon & its myelin sheath undergo anterograde degeneration (shown for the green neuron), with resulting denervation atrophy of the myocytes within its motor units.

◘ 4.28: **Peripheral neuropathy: Sural nerve, X335.** A man of 43 who had drunk 25 pints of beer/day for years, P/ W S&S of peripheral neuropathy. Sural nerve biopsy, **stain for myelin {Solochrome cyanin, deep blue, arrow**) shows marked segmental ***demyelination of all the nerve fibers.*** Another special stain however showed that the ☺ axons are intact.



★ **With repetitive cycles of demyelination & remyelination,** there is an accumulation of tiers of Schwann cell processes that, on transverse section, appear as concentric layers of Schwann cell cytoplasm & redundant basement membrane that surround a thinly myelinated axon **(*onion bulbs*) (F23-33**).

★In time, many chronic demyelinating neuropathies give way to axonal injury.

Table 23-4. Causes & Types of Peripheral Neuropathies

Nutritional & Metabolic Neuropathies

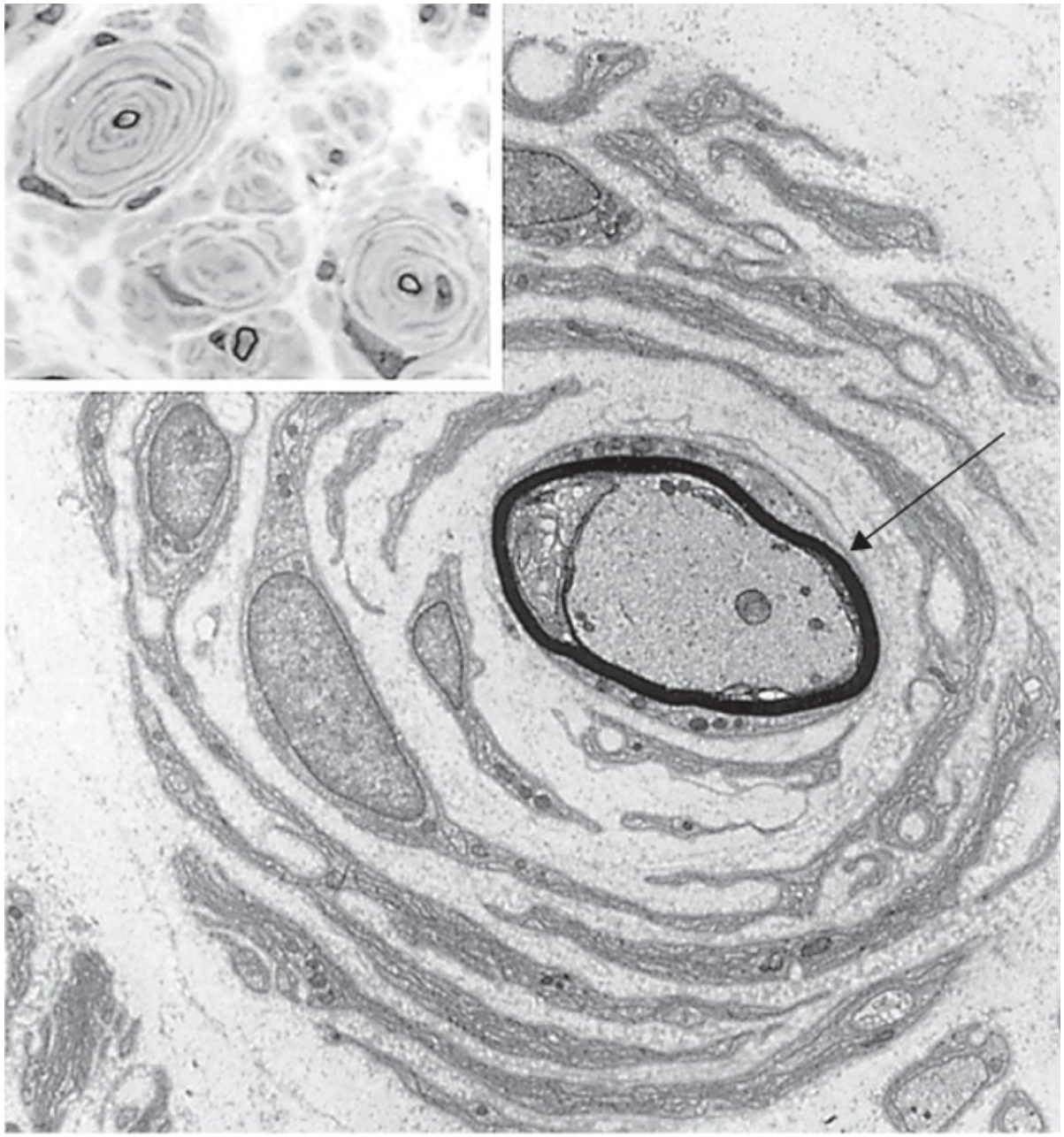
Diabetes, *alcoholism* (■ 4.28), thiamine or phyridoxine deficiency, renal failure

Toxic Neuropathies

cisplatin vincristine, organic solvents, Lead, arsenic,

Inflammatory Neuropathies

Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathy, vasculitic neuropathy, leprosy, sarcoidosis



F23-33: **EM micrograph of a single, thinly myelinated axon** (arrow) surrounded by concentrically arranged Schwann cells, forming an onion bulb.

***Inset*,** Light microscopic LP appearance of an onion bulb neuropathy, characterized by “onion bulb” surrounding axons.

Hereditary Neuropathies

Hereditary motor & sensory neuropathies (Charcot-Marie-Tooth disease, Refsum disease, Dejerine-Sottas disease), hereditary sensory neuropathies, leukodystrophies

Miscellaneous

Amyloid neuropathy, paraneoplastic neuropathies, neuropathies associated with immunoglobulin abnormalities

Axonal {*Wallerian*} Degeneration

★ **Axonal degeneration is the result of primary destruction of the axon,** due either to a:
(1) <u>focal</u> event occurring at some point along the length of the nerve e.g., **trauma or ischemia,** or to
(2) a more <u>generalized</u> abnormality affecting the neuron cell body (*neuronopathy*) or its axon (*axonopathy*)}**,**
with secondary disintegration of its myelin sheath.

★When axonal injury occurs as the result of a **focal lesion**, such as traumatic transection (cut) of a nerve, the distal portion of the fiber undergoes ***Wallerian degeneration*** (F23-32).

★ **Within a day**, the axon breaks down, & Schwann cells begin to degrade the myelin & then engulf axon fragments, forming small oval compartments **(*myelin ovoids*).** Macrophages phagocytose axonal & myelin-derived debris. The stump of the proximal portion of the cut or severed nerve shows degenerative changes involving only the most distal two or three internodes & then undergoes regenerative activity.

★ **The proximal stumps of degenerated axons can develop new growth cones (►) as the axon regrows,** cones use the Schwann cells vacated by the degenerated axons to guide them, if properly aligned, with the distal nerve segment.
★ The presence of **(*regenerating cluster*)** of axons, a multiple, closely aggregated, thinly myelinated small-caliber axons is evidence of regeneration

★ ***Regrowth*** *of axons is a* ***slow,*** *1-2 mm per day,* limited by the rate of the slow component of axonal transport, the movement of tubulin, actin, & intermediate filaments. However, axonal regeneration accounts for some of the potential for functional recovery following peripheral axonal injury.

Guillain-Barré Syndrome

★ **This is one of the most common life-threatening diseases of the peripheral nervous system.**

★ It may develop **spontaneously** or **after a systemic infection** (usually viral) or other stress. Patients present with **rapidly progressive, ascending motor weakness** that may lead to **death** from failure of respiratory muscles.

★ Sensory involvement is usually much less striking than is motor dysfunction.

◘ H, there is **segmental demyelination** with **scant infiltration** of peripheral nerves by macrophages & reactive lymphocytes.

★**CSF:** contains increased levels of protein, but only a minimal cellular reaction.

★ Because of those cases with infectious antecedents, an immunologic basis is considered most likely; treatments include **plasmapheresis** or intravenous immunoglobulin, which can shorten the course of the disease. ☺ With **supportive care**, most affected individuals recover over time.

Tumors (T) of the Peripheral Nervous System

★ These T arise from cells of the peripheral nerve, including Schwann cells, perineurial cells, & fibroblasts.

★ Many express **Schwann cell characteristics, including mainly the presence of S-100 antigen** as well as the potential for melanocytic differentiation.

★ **Recall:** as nerves exit the brain & spinal cord, there is a transition between myelination by oligodendrocytes & myelination by Schwann cells.
★This occurs within **few millimeters** of the substance of the brain; therefore; in addition to arising along the peripheral course of nerve… ☹ remember that
➔ **these peripheral nerves tumors can arise within the confines of the dura** causing changes in adjacent brain or spinal cord!

Schwannoma

★Benign T arising from Schwann cells.

★**Symptoms** are referable to **local compression of the**
(I) involved nerve, or
(II) of adjacent structures (such as brain stem or SC).

★They are often encountered **within the cranial** vault in the cerebellopontine angle, where they are ***attached to the vestibular branch of the 8th nerve*** (F23-34A). These patients often present with tinnitus & hearing loss, & the T is often referred to as an **acoustic neuroma**, although it is more accurately called a **vestibular schwannoma.**

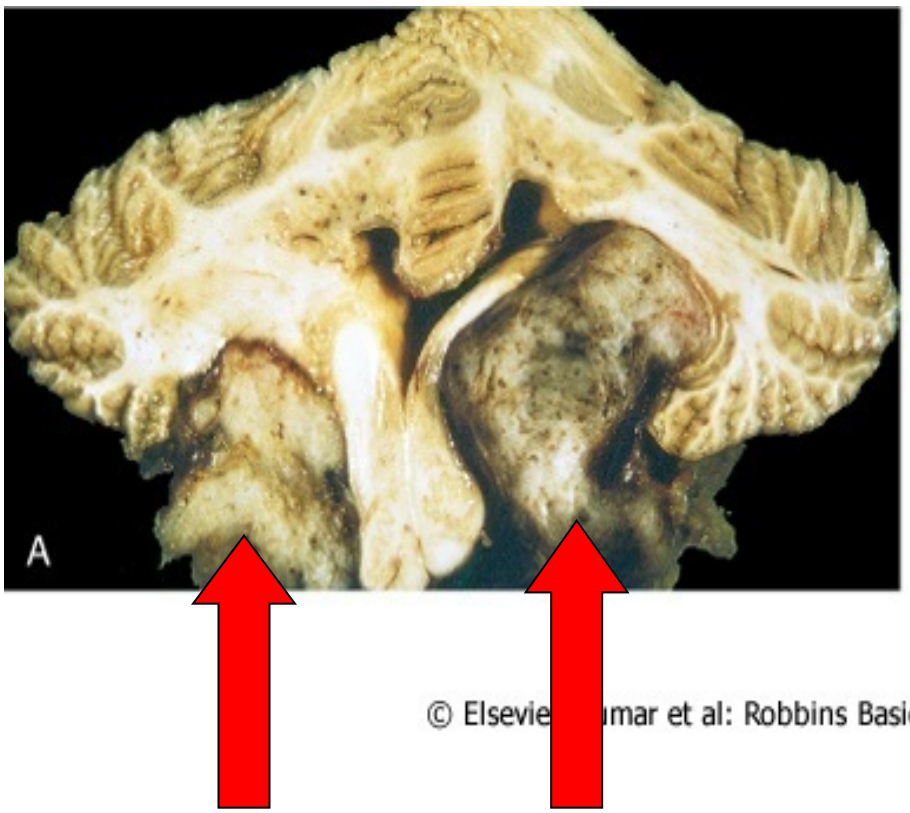
★Elsewhere **within the dura**, sensory nerves are preferentially involved, eg branches of the **trigeminal nerve & dorsal roots**.

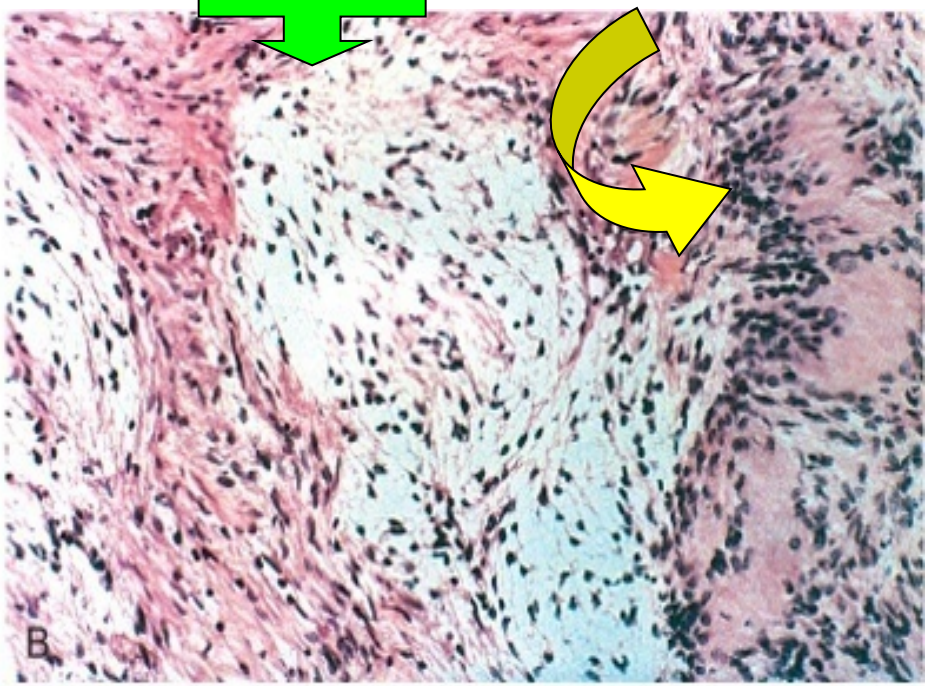
★ When **extradural**, schwannomas are most commonly found in association with **large nerve trunks**, where motor & sensory modalities are intermixed. Sporadic schwannomas are associated with mutations in the *NF2* gene on chromosome 22.

F23-34: **Schwannoma.**

A, Bilateral eighth (8th) cranial nerve **Schwannomas.**

B, Tumor showing cellular areas (**Antoni A**), including **Verocay** bodies (far right), as well as looser, myxoid regions (**Antoni B**) areas.





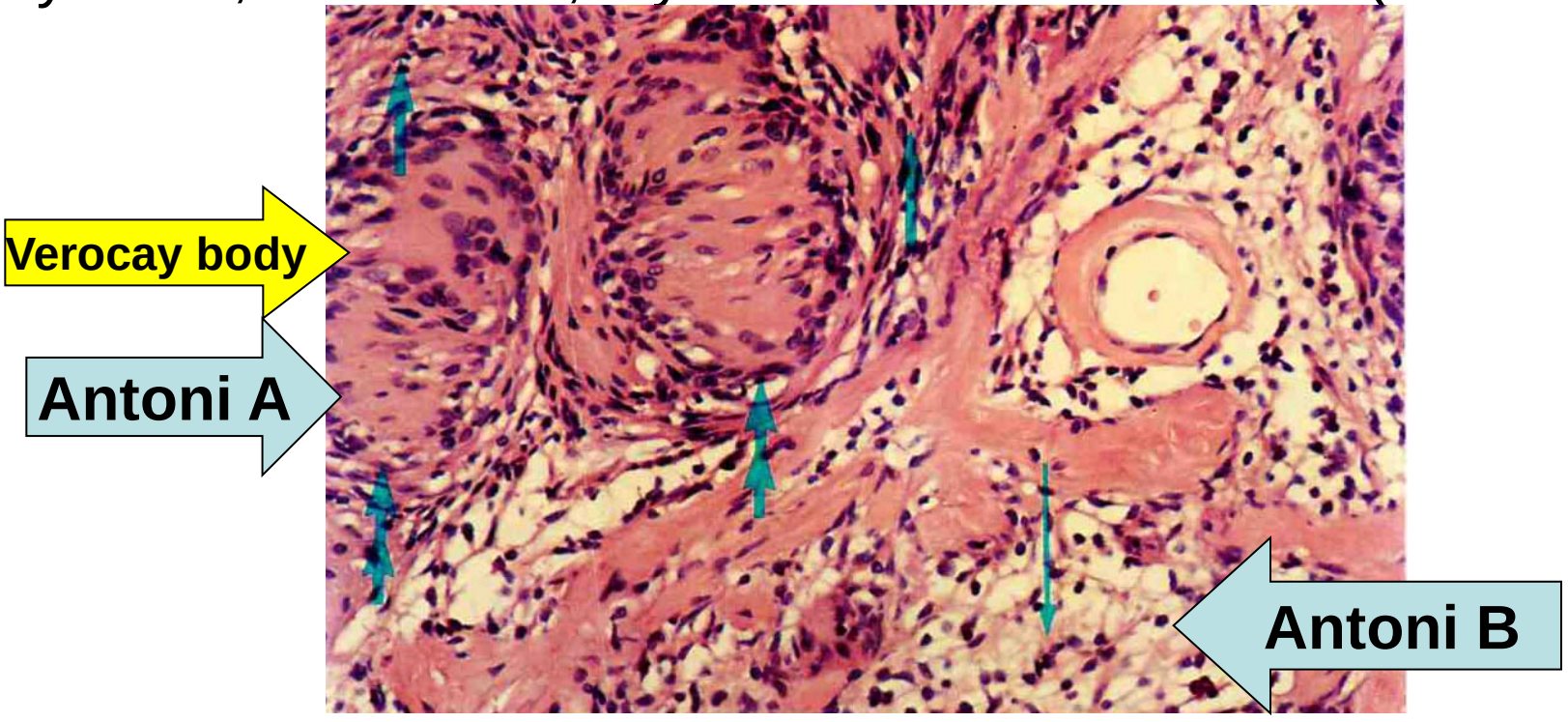
►**GROSSLY,** Schwannomas are encapsulated, well-circumscribed T that are **attached to the nerve but can be separated from it,** forming firm, gray masses but may also have areas of cystic & xanthomatous change.

◘ H, Two growth patterns are seen (F23-34B & ◘ 4.46).
(I) **In the Antoni A pattern of growth**, elongated cells with cytoplasmic processes are arranged in fascicles in areas of moderate to **high cellularity** with little stromal matrix; the "nuclear-free zones" of processes that lie between the regions of nuclear **palisading** are termed **Verocay bodies**.

(II) **In the Antoni B pattern of growth,** the T is **less densely** cellular with a loose meshwork of cells along with microcysts & myxoid changes.

★ The individual T cells (in both growth patterns) is similar, with elongated cell cytoplasm & regular oval nuclei.
★ Because schwannoma **displaces the nerve of origin** as it grows, axons are largely excluded from the T.
★T are usually **uniformly immunoreactive for S-100 protein.**

◘ 4.46: **Schwannoma: Spinal nerve X235. (I)** The **Antoni type A** tissue is highly cellular (thick A), consisting of elongated tumor cells arranged as long eosinophilic cords & compact ovoid bodies (Verocay bodies, double arrows). The nuclei are elongated, round & most of them are palisaded & located at the periphery of the ovoid bodies, whereas the centers of the bodies are occupied by a mass of fibrillary eosinophilic cytoplasm.
(II) The **Antoni type B, less densely** cellular tumor cells with very loose, vacuolated, myxomatous stromal tissue (thin arrow).



Neurofibroma

★ The most common form of neurofibroma occurs in the **skin (*cutaneous neurofibroma*)** or in peripheral nerve **(*solitary neurofibroma*)**. These T arise sporadically or in association with type 1 neurofibromatosis (NF1).

Cutaneous neurofibroma

★ Present as skin **nodules**, sometimes with overlying hyperpigmentation; they may grow to be large & become pedunculated. The **risk of malignant transformation** from these T is extremely small, & **cosmetic** concerns are their major morbidity.

►**GROSSLY,** they present in the dermis & subcutaneous fat, as a **well-demarcated, unencapsulated, non invasive** T.

◘ T composed of spindle cells with highly collagenized stroma & containing little myxoid material.

Solitary neurofibroma within peripheral nerves is of identical histologic appearance.

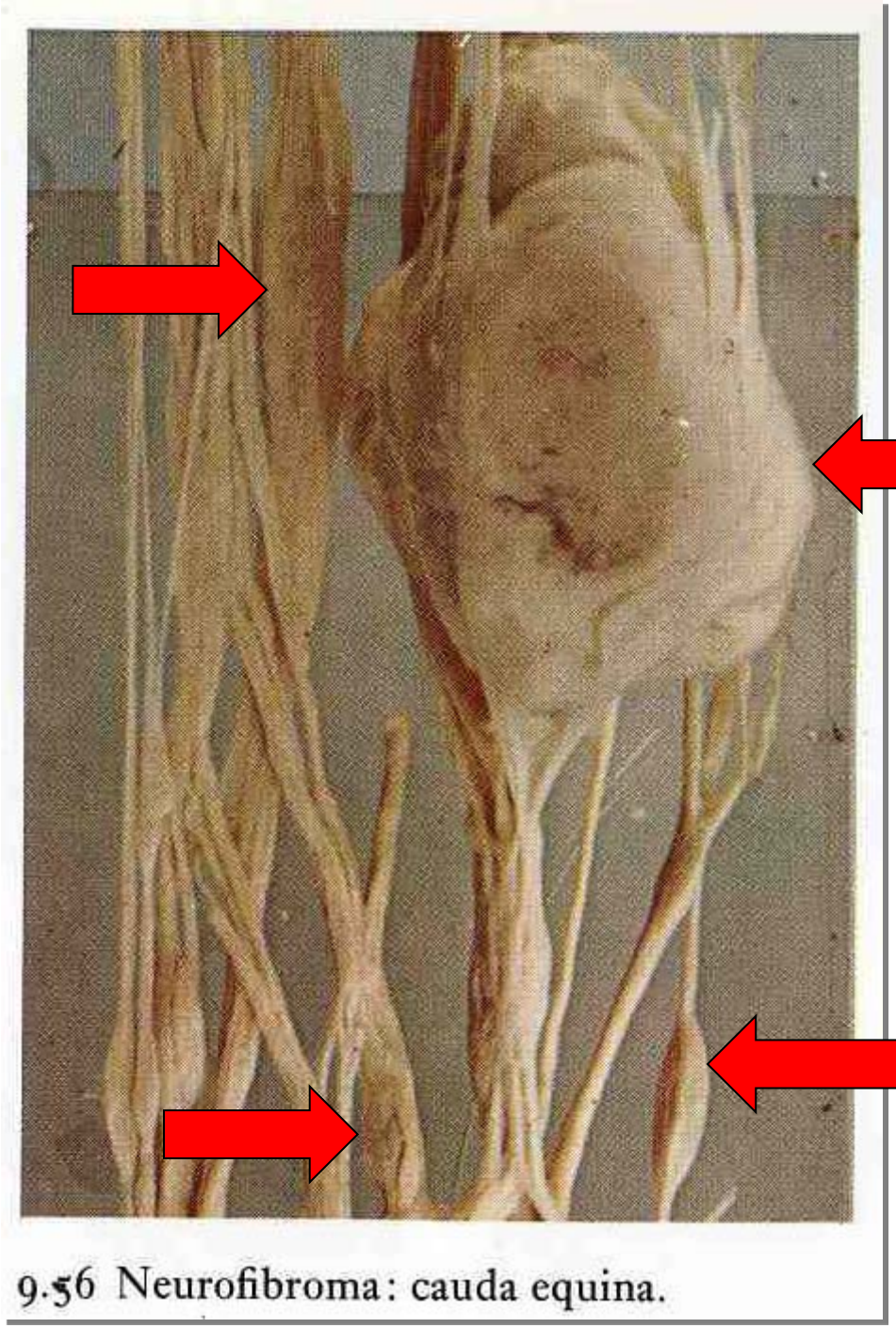
Plexiform neurofibroma

Mostly arising in individuals with NF1. Of major concern is the:
(1) Difficulty in surgical removal of these plexiform **T** when they *involve major nerve trunks* & their
(2) Potential for *malignant transformation.*

► **GROSSLY,** these T may arise anywhere along a nerve, although the ***most common*** **site is the *large nerve trunks*** . They are frequently ***multiple.***

☺ Unlike schwannomas, ☹ **it is not possible to separate the T from the nerve**. At the site of each lesion, the host nerve is irregularly expanded, as **each of its fascicles is infiltrated by the T** (F 9-56). The proximal & distal ends of the **T** have poorly defined margins, as fingers of **T** cells insert themselves between the nerve fibers.

◘ H, the lesion has a loose, myxoid background with a low cellularity. A number of cell types are present, including **Schwann** cells with typical elongated nuclei & extensions of pink cytoplasm, larger multipolar **fibroblastic** cells, & a sprinkling of inflammatory cells, often including mast cells.



9.56 Neurofibroma: cauda equina.

F 9-56: **Plexiform neurofibroma**: **cauda equina.**

A large, ovoid, lobulated neurofibroma has arisen from the nerve sheaths of the cauda equina.

Several thickened nerves blend with the capsule of the tumor.

Many of the other nerves show small fusiform swellings (lower right).

Malignant Peripheral Nerve Sheath Tumor

★ These are highly malignant sarcomas that are locally invasive, frequently leading to multiple recurrences & eventual metastatic spread. Despite their name, these T do not arise from malignant transformation of schwannomas. Instead, they (I) **arise de novo** or (II) **from transformation of a plexiform neurofibroma**. These T can also occur after radiation therapy.

►**GROSSLY,** the T are **poorly defined** masses with frequent infiltration along the axis of the parent nerve as well as **invasion** of adjacent soft tissues. **Necrosis** is common.

◘ H, the T cells resemble Schwann cells, with elongated nuclei & prominent bipolar processes. Fascicle formation may be present. Mitoses, necrosis, & extreme nuclear anaplasia are common. Some, but not all, malignant peripheral nerve sheath T, **are immunoreactive for S-100 protein**.

FAMILIAL TUMOR SYNDROMES

★ Several inherited syndromes are associated with an ↑ risk of particular types of T. Those discussed here are inherited diseases characterized by the development of hamartomas & T throughout the body with particular involvement of the nervous system. Most of these syndromes are linked to loss of T suppressor genes. Symptoms are referable in part to the location of hamartomas or T; developmental delay & seizure disorders may contribute to disability in some affected individuals.

Type 1 Neurofibromatosis (NF1)

➔ An autosomal **dominant** disorder characterized by: multiple **neurofibromas** (solitary & plexiform) + **gliomas** of the optic nerve + pigmented nodules of the iris **(*Lisch nodules***) + cutaneous hyperpigmented macules (***café au lait spots***).

•With a frequency of **1/3000** it is a common genetic disorders, ☹ **Risk** of individuals with NF1 neurofibromas to **undergo malignant transformation** is at a **higher rate** than that observed for neurofibromas without NF1 mutation.

★ This is especially true for plexiform neurofibromas. The *NF1* gene is a tumor suppressor gene, but how *NF1* mutations lead to **T** development? is unknown.

★ The **course** of the disease is **highly variable** & independent of the particular mutation, with some individuals carrying a mutated gene & having no symptoms, while others develop progressive disease with spinal deformities, disfiguring lesions, & compression of vital structures, including the SC.

Type 2 Neurofibromatosis

➔ This is a **rare** autosomal **dominant** disorder {frequency of **1 in 40,000 to 50,000}** in which patients develop a range of tumors, most commonly:

Bilateral vestibular (acoustic) **schwannomas +** Multiple **meningiomas** + **Gliomas**, typically ependymomas of the SC + non-neoplastic **hamartomas** within the nervous system, where Schwann cells or glial cells are present in small collections in inappropriate places.

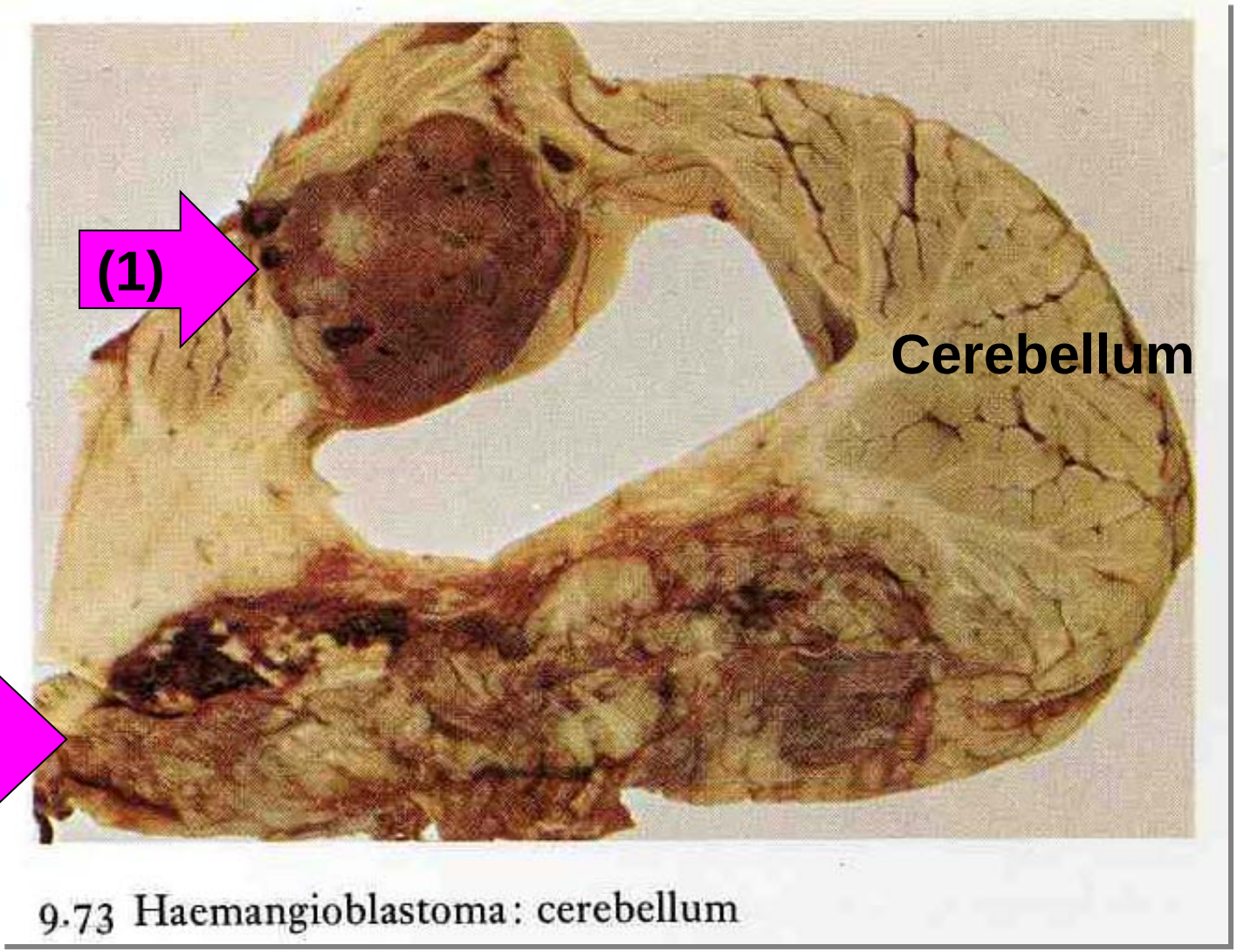
Von Hippel-Lindau Disease

★Rare **autosomal dominant inherited disease {**frequency is 1 in 30,000 to 40,000} **duo to** Missense mutations in the tumor-suppressor gene *VHL.* Affected individuals develop:
(1) Hemangioblastomas within the cerebellar hemispheres, retina, & less commonly the brain stem & SC;
(2) Cysts of the pancreas, liver, & kidneys, &
(3) High risk to develop adrenal pheochromocytoma & Renal cell carcinoma.

►**GROSSLY,** the main neurologic lesion is the **cerebellar capillary hemangioblastoma** (F 9-73), a highly vascular T that occurs as a mural nodule associated with a large, fluid-filled cyst.

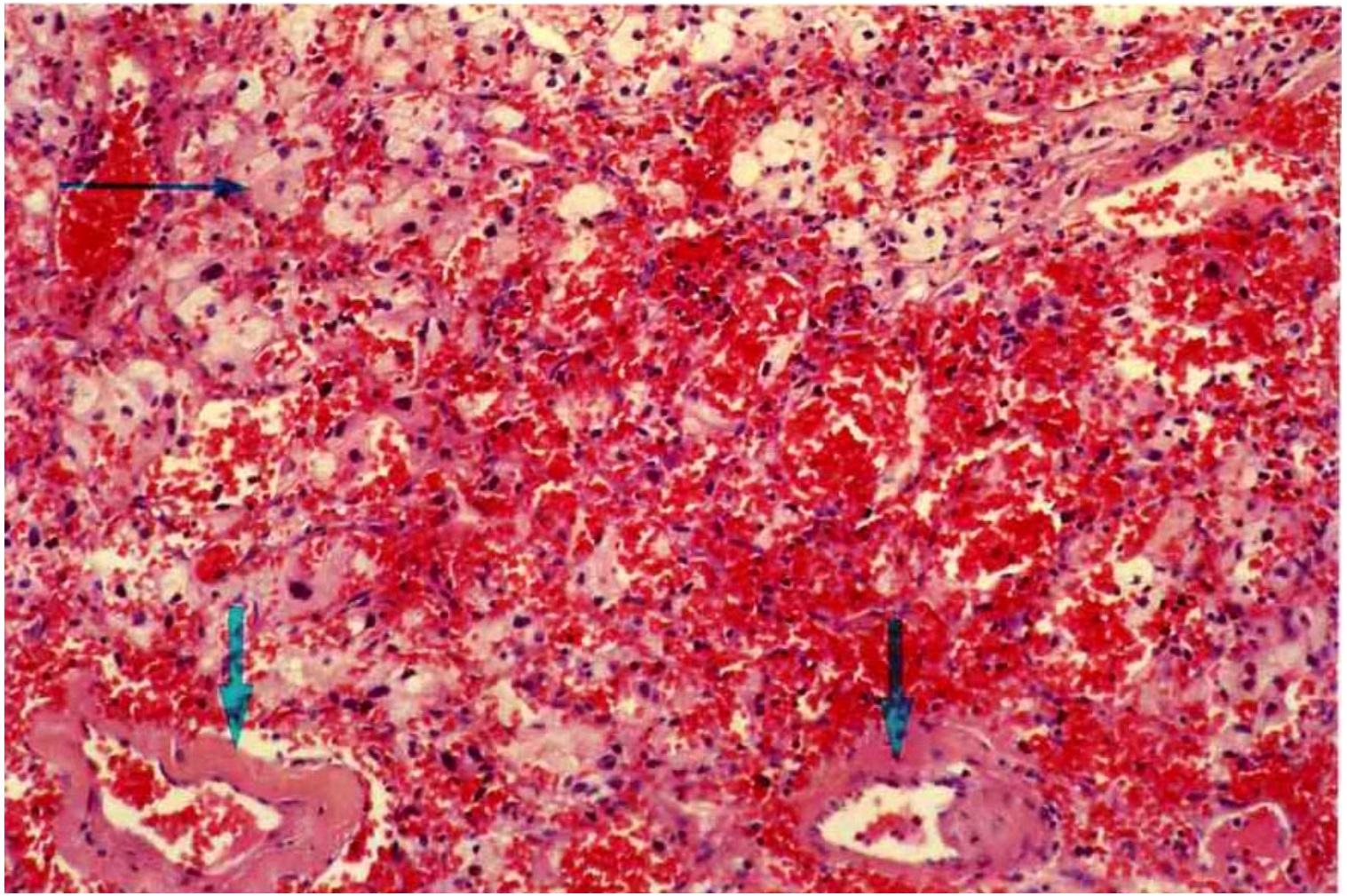
◘ 4.43, H, It consists of variable proportions of (1) thin-walled **capillaries** with (2) intervening **stromal** cells showing vacuolated, lightly PAS-positive, lipid-rich cytoplasm & dens basophilic nuclei.

F 9-73: **Hemangioblastoma: cerebellum.** The lateral lobe of the cerebellum contains large cyst cavity with two tumor nodules in its wall: **(1)** round, red-brown at top, & **(2)** larger brownish necrotic tumor mass in the bottom.



9.73 Haemangioblastoma: cerebellum

◘ 4.43: **Hemangioblastoma, Cerebellum X150.** Consisting of (1) large number of very thin-walled dilated capillaries, with foci of hemorrhages, (2) intervening stromal cells with vacuolated lipid-rich cytoplasm & dens basophilic nuclei (thin arrow).



Tuberous Sclerosis (TS)

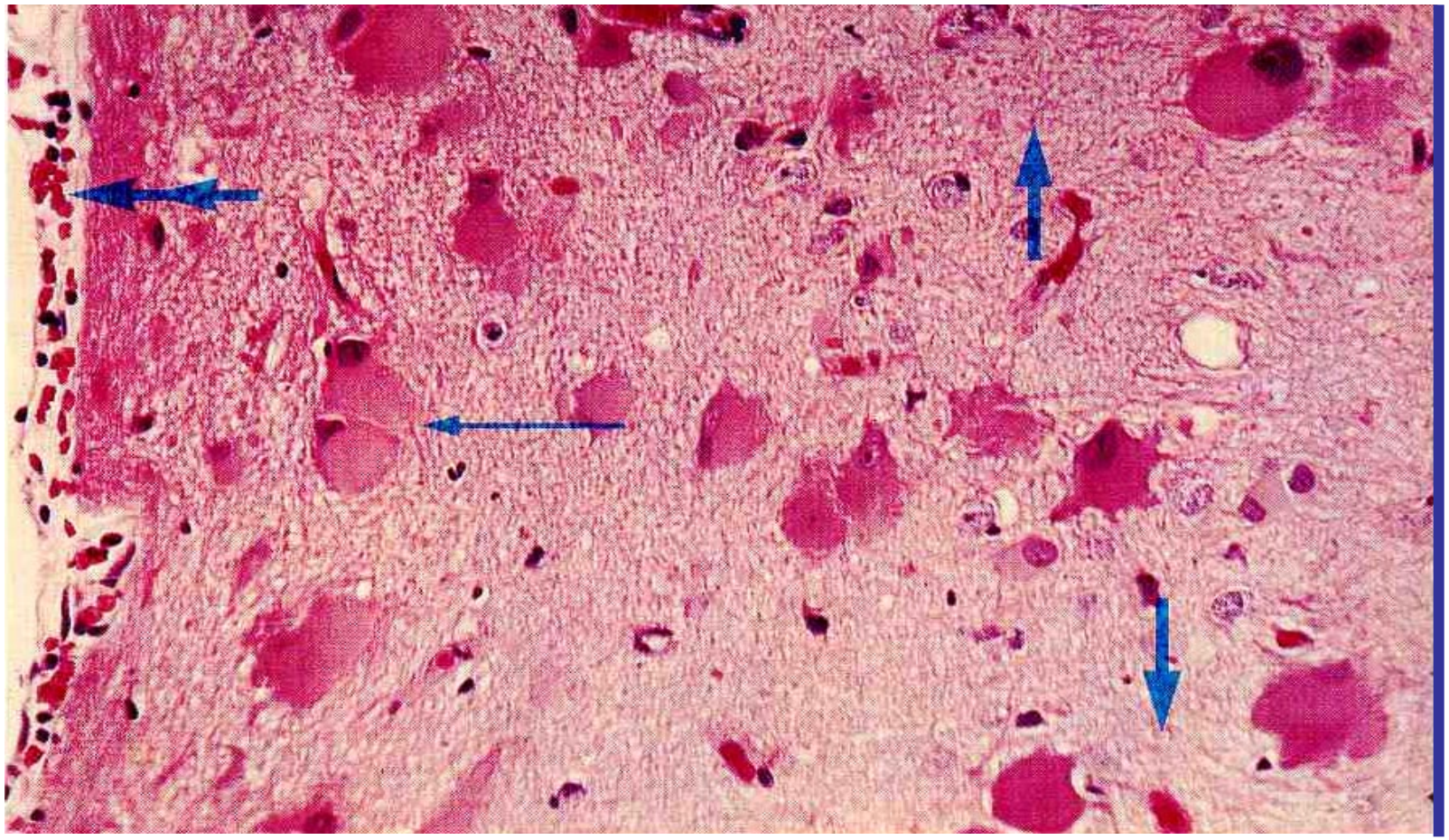
★ An **autosomal dominant syndrome,** characterized by the development of hamartomas & benign T involving the brain & other tissues; including:

• **CNS hamartomas** are (1) **cortical tubers** (◘ 4.13), associated with seizures, which can be difficult to control with antiepileptic drugs, & **(2) subependymal hamartomas**

• **Extracerebral lesions** include ➔ **renal angiomyolipomas** + retinal glial hamartomas + pulmonary lesions + cardiac rhabdomyomas + **Cysts** of the liver/kidneys/& pancreas +
• **Cutaneous lesions** include angiofibromas, leathery thickenings in localized patches, hypopigmented areas , & subungual (under the nail) fibromas.

► **Tuberous Sclerosis** results from disruption of ***TSC1*** tumor suppressor genes, which encodes hamartin, or ***TSC2,*** which encodes tuberin. These two proteins regulate protein synthesis & cell proliferation. Abnormalities of the proteins may alter neuronal proliferation, differentiation, & migration.

◘ 4.13: **Tuberous sclerosis; Brain.** Part of Cortical hamartomas nodule (likened to **potatoes**), bounded by a dilated thin-walled BV (double arrow). The normal cortex has been replaced by tissue consisting of: (I) Abundant **glial fibers** (thick arrow) & (II) Characteristic TS **bizarre giant cells** (thin arrow) some have features of neurons & others of astrocytes.



►**GROSSLY, cortical hamartomas** of TS are firm areas of the cortex that, in contrast to the softer adjacent cortex, have been **likened to potatoes, hence the name "tubers."**

◘ H, these hamartomas composed of **haphazardly arranged neurons** that lack the normal laminar organization of the cortex. These large cells may express a **mixture of glial & neuronal features**, having large vesicular nuclei with nucleoli, resembling neurons, & abundant eosinophilic cytoplasm like gemistocytic astrocytes. Similar hamartomatous features are present in the **subependymal nodules,** where the large astrocyte-like cells cluster beneath the ventricular surface.

☺ **END of CNS I+II Lectures in 133 W + 95F = 230 PPP;**

@ 7-4-2019, Lectures prepared by Associated Professor Dr. Mohammad Kamel Alwiswasi, MBChB, PhD, FRC Path