Reference: ROBBINS BASIC PATHOLOGY, By Kumar et al. 9th Ed. 2013: CNS II In 80 PPP @ April 2020: Lectures prepared by Associated Professor Dr. Mohammad Kamel Alwiswasi, MBChB, PhD, FRC Path

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, CNS tumors are

😐 **(I) Histologically, the 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 3 major types are: ★ ***astrocytomas*** ★ ***oligodendrogliomas*** ★ ***ependymomas.*** ***Astrocytoma*** ★ the most common two types are (1) diffuse or fibrillary astrocytoma & (2) 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.

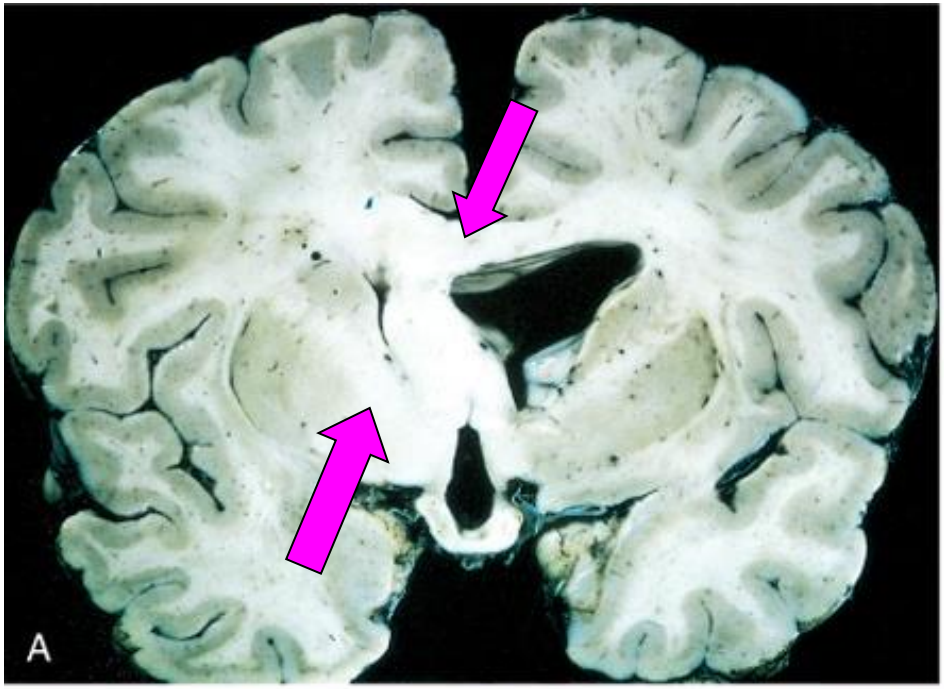
★classified histologically into 3 groups: **well-differentiated**, **anaplastic astrocytoma, & glioblastoma multiforme (GBM)** which correlates well with clinical course & outcome.

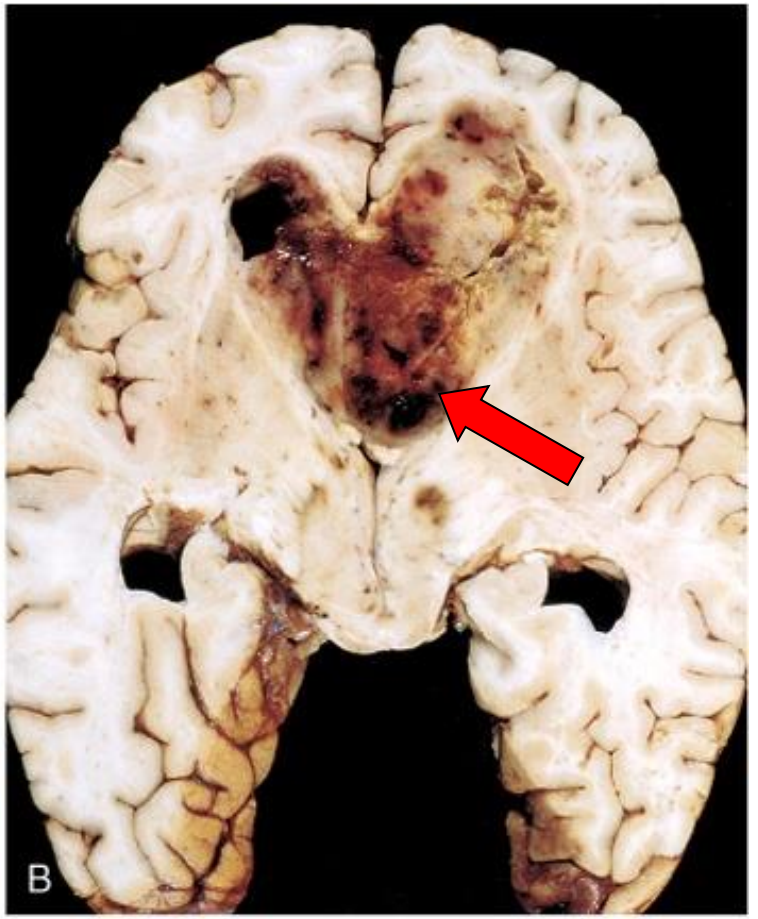
• **Well-differentiated astrocytomas** ➔progress slowly, with a **mean survival of more than 5 years.** Eventually, however, patients usually enter a period of **rapid clinical deterioration** that is generally **correlated** with the appearance of **anaplastic** features & more rapid **T** growth**.**

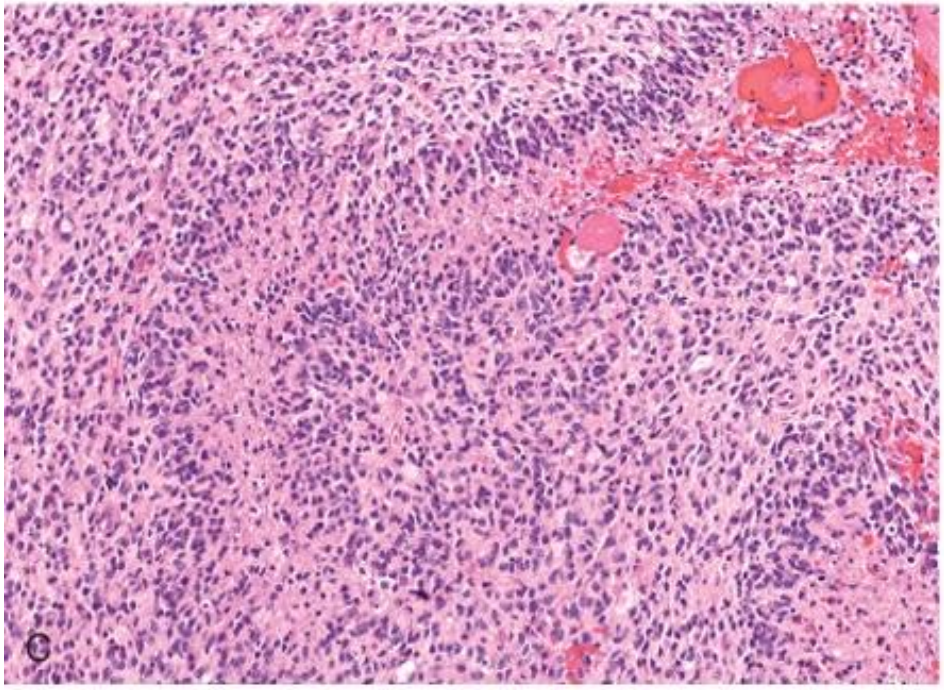
• Many patients present with highest grade, **GBM, from the start** rather than having their **T** evolve from a lower grade **T** ☠ **GBM** prognosis is **very poor;** & current **state-of-the-art treatment**, comprising resection (when feasible) together with radiotherapy & chemotherapy, yields a mean 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 **GBM, 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.**

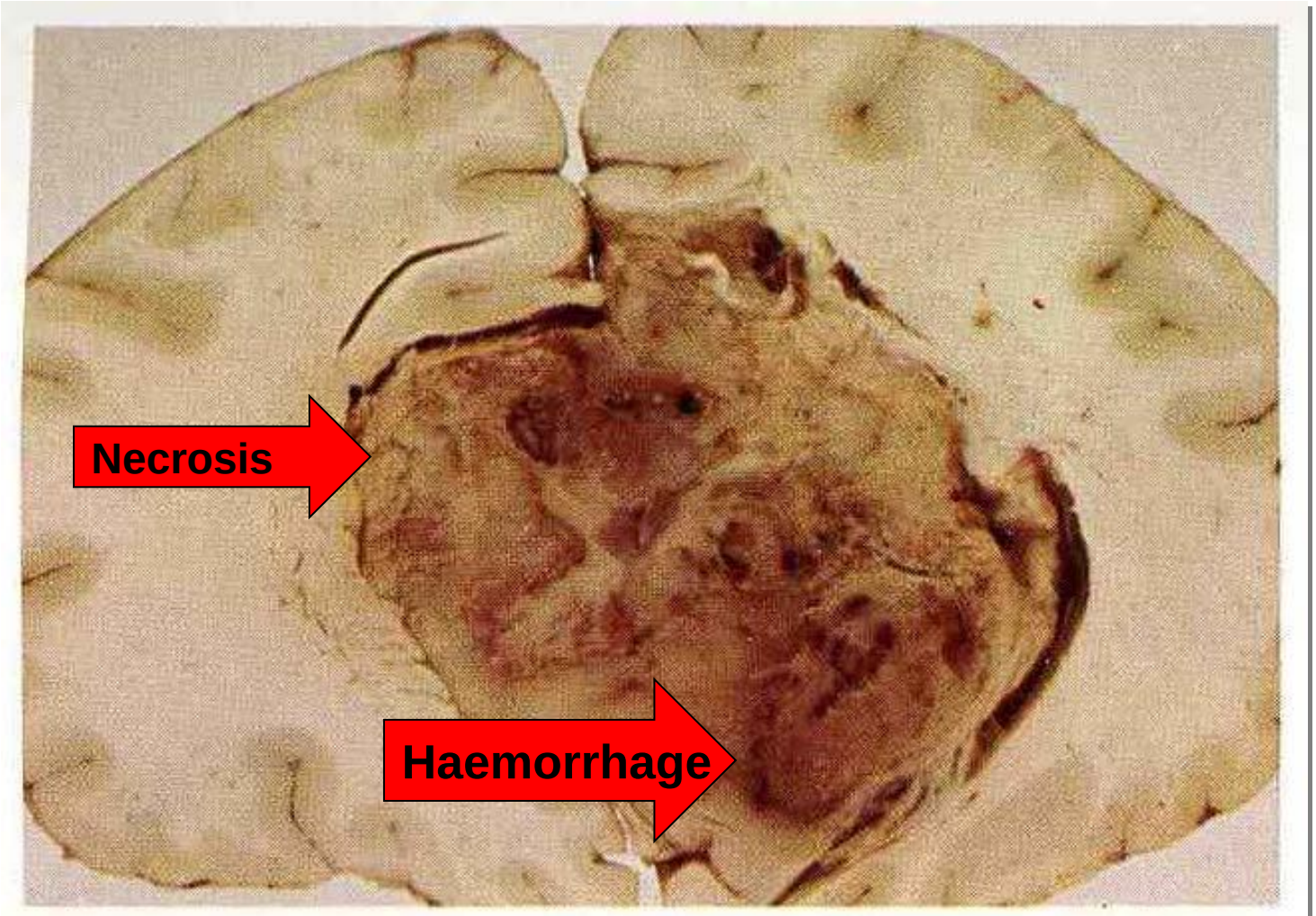






F23-22: **A, Low-grade astrocytoma** is seen as expanded white matter of the left cerebral hemisphere & thickened corpus callosum & fornices.
Glioblastoma: B, Necrotic, hemorrhagic, infiltrating **T;** histologically **C,** show (1) high cellularity + (2) pseudo-palisading of **T** cell nuclei around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

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



9.67 Glioblastoma multiforme

◘ (1) **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.

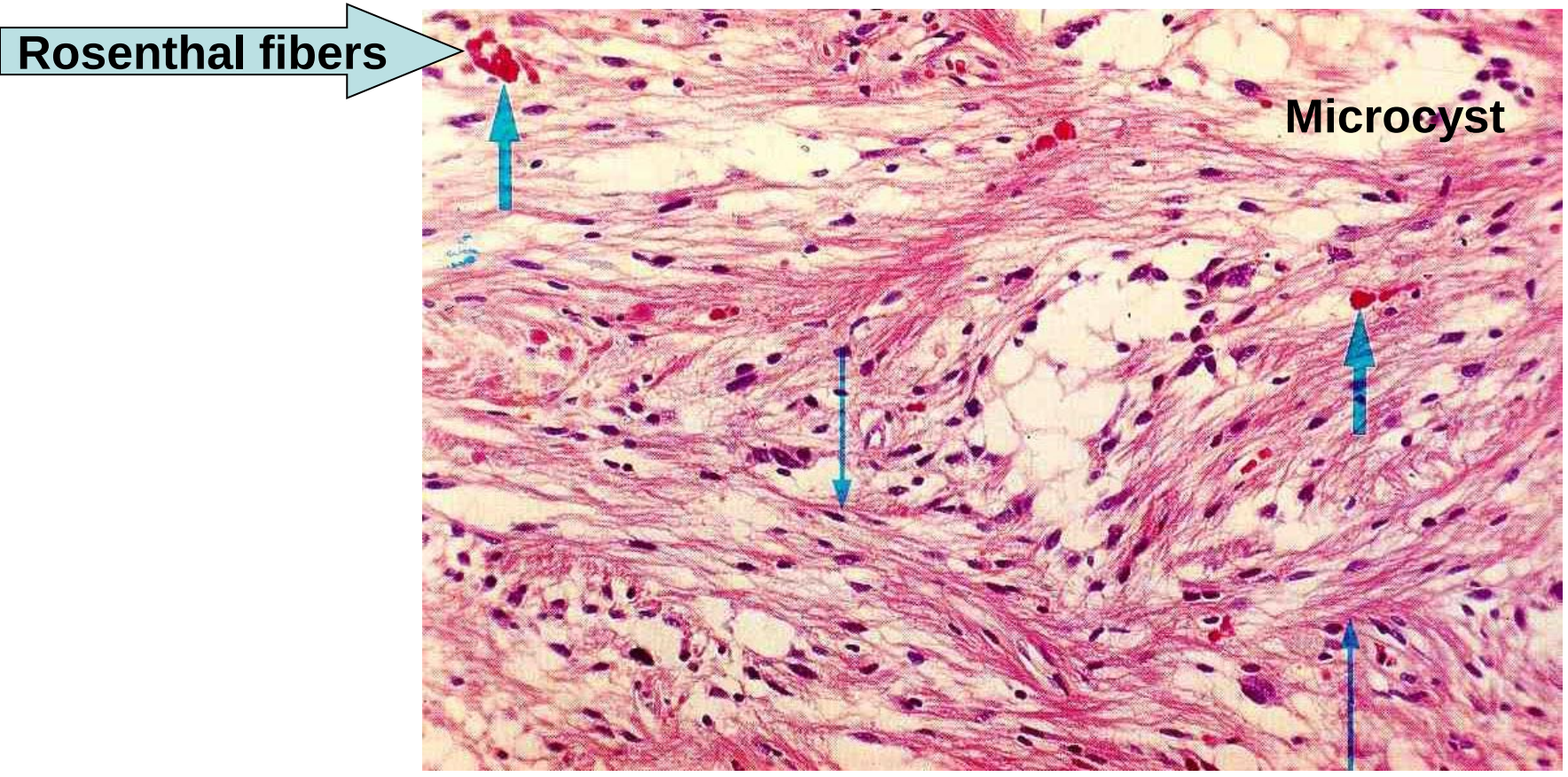
☹The **T is infiltrative & transition between neoplastic & normal tissue is indistinct (not clear); & T** cells can be seen infiltrating normal tissue at some distance from the main lesion.

◘(2) **Anaplastic astrocytomas** show more dense cellularity, greater nuclear pleomorphism, & ↑ mitoses.

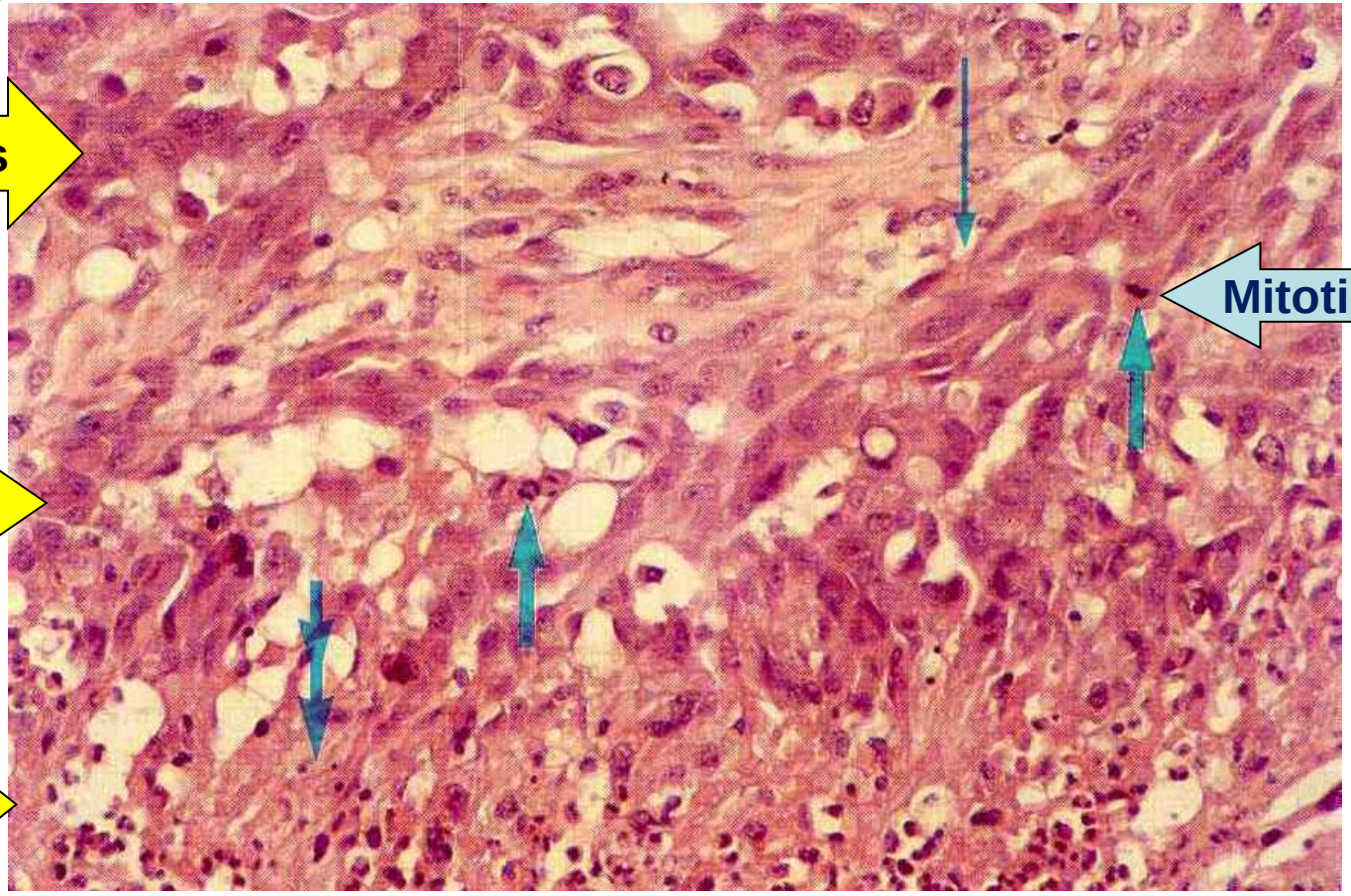
◘ (3)The highest grade **GBM tumor** has a histologic appearance similar to anaplastic astrocytoma with the additional features of:
(1) palisading necrosis (◘ 4.35), &
(2) pseudo-palisading nuclei (F23-22C) & **(3) vascular or endothelial cell proliferation (**◘4.36).

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

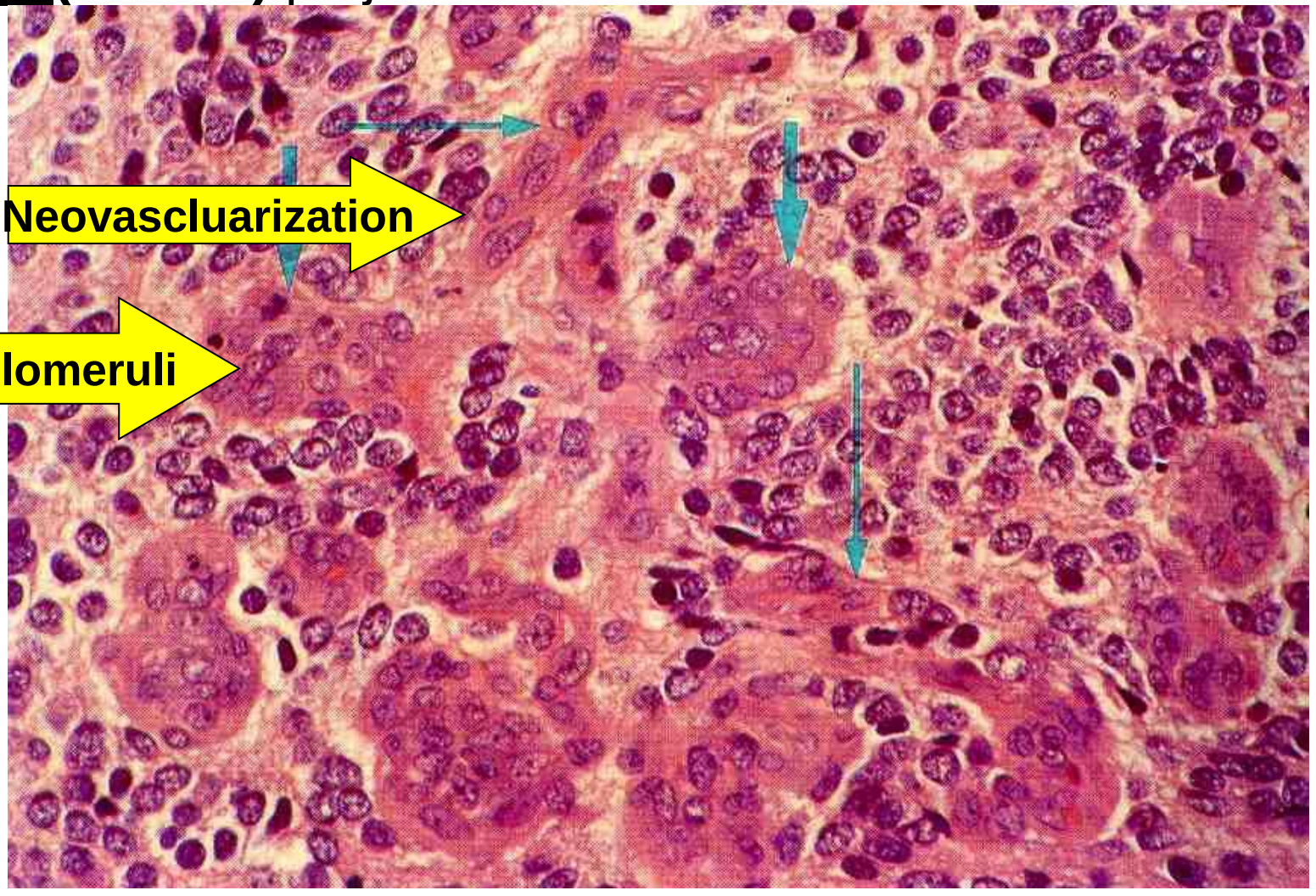
Consist of mature-looking neoplastic astrocytes with ill-defined cytoplasmic boundaries & pleomorphic ovoid/elongated basophilic nuclei. Their **neurofibrillary processes** are well-developed & abundant & arranged in large eosiniphilic bundles (thin A), within which there are collections of fluid (**microcysts**).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



◘ 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.

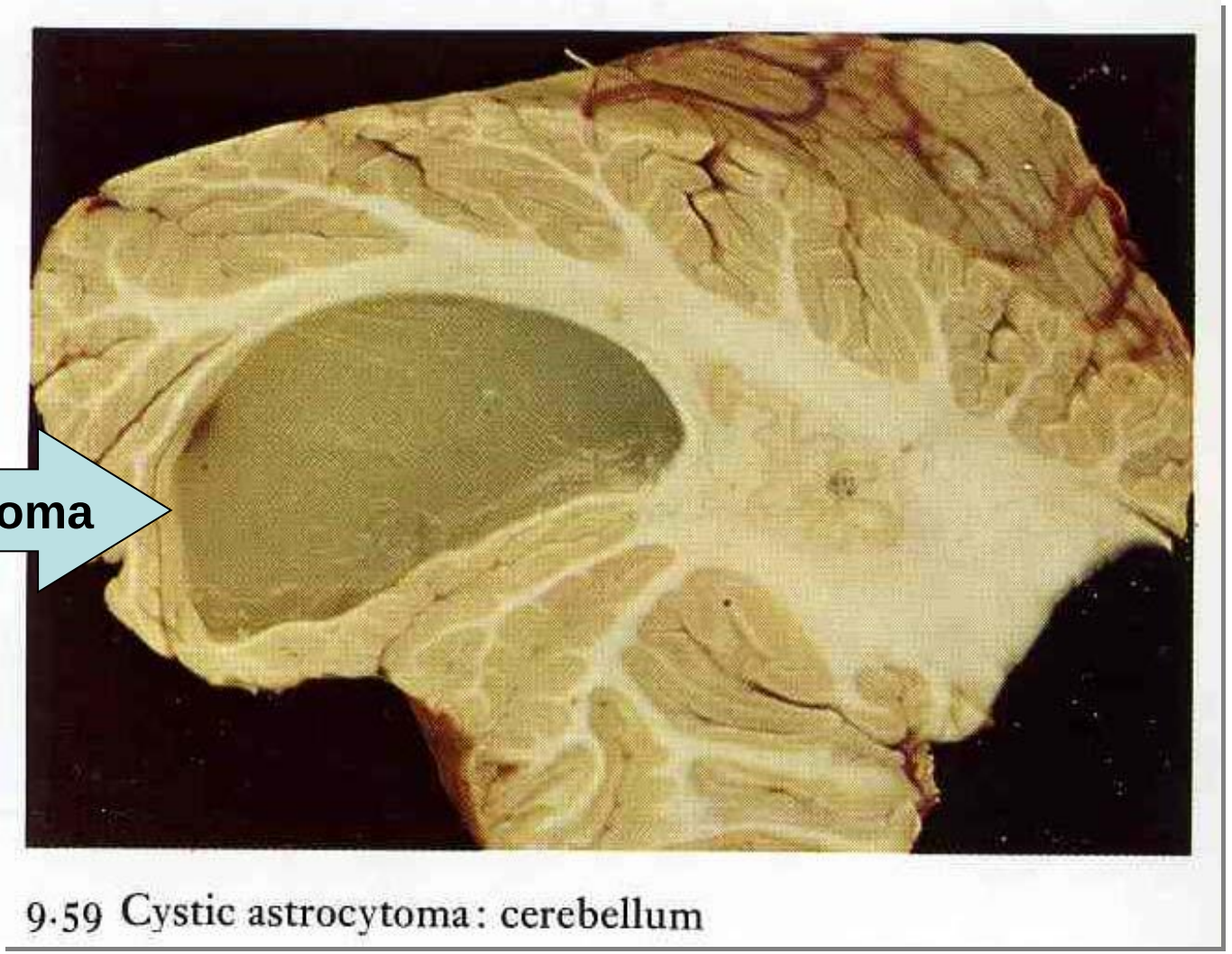


Pilocytic Astrocytoma (F9-59)

★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**.

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.

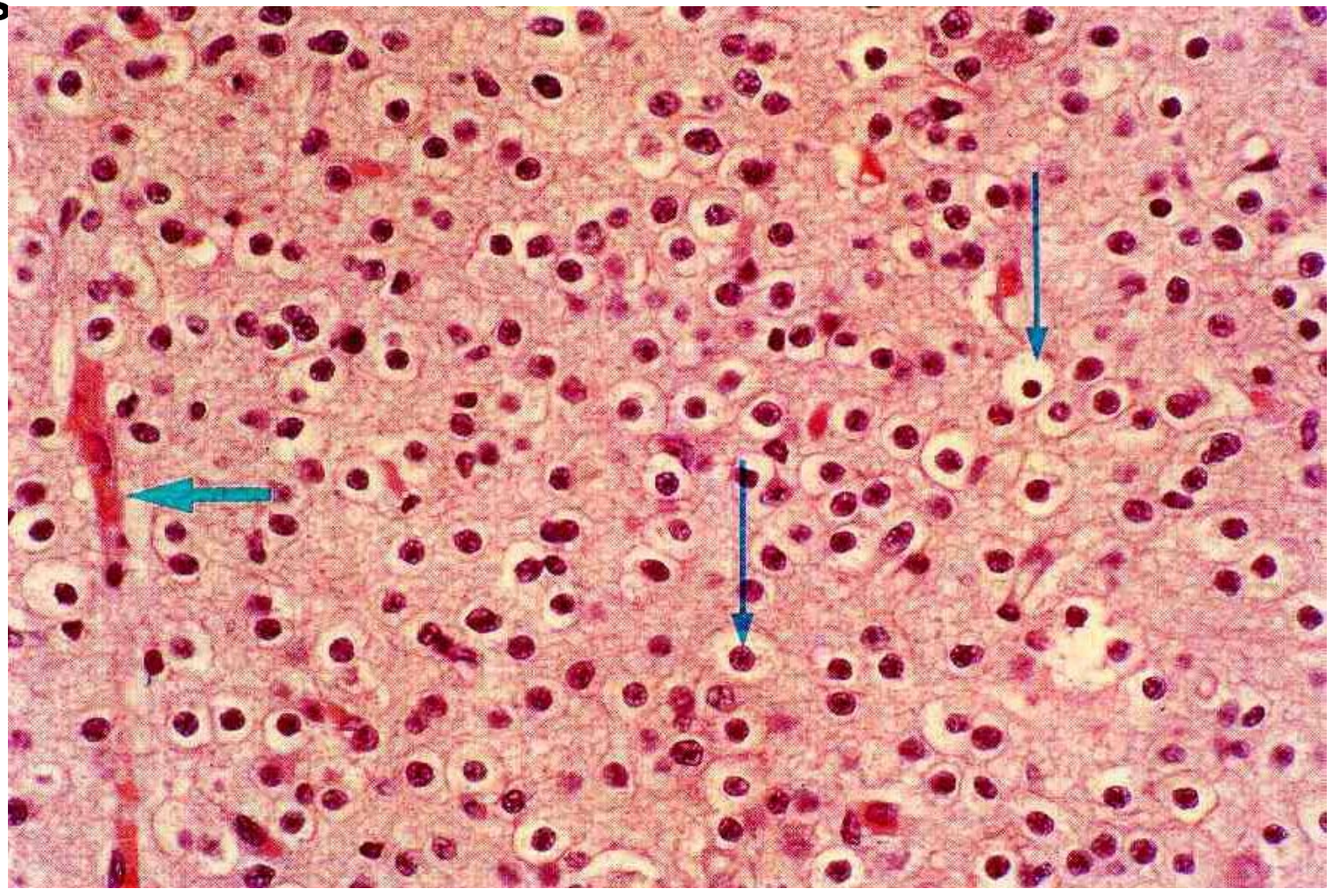
•The most common genetic findings are loss of heterozygosity for chromosomes 1p 7 19q. • Patients may have had neurologic complaints, including **seizures**.

►**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.

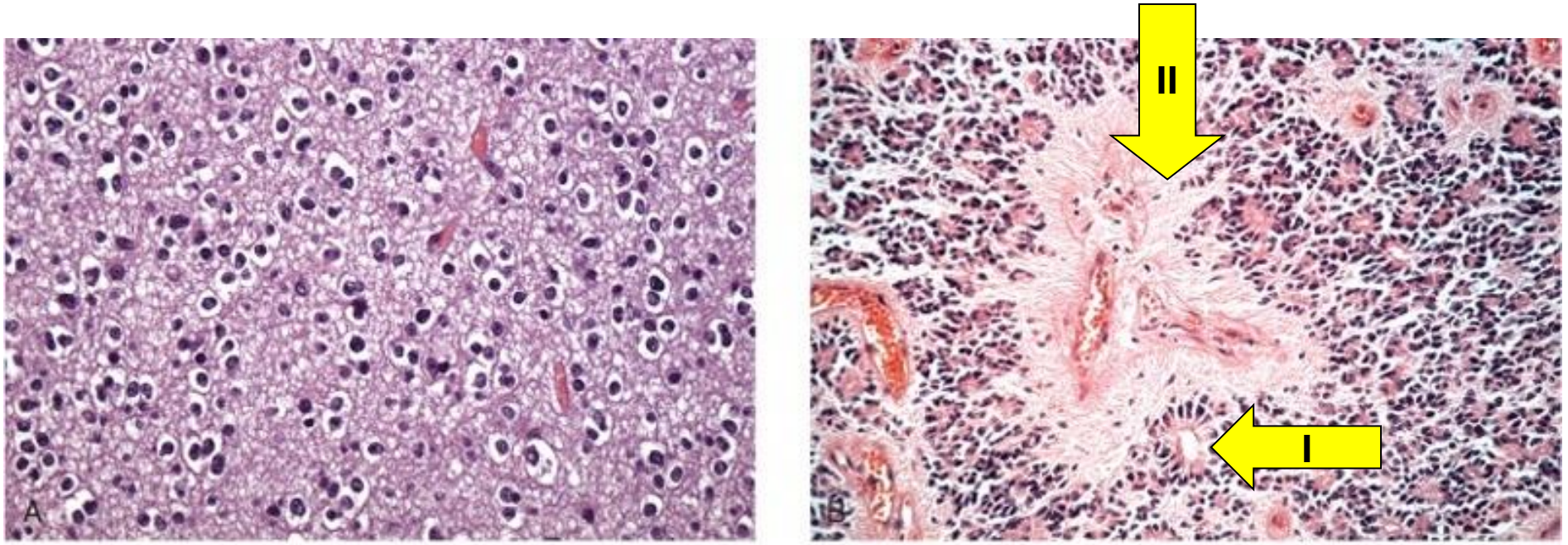
• **Prognosis** is better than that of astrocytomas.
Combine surgery, chemotherapy, & radiotherapy yields an average survival of 5 to 10 years.
☹ Anaplastic oligodendroglioma have worse prognosis.

◘ 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).

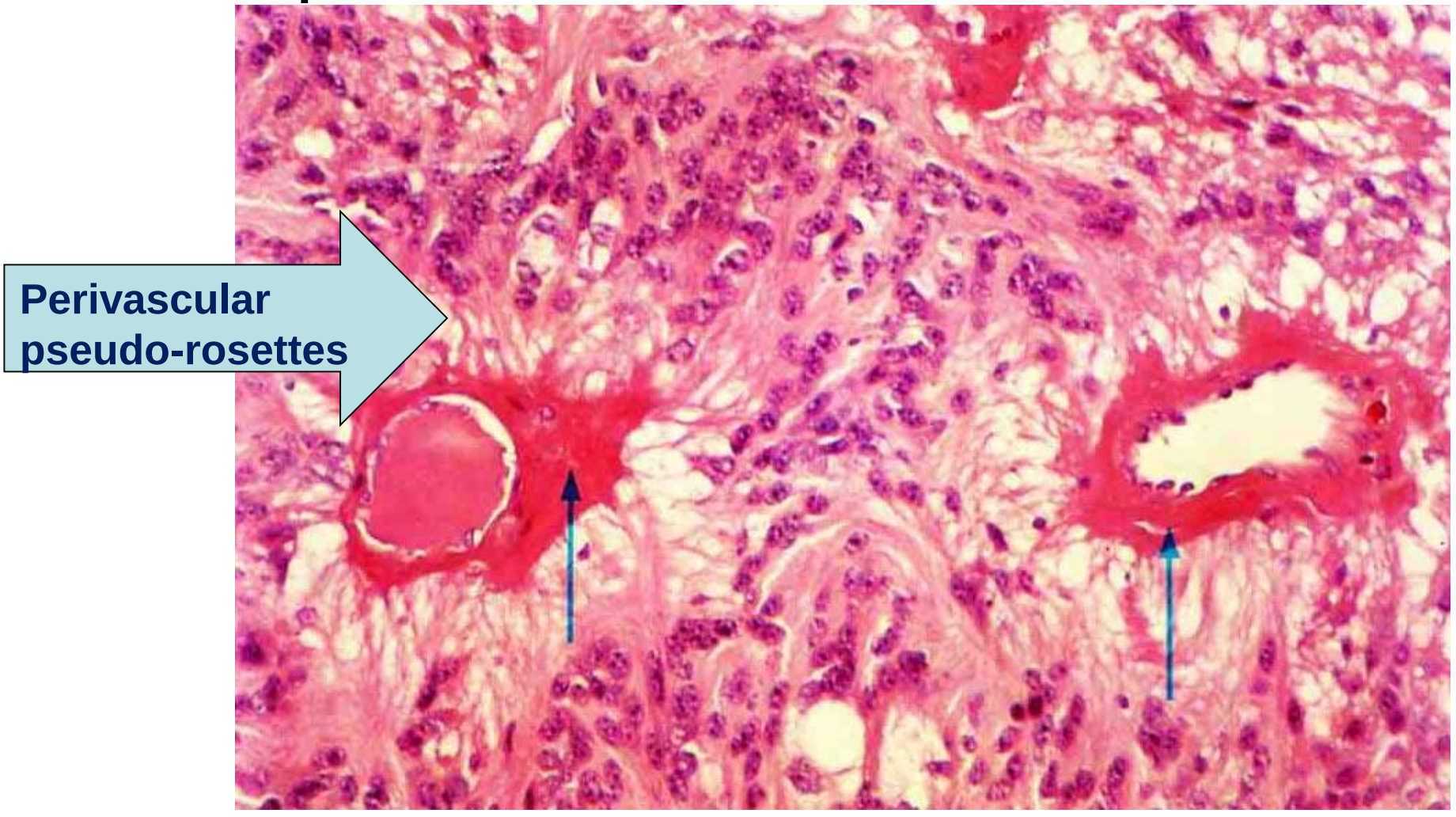
• **Anaplastic ependymomas** show ↑ cell density & mitotic rates, necrosis, & less evident ependymal differentiation.

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).

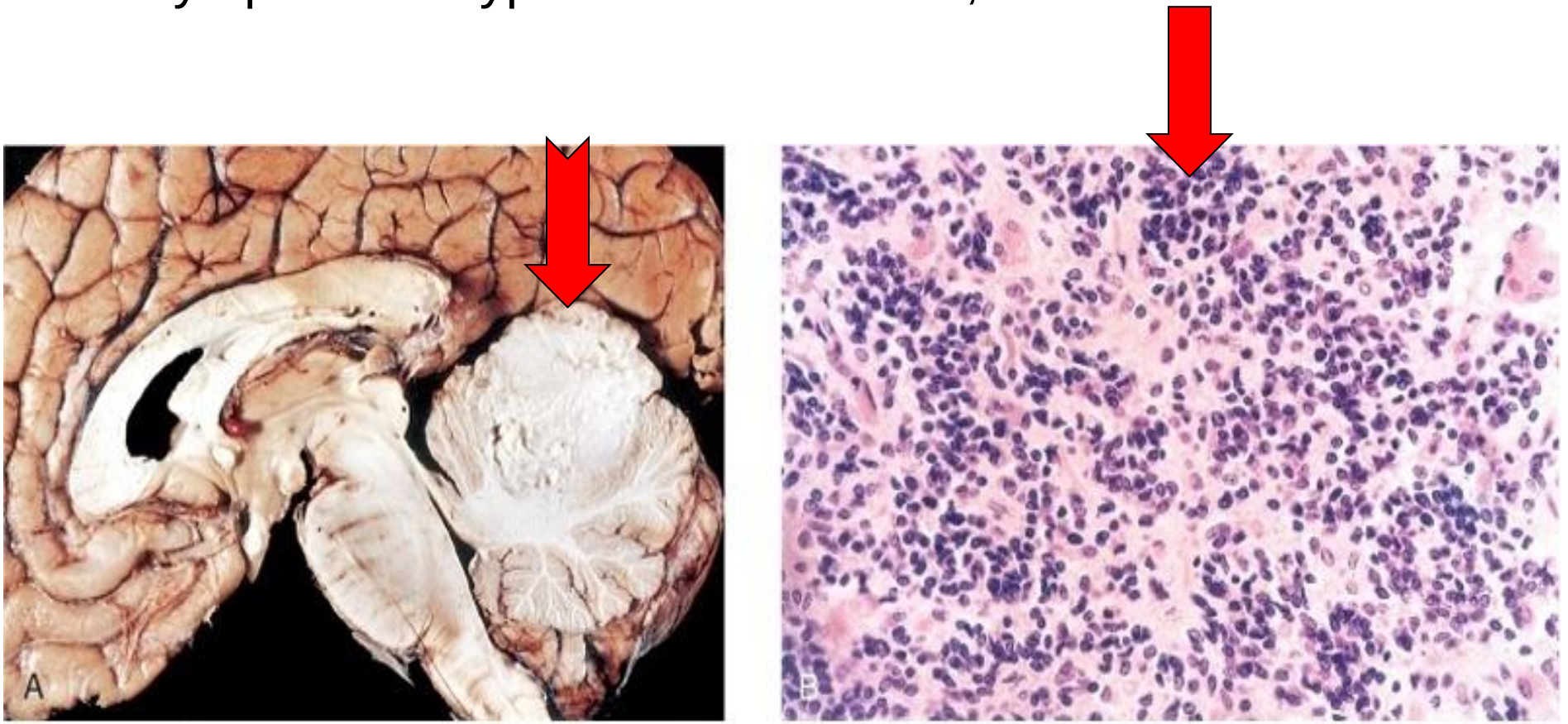
►**Grossly**, in children, medulloblastomas are located in the **midline of the cerebellum**; lateral **T** occur more often in adults. **T** is well **circumscribed, gray, & friable**, & may be seen extending to the surface of the cerebellar folia (F 9-72) & **involving the leptomeninges** (F23-24A).

◘ **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.

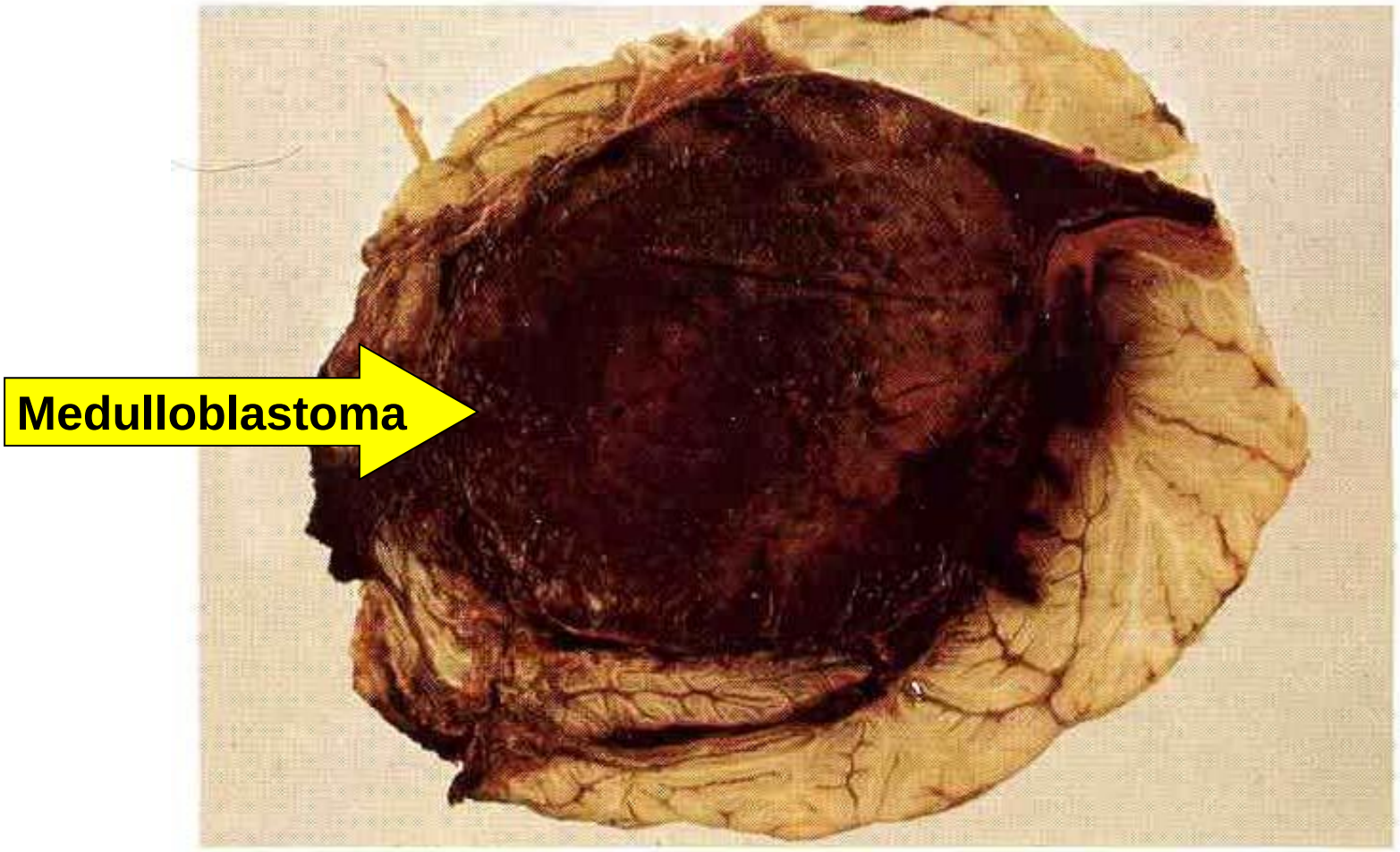
F23-24: **Medulloblastoma: Brain**

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

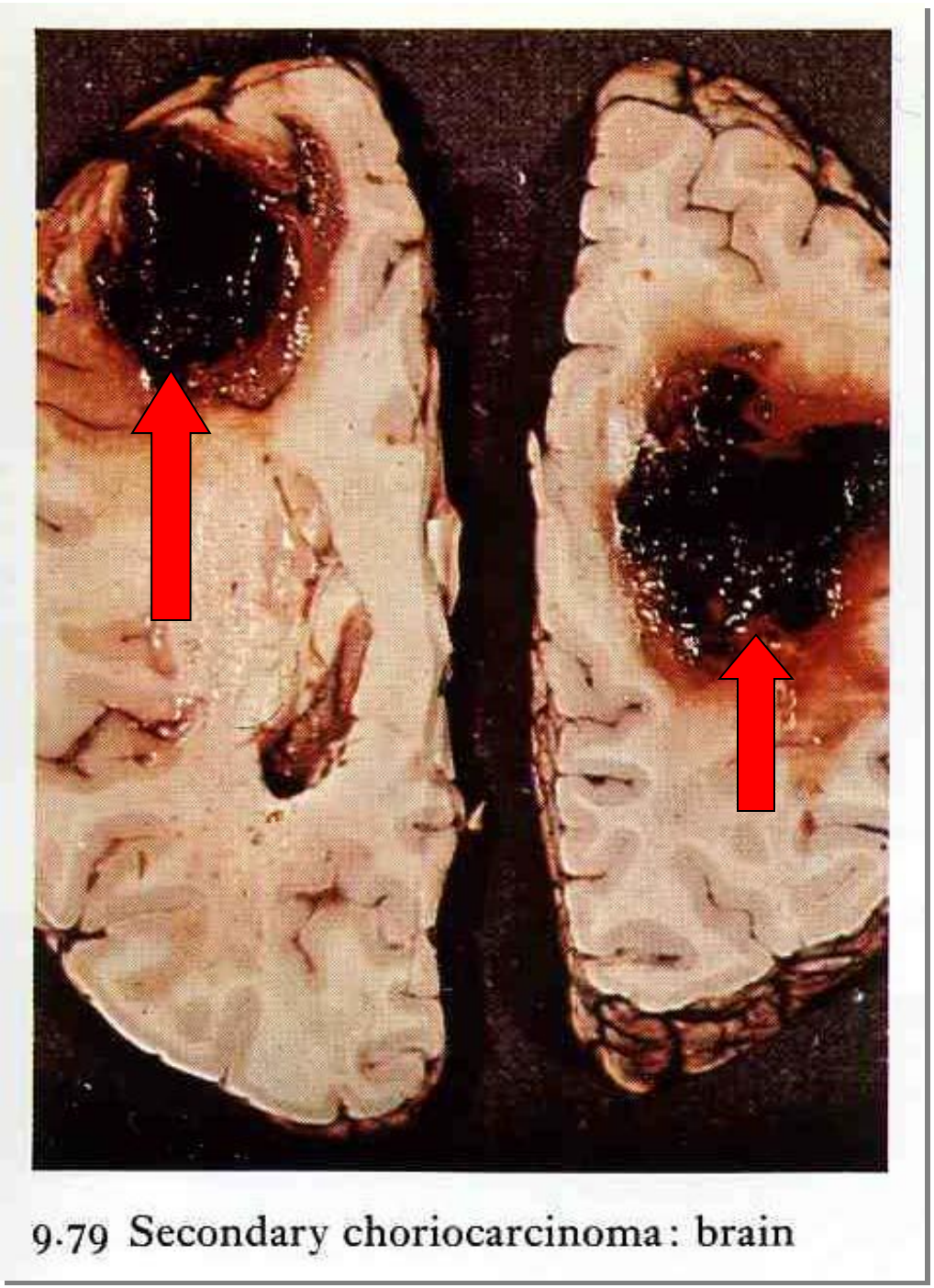
- accounts for 2% of extranodal lymphomas & 1% of intracranial tumors.
- The **most common CNS neoplasm in immunosuppressed** individuals (including transplant recipients & AIDS patients); in which lymphomas are nearly **all driven by Epstein-Barr virus.**
- In nonimmunosuppressed populations the incidence ↑ 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.**

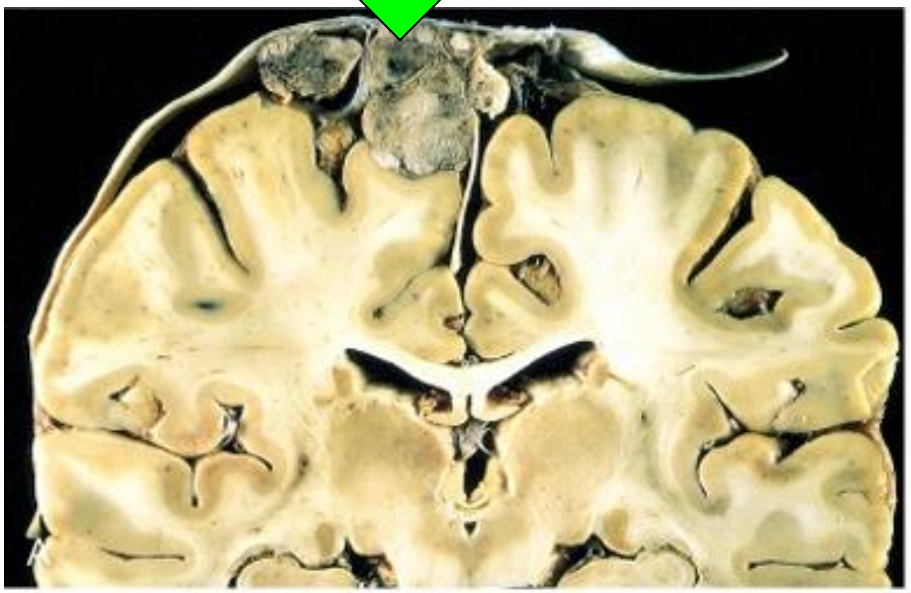
★They usually present with• **vague** nonlocalizing symptoms, or with • **focal findings** due to compression of underlying brain.

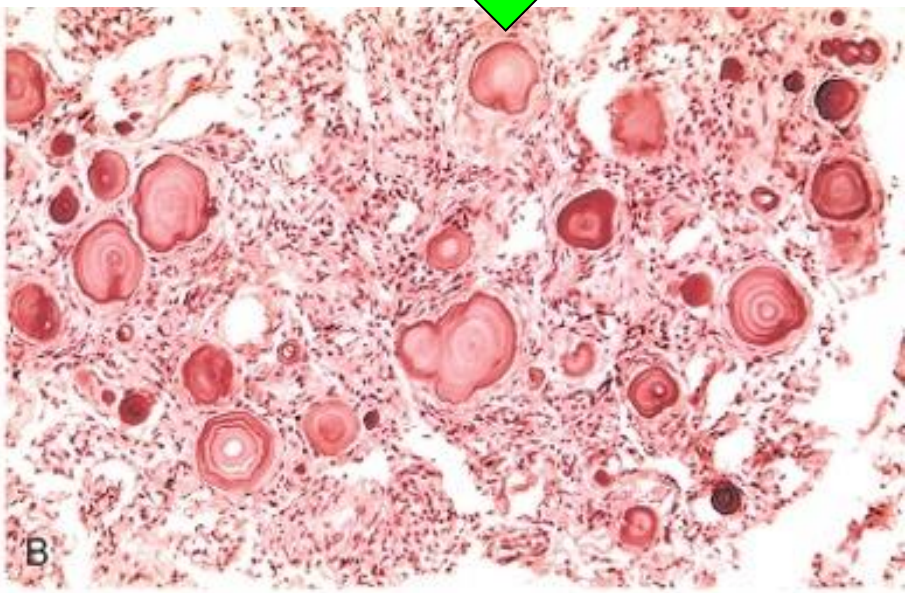
• When **multiple meningiomas** are present, especially in association with 8th nerve schwannomas or glial **T**, a possible diagnosis of **neurofibromatosis type 2** should be considered.

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

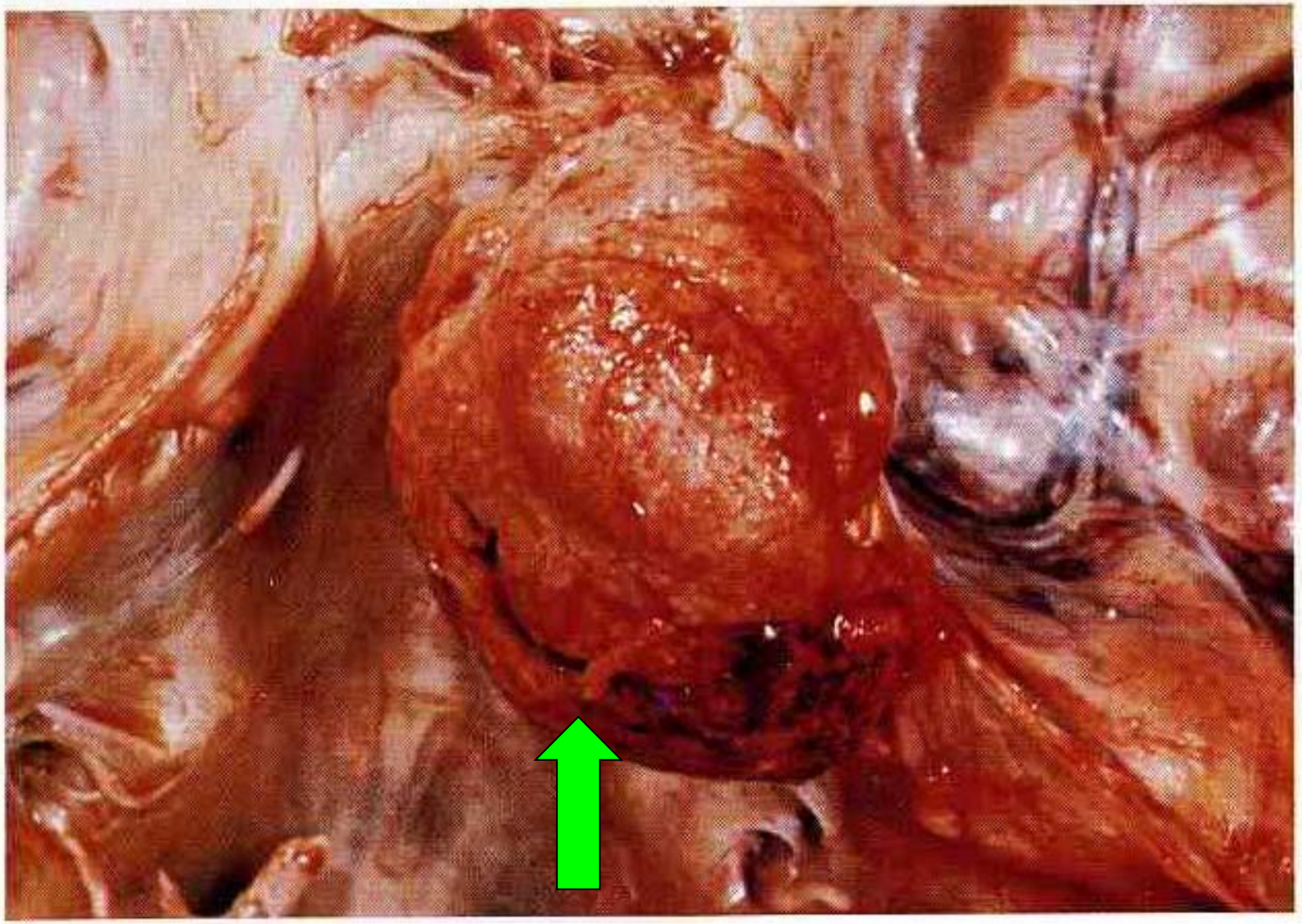
►**Grossly**, meningiomas grow as • **well-defined dural-based masses** that • **compress underlying brain** but are **easily separated from it** (F23-25A & F 9-51). Extension into the overlying bone may be present.

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).

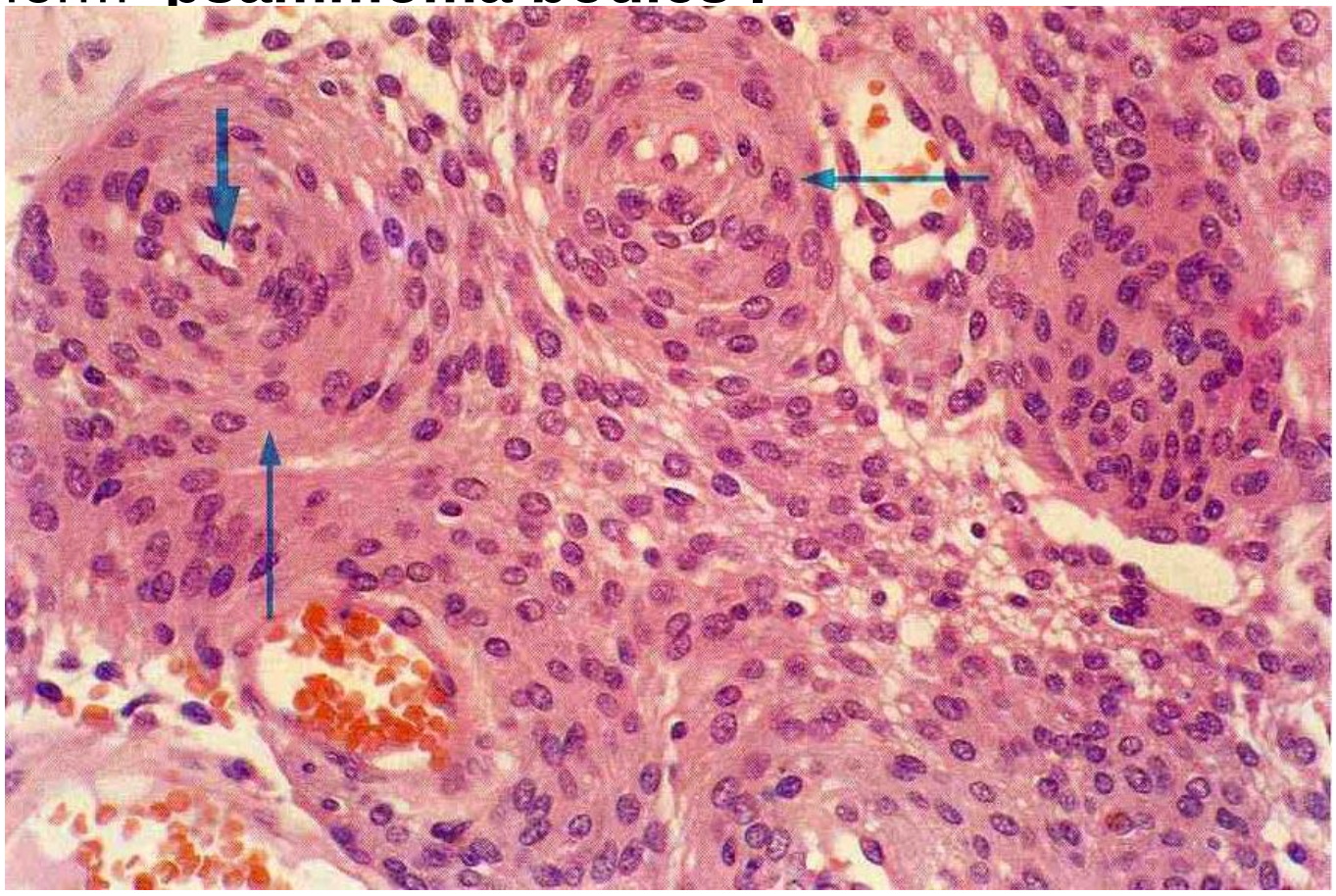
Atypical meningiomas

• **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.

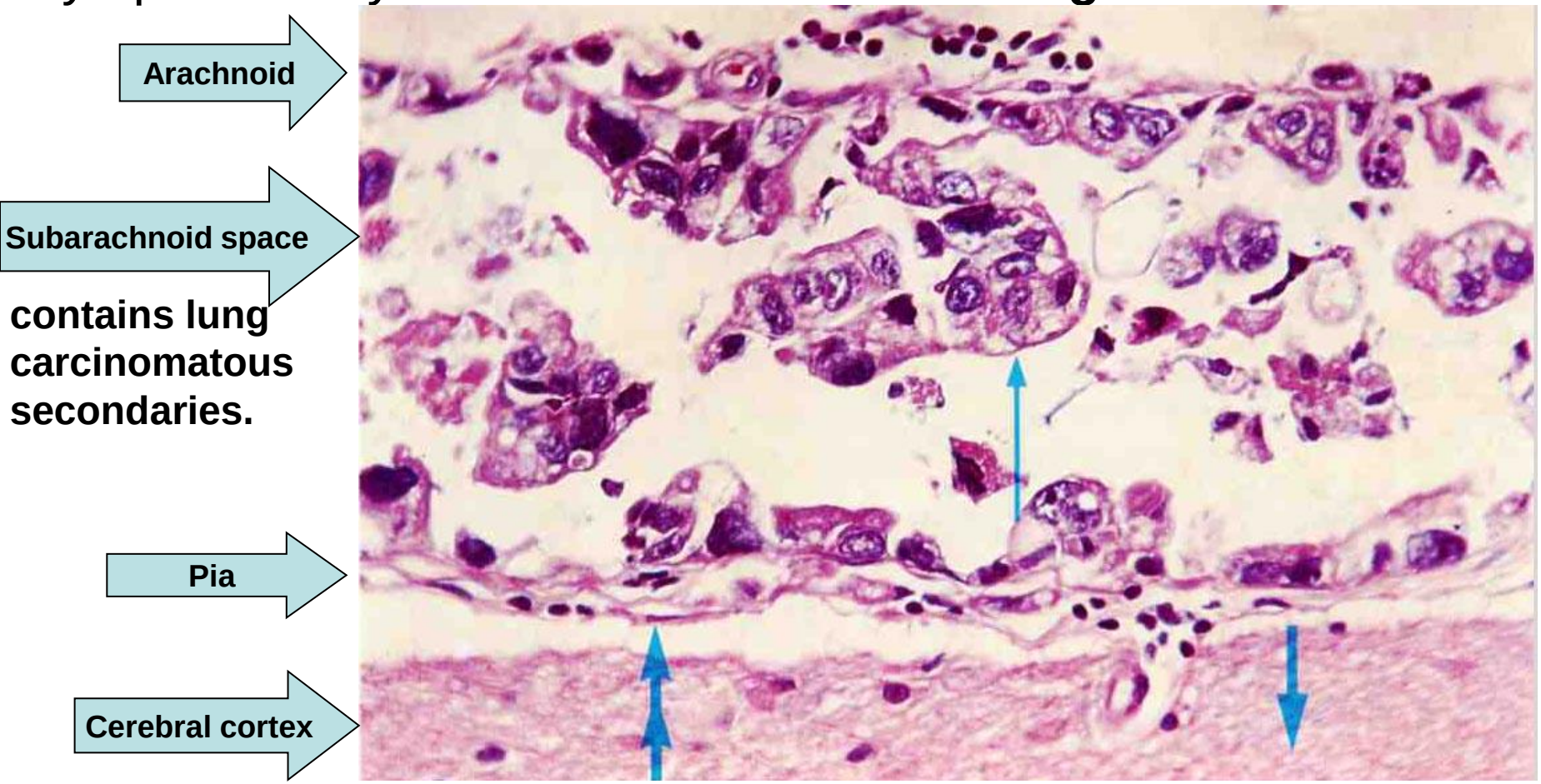
★***Paraneoplastic syndromes*** may involve the peripheral & CNS, sometimes, **even before** the clinical recognition of the malignant **T**. These syndromes are most **commonly** associated with **small-cell ca of the lung.**

★Characteristic paraneoplastic syndromes patterns include:

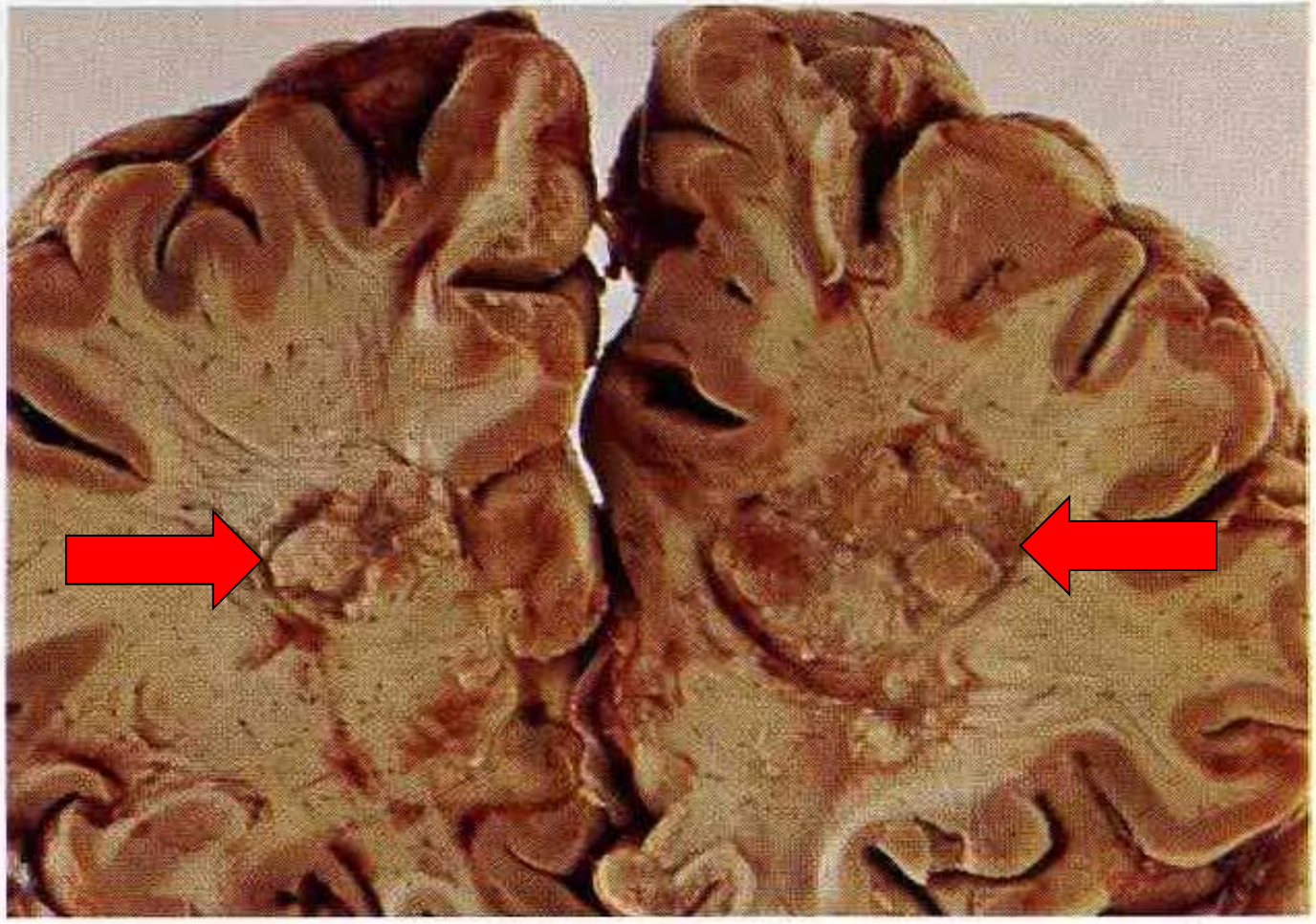
- ***Limbic encephalitis*** causing a subacute dementia,
- ***Subacute cerebellar degeneration*** resulting in ataxia, with destruction of Purkinje cells,
- **S*ubacute sensory neuropathy*** leading to altered pain sensation with loss of sensory neurons from dorsal root ganglia.

◘ 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.**

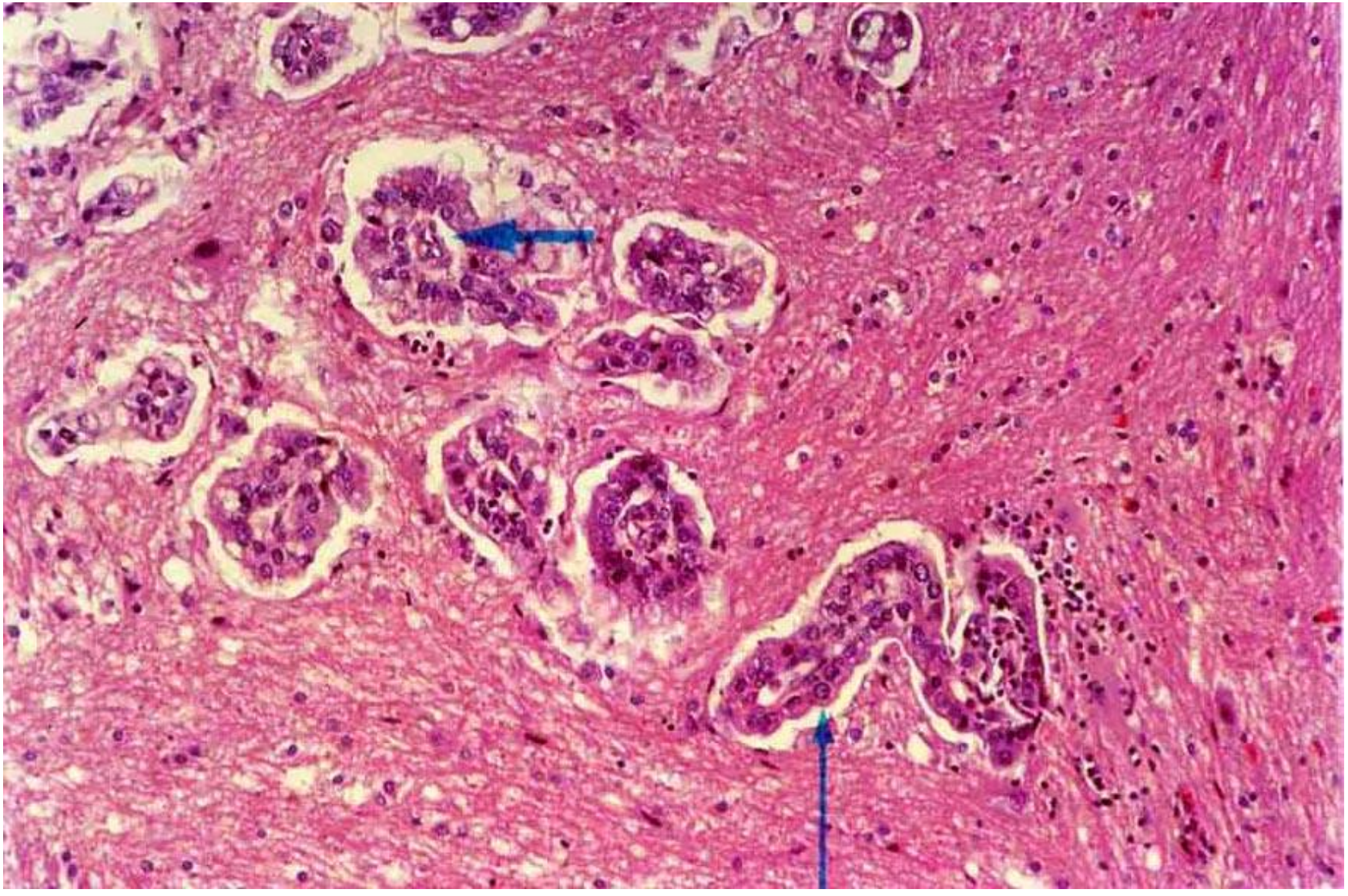


F 9-76: **Secondary carcinoma: brain.**
The patient had carcinoma of the **breast**. Frontal region section shows two large necrotic secondary deposits in the central white matter of both cerebral hemispheres.

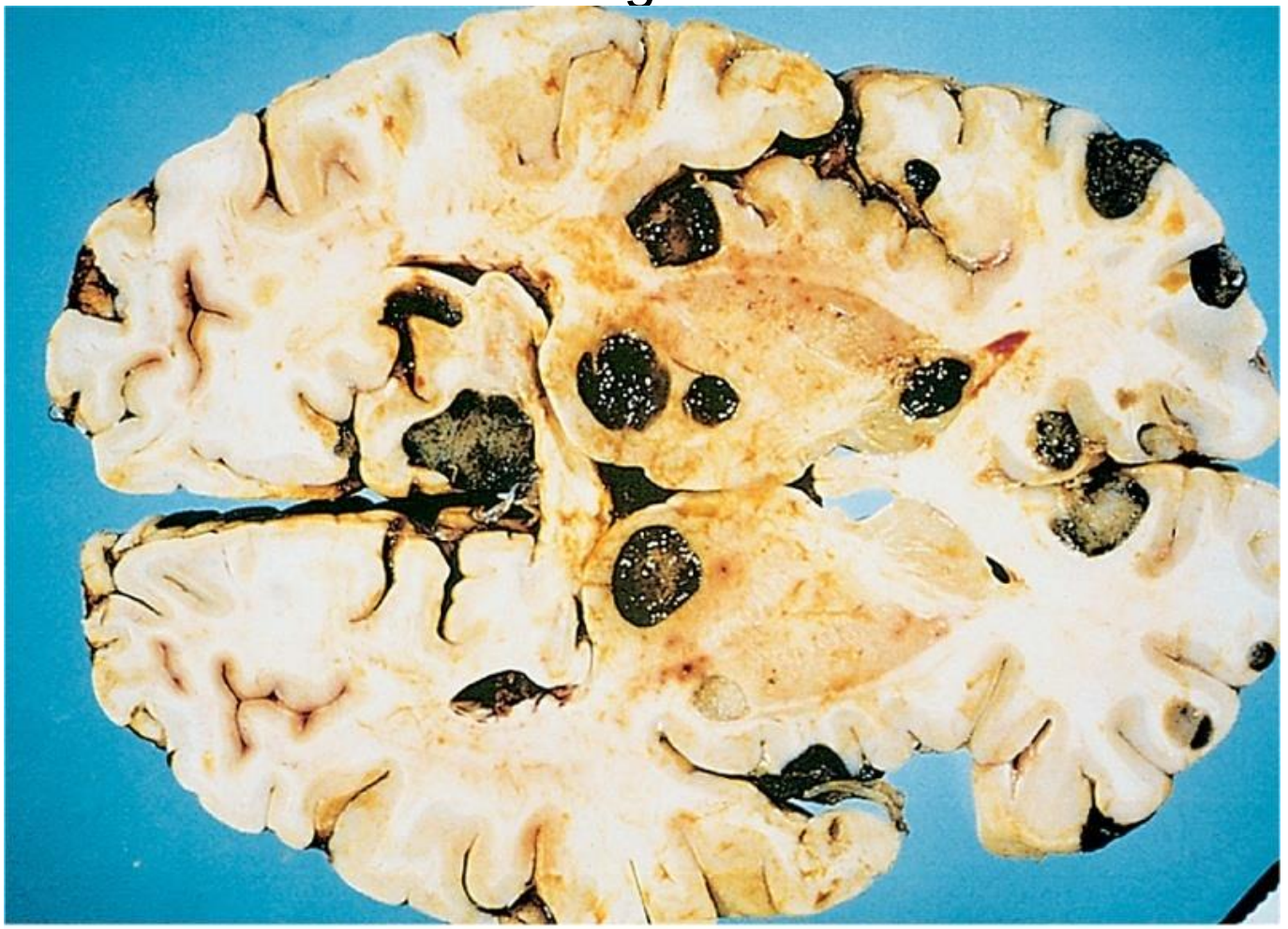


9.76 Secondary carcinoma: brain

◘ 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.

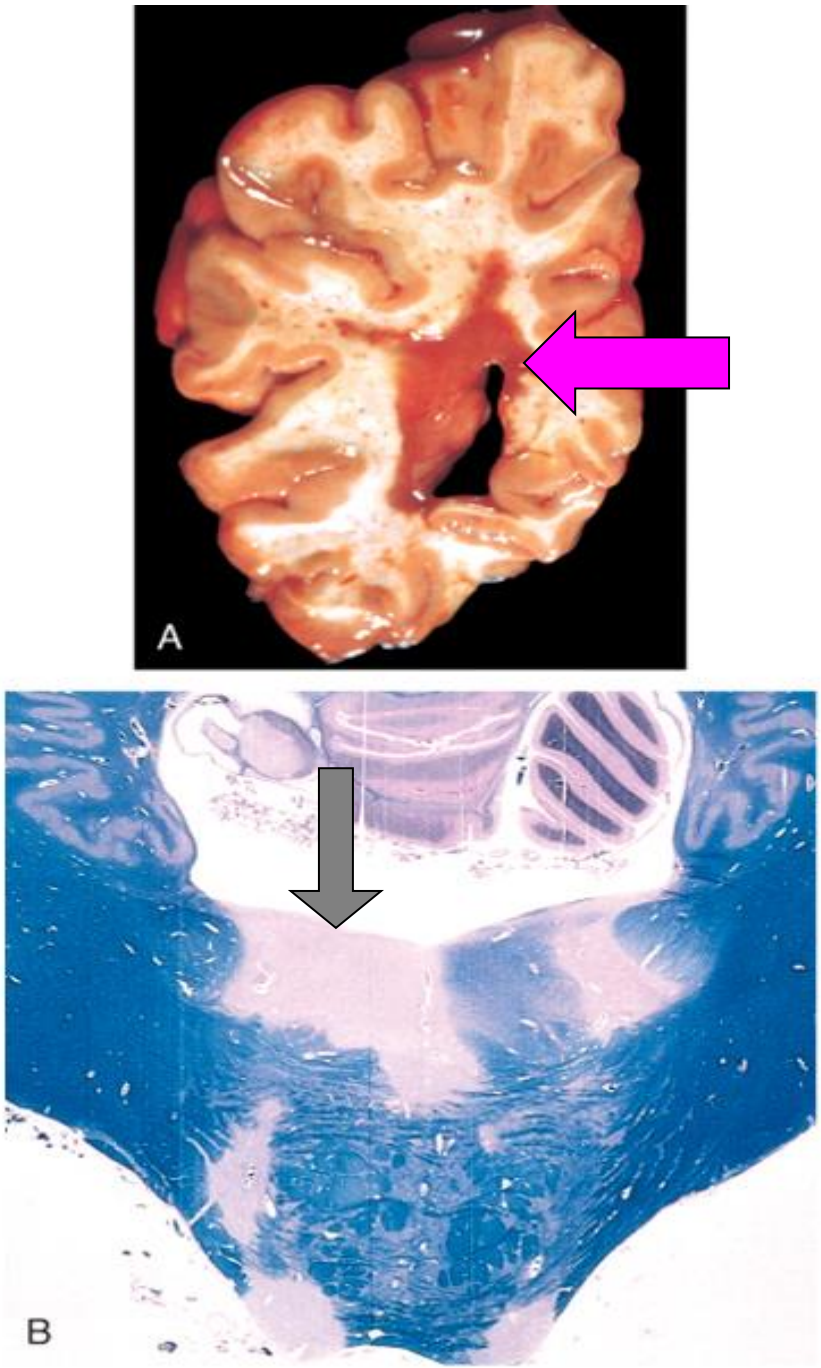
★ **Plaques** commonly occur **beside the ventricles, & are** frequent in the optic nerves & chiasm, brain stem, ascending & descending fiber tracts, cerebellum, & spinal cord (F23-27A & 9-26 & 27),
◘ H, the lesions have **sharply** defined borders {F23-27B & ◘ 4.21&23},

★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

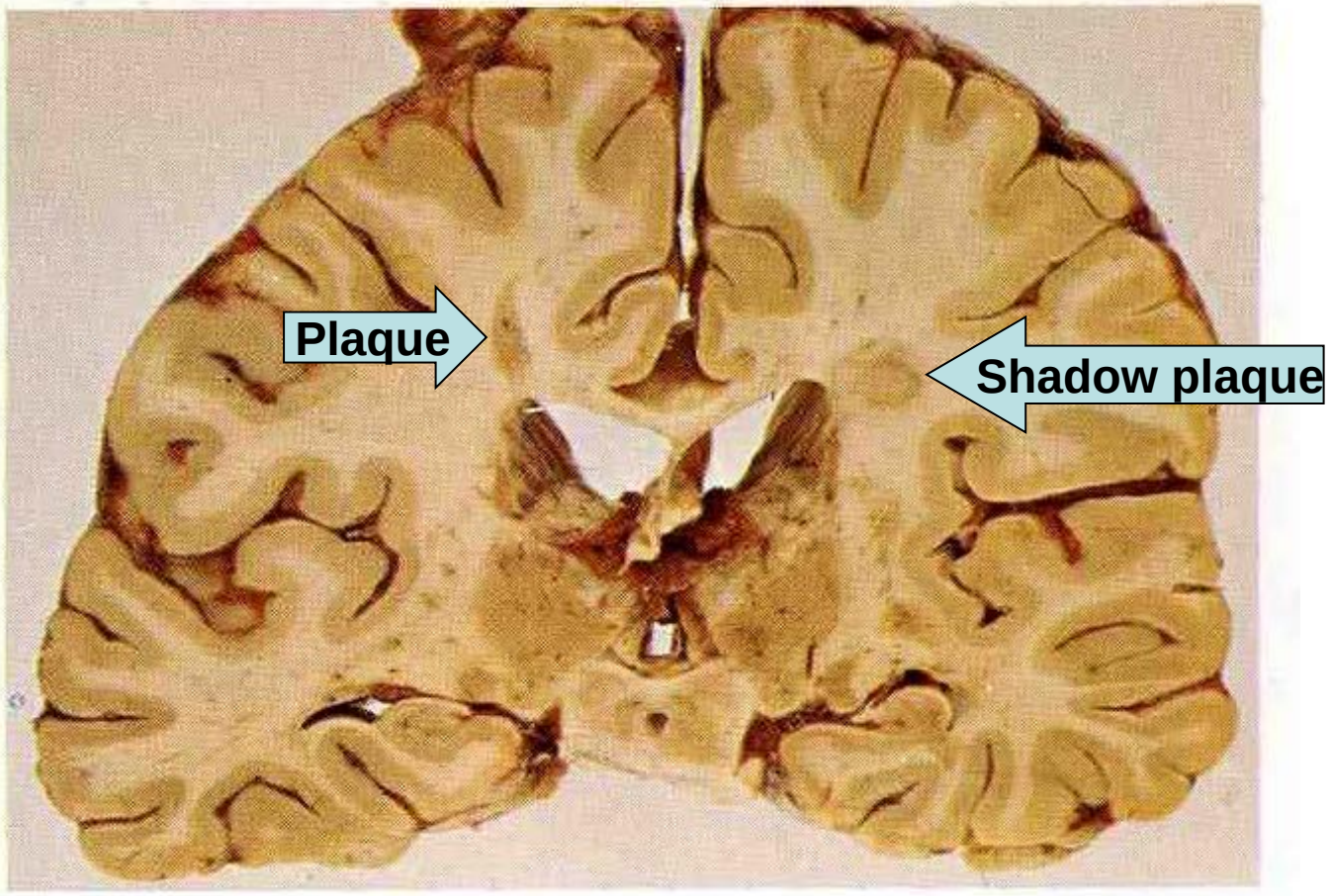
(4) Small active plaques are often **centered** on small veins, &
(5) **Axons are relatively preserved**, although they may be reduced in number.



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.

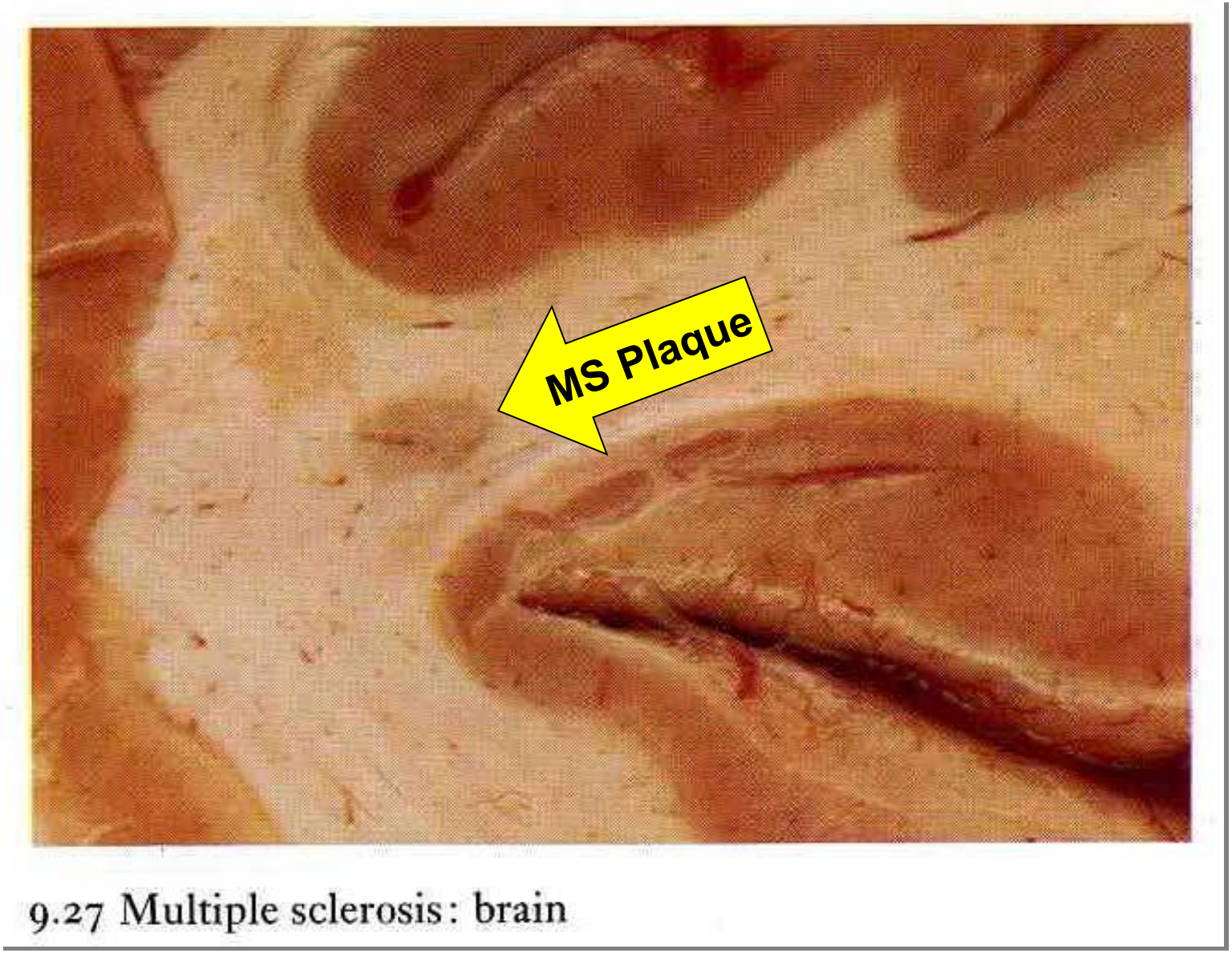
B, Unstained region of demyelination (**MS plaque**) around the fourth ventricle. (Luxol fast blue-PAS stain for myelin.)

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’.**



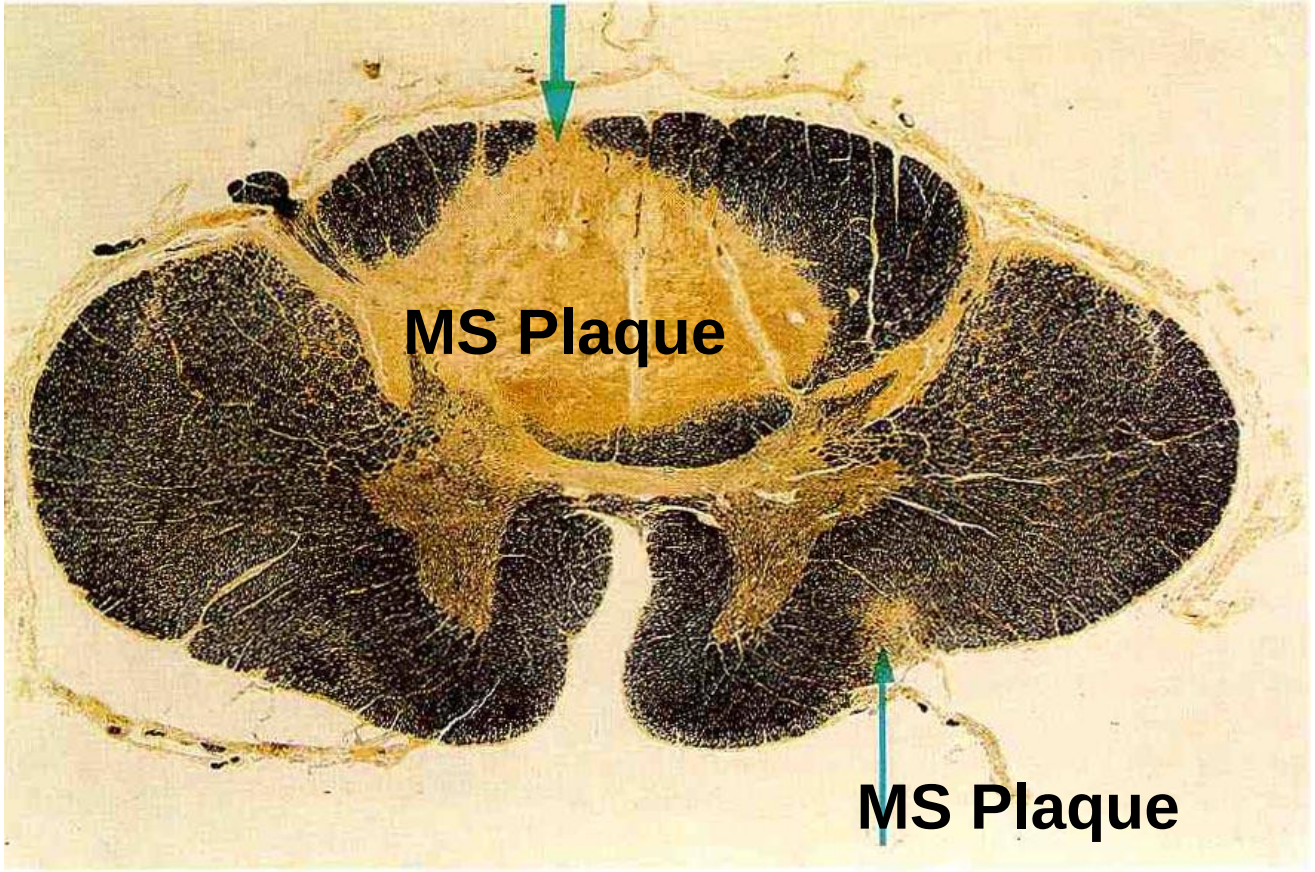
9.26 Multiple sclerosis: brain

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.

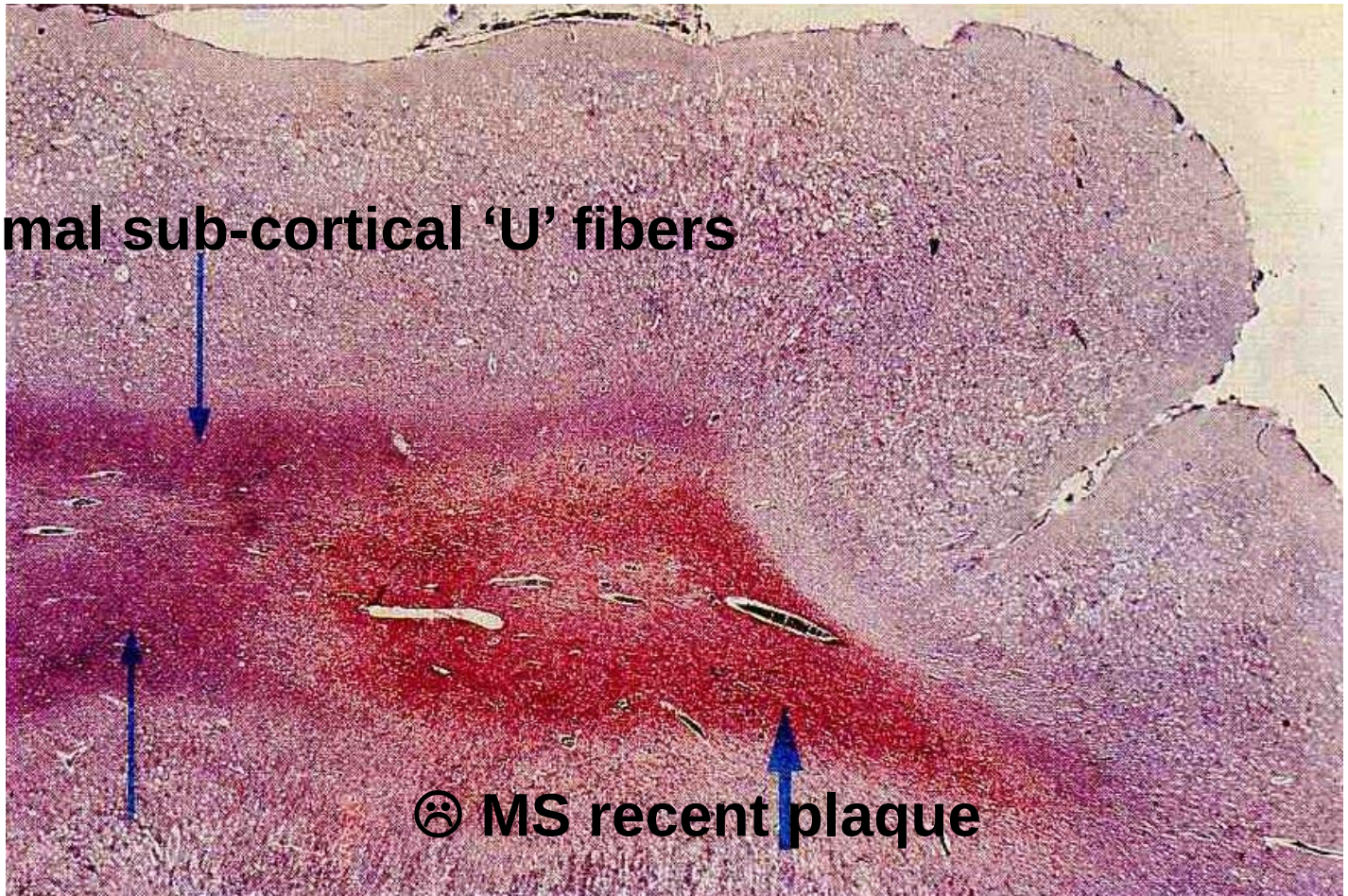


9.27 Multiple sclerosis: brain

◘ 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.

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;

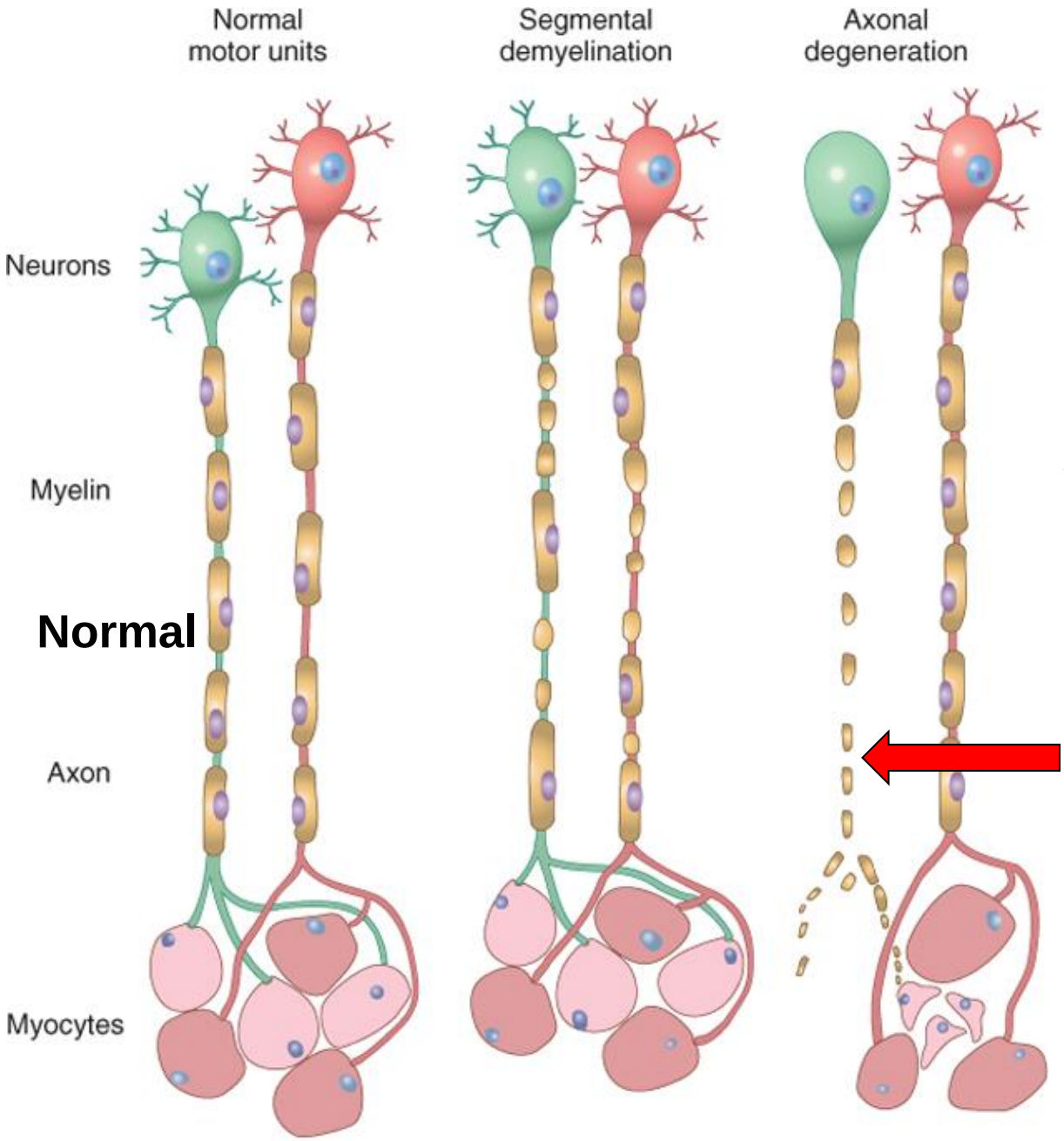
☺ **there is no primary abnormality of the axon.**

★ 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.

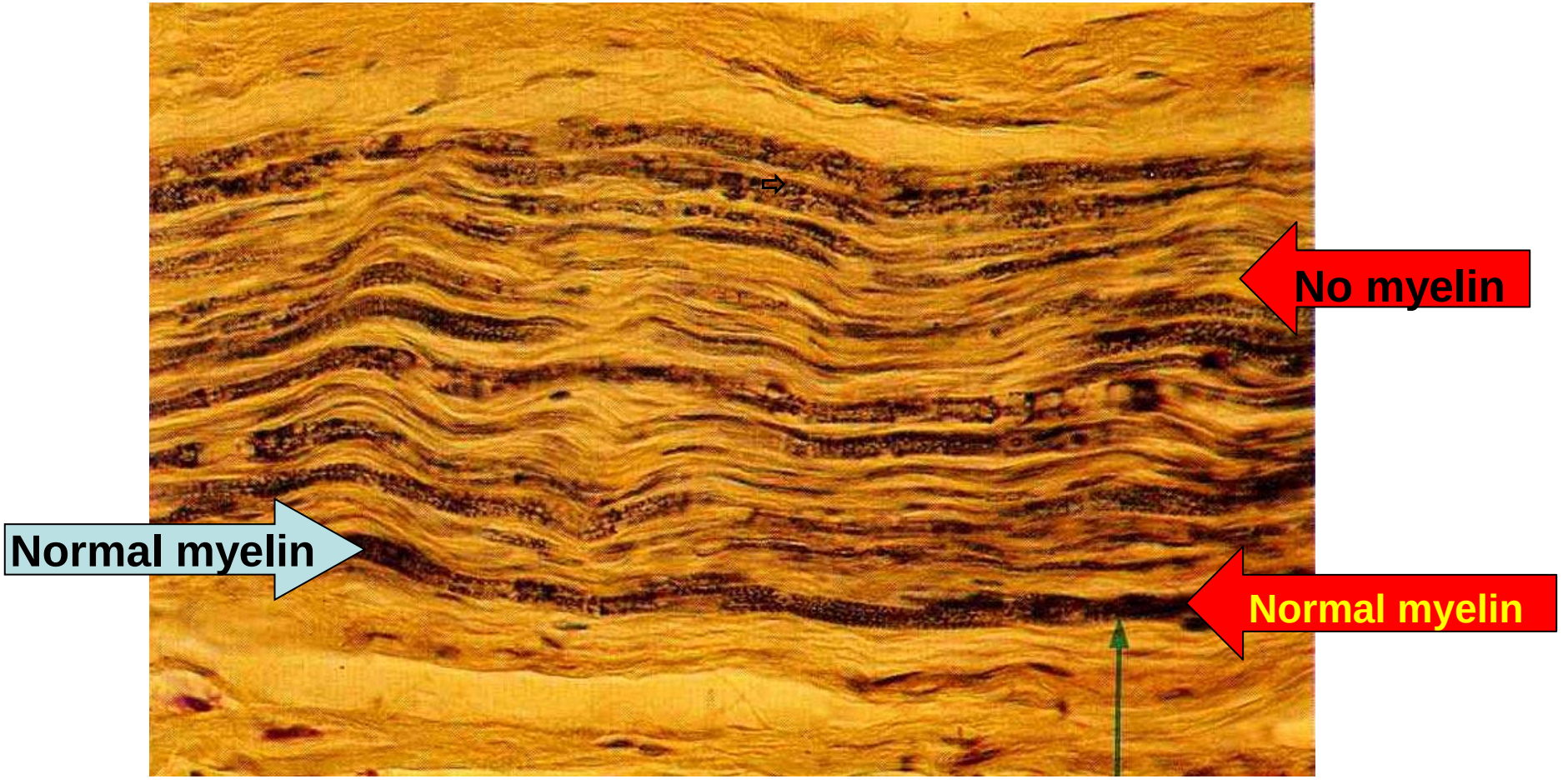


F23-32: ★**Two adjacent Normal motor units**.

★ **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

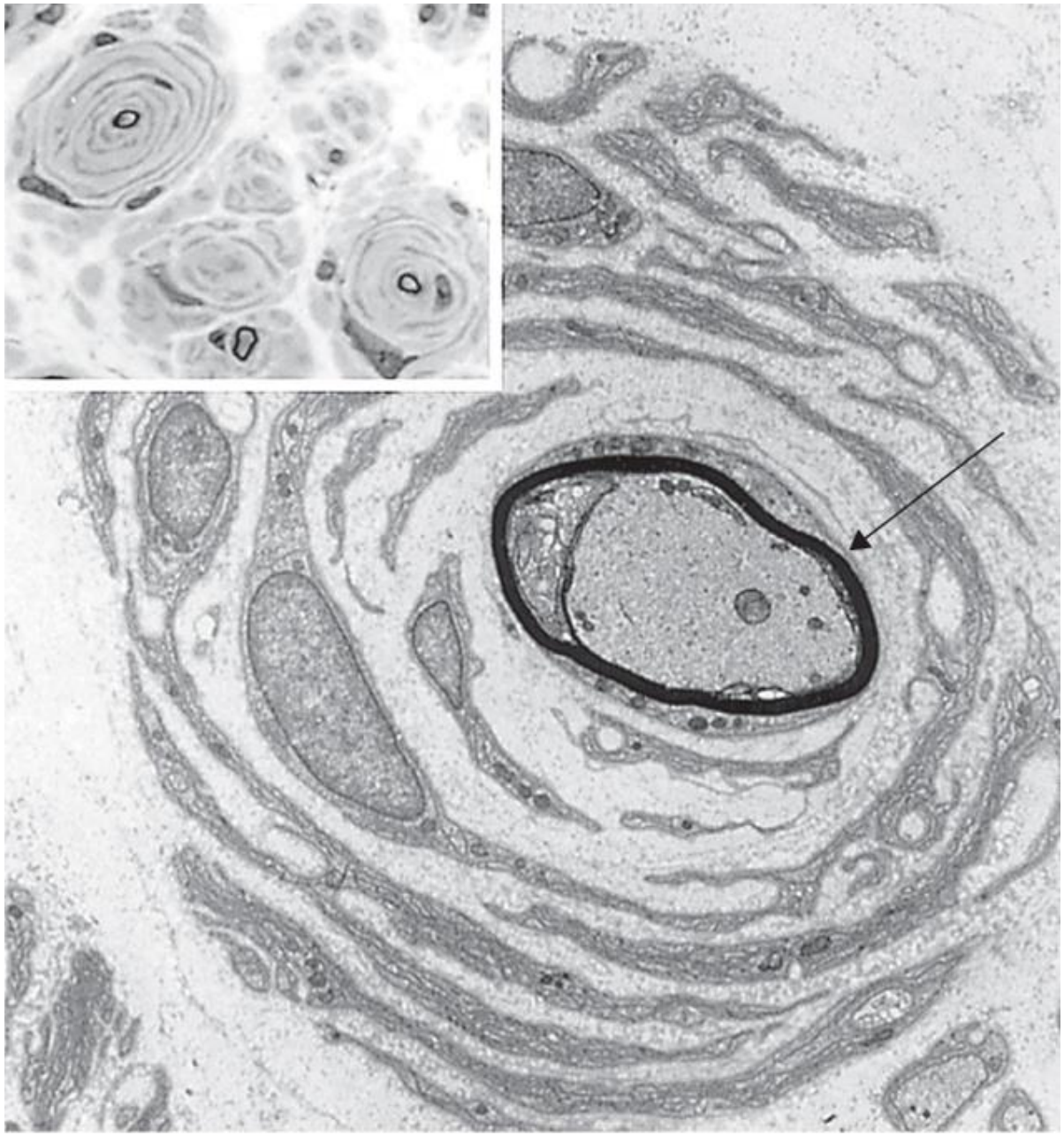
Diabetes, *alcoholism* (■ 4.28), thiamine or phyridoxine deficiency, renal failure

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.**

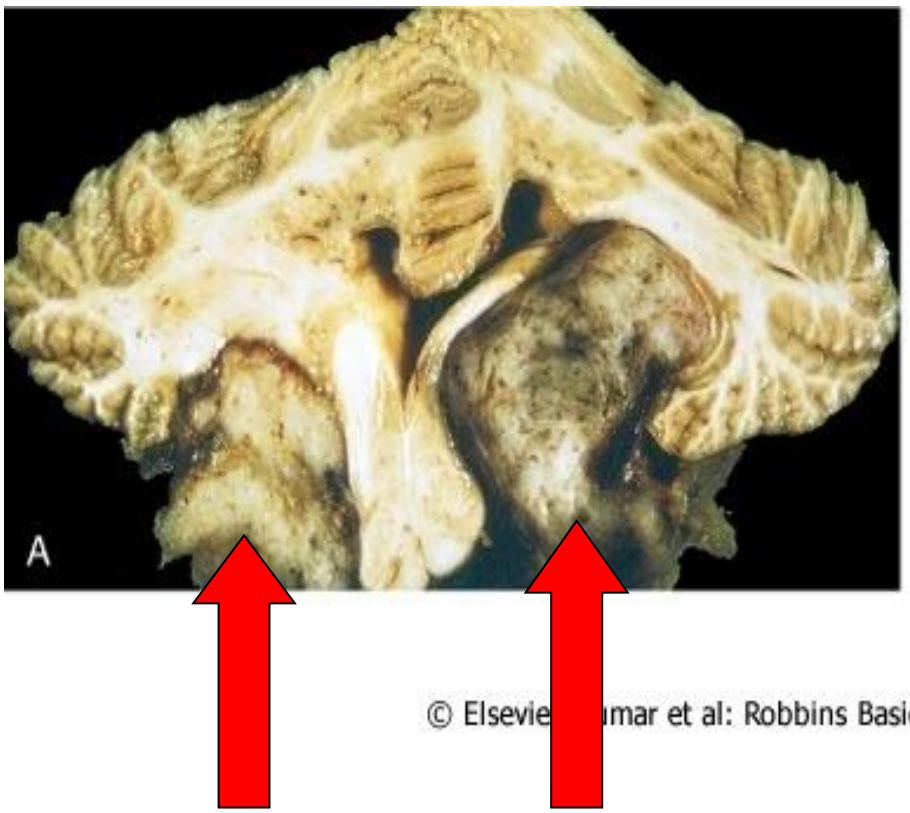
★Elsewhere **within the dura**, sensory nerves are preferentially involved, eg branches of the **trigeminal nerve & dorsal roots**.

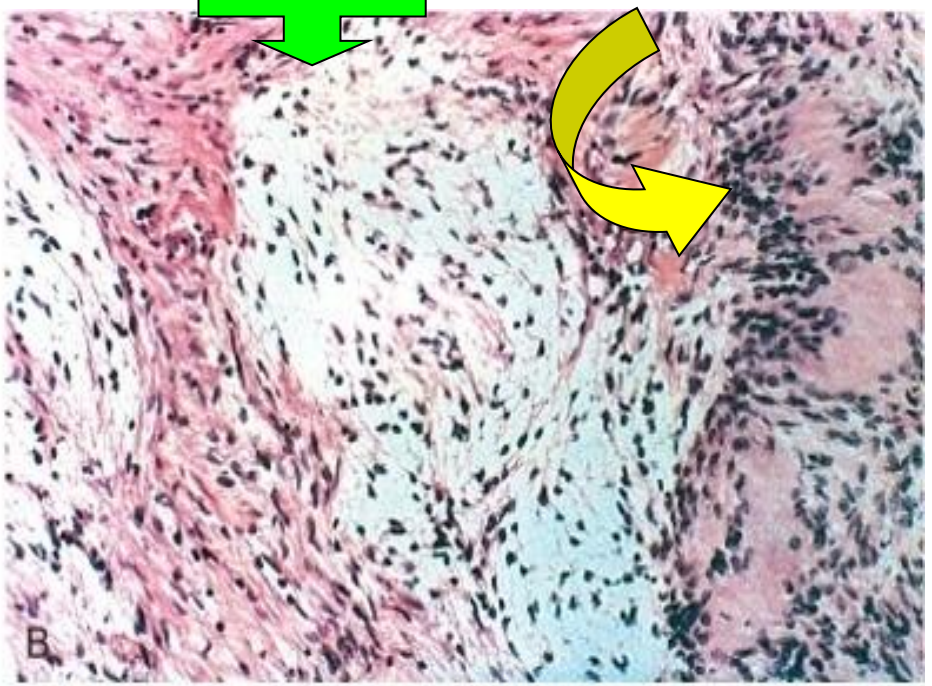
★ When **extradural**, schwannomas are most commonly found in association with **large nerve trunks**, where motor & sensory modalities are intermixed. Sporadic schwannomas are associated with mutations in the *NF2* gene on chromosome 22.

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.





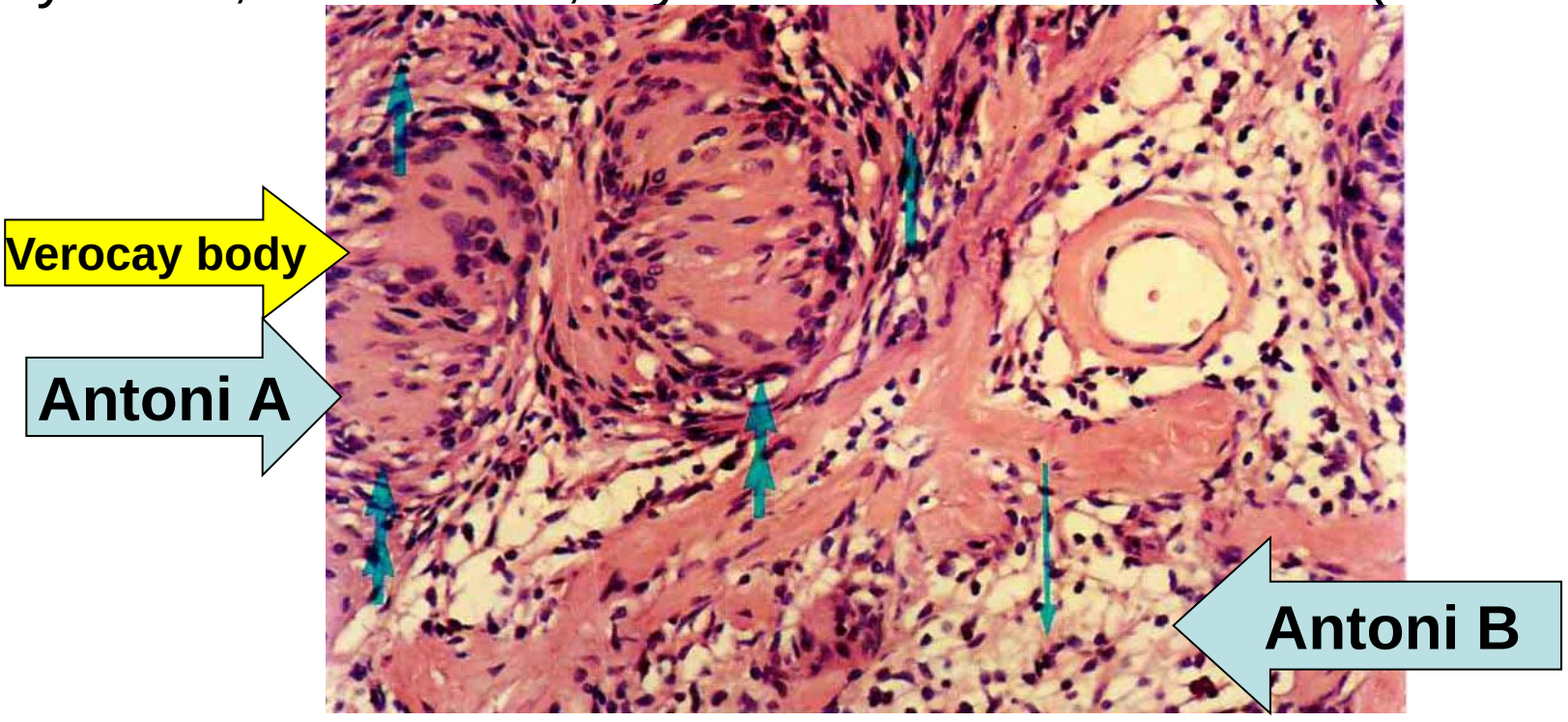
►**GROSSLY,** Schwannomas are encapsulated, well-circumscribed T that are **attached to the nerve but can be separated from it,** forming firm, gray masses but may also have areas of cystic & xanthomatous change.

◘ 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.

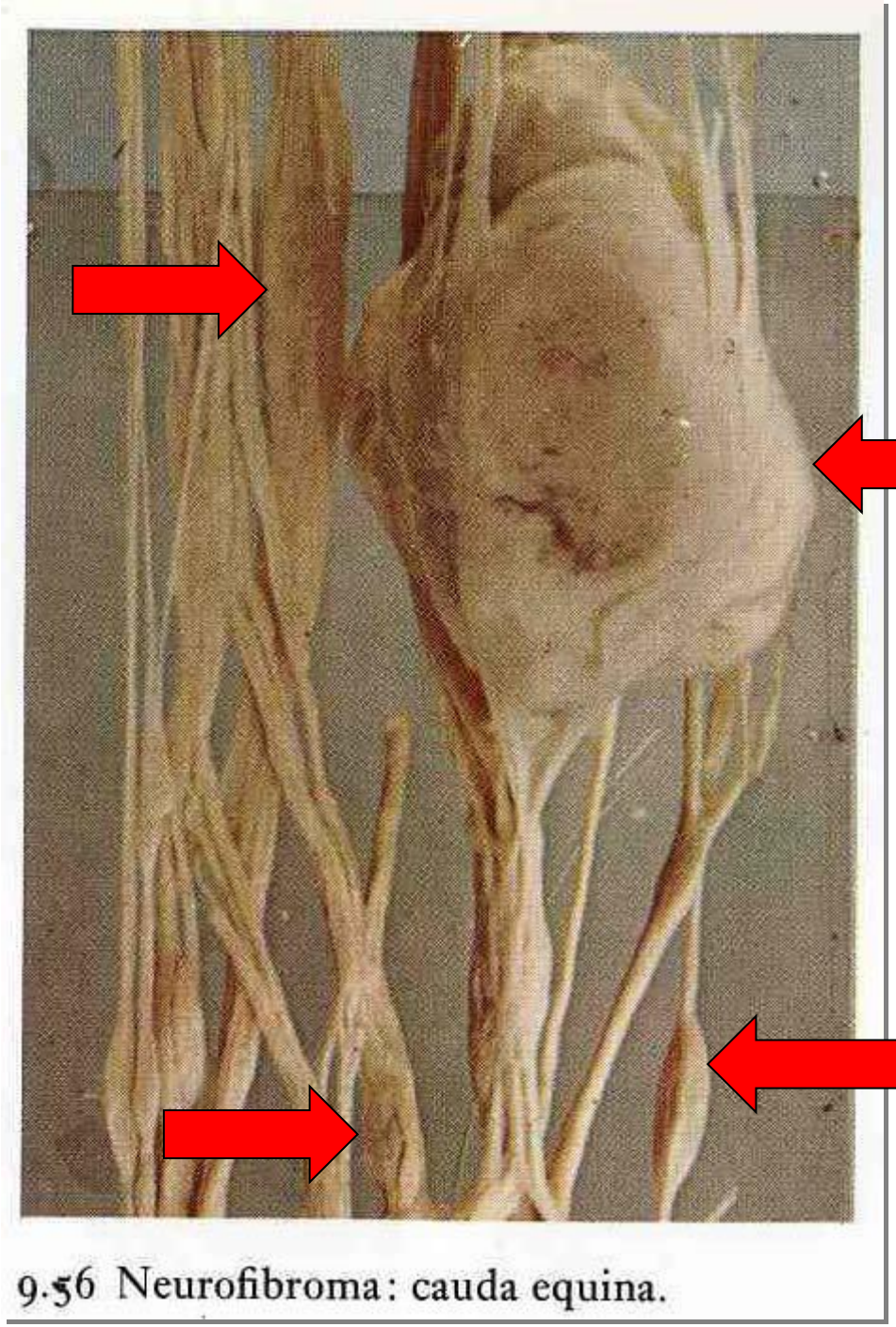
Plexiform neurofibroma

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.**

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.

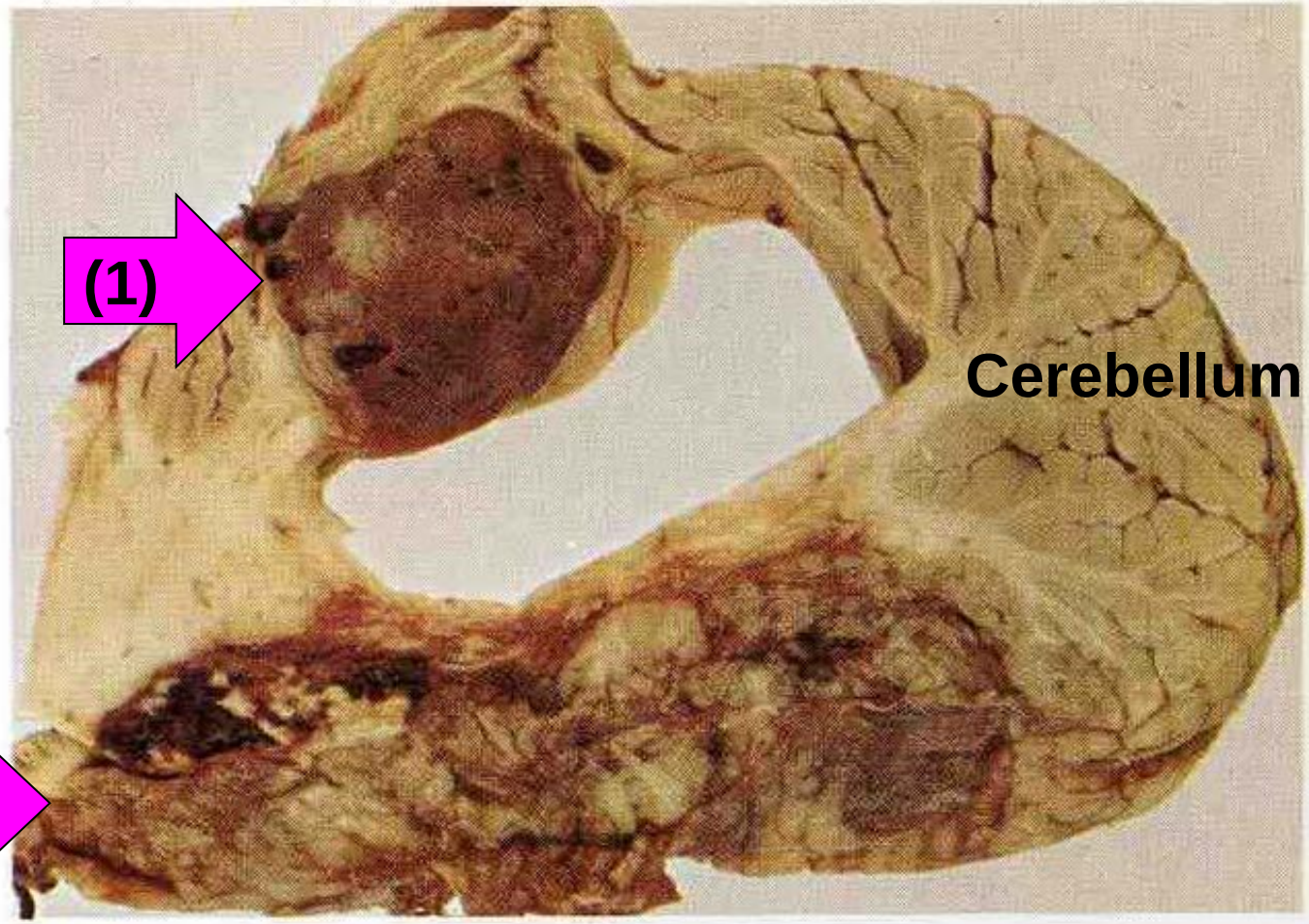
Von Hippel-Lindau Disease

★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.

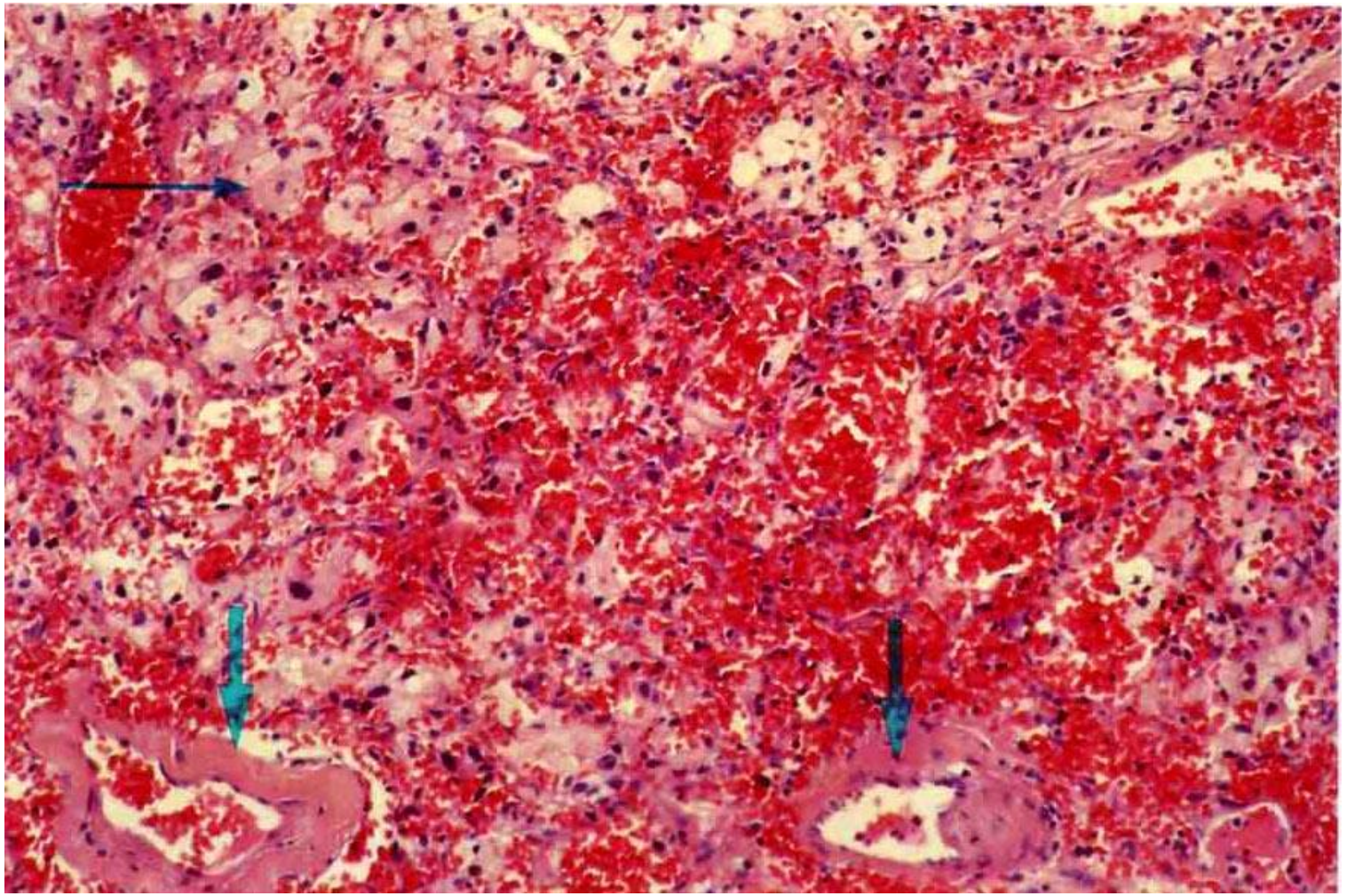
◘ 4.43, H, It consists of variable proportions of (1) thin-walled **capillaries** with (2) intervening **stromal** cells showing vacuolated, lightly PAS-positive, lipid-rich cytoplasm & dens basophilic nuclei.

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)

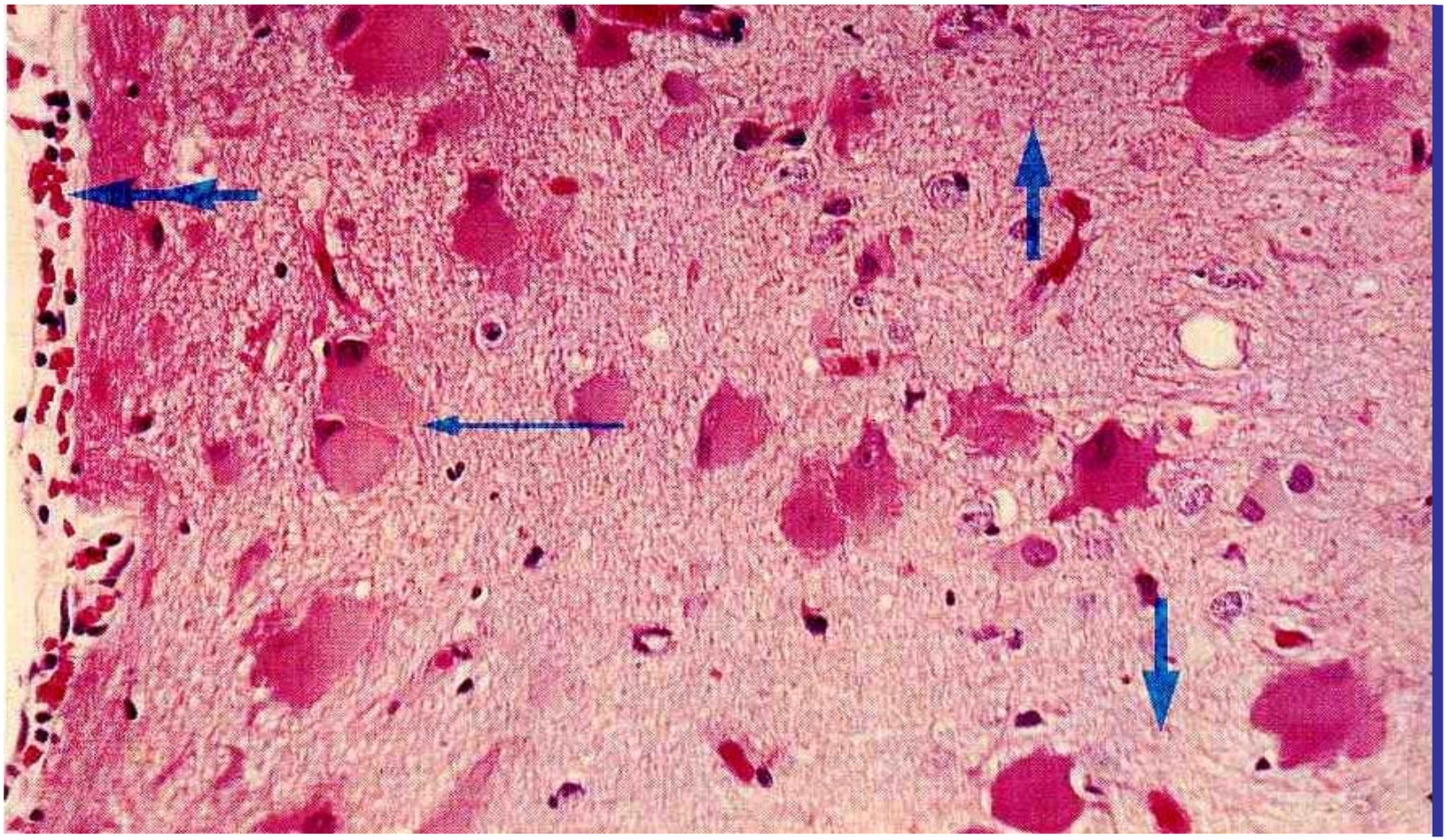
★ An **autosomal dominant syndrome,** characterized by the development of hamartomas & benign T involving the brain & other tissues; including:

• **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 II Only Lectures in 80 PPP**

@ April 2020 Lectures prepared by Associated Professor Dr. Mohammad Kamel Alwiswasi, MBChB, PhD, FRC Path

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 <u>Routes</u>** 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 <u>a lumbar puncture needle</u>.

(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.

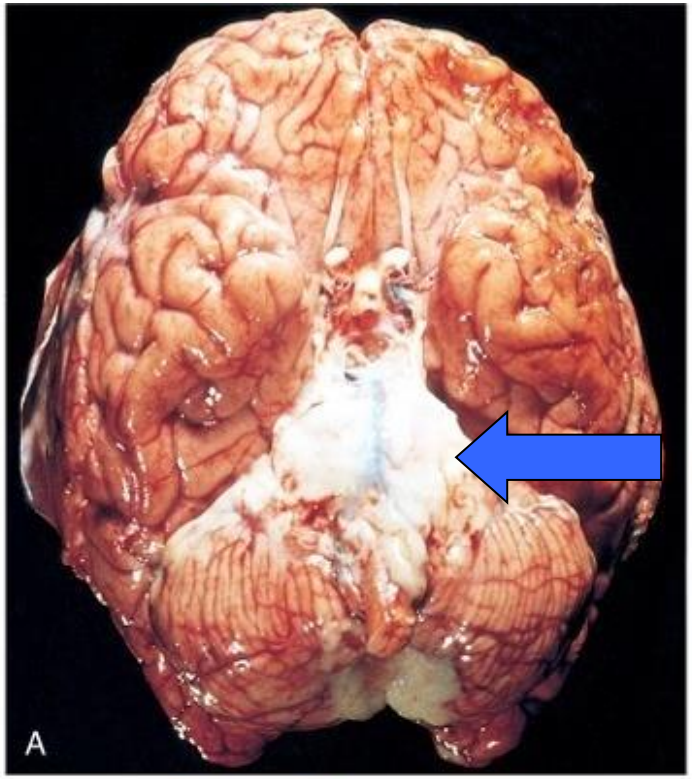
►All patients typically show (1) **systemic signs of infection** superimposed on clinical evidence of (2) **meningeal irritation** & neurologic impairment-including, headache, **neck stiffness**, photophobia, irritability, & clouding of consciousness.

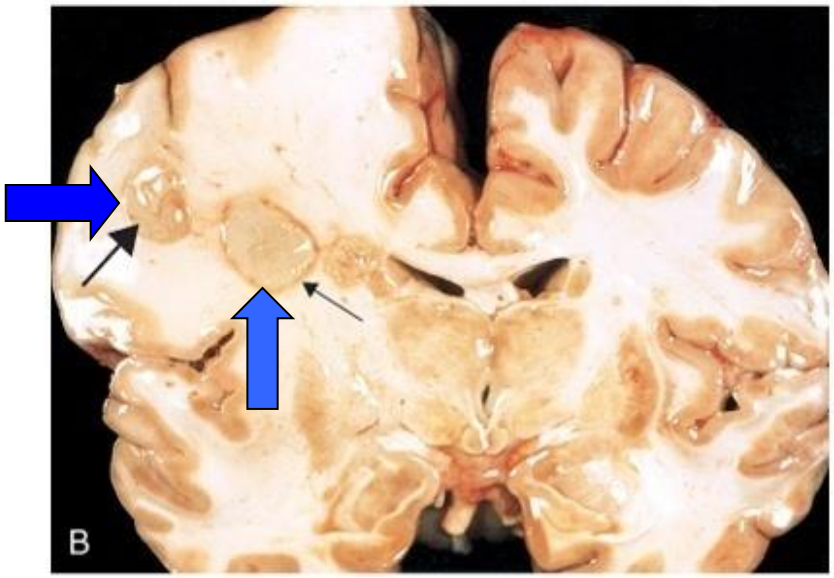
▼**CSF exam. is essential for diagnosis.** It reveals an: ↑ pressure +↑ neurophils +↑ protein & ↓ glucose. Bacteria may be seen on a smear or can be culture.

☠ 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**.





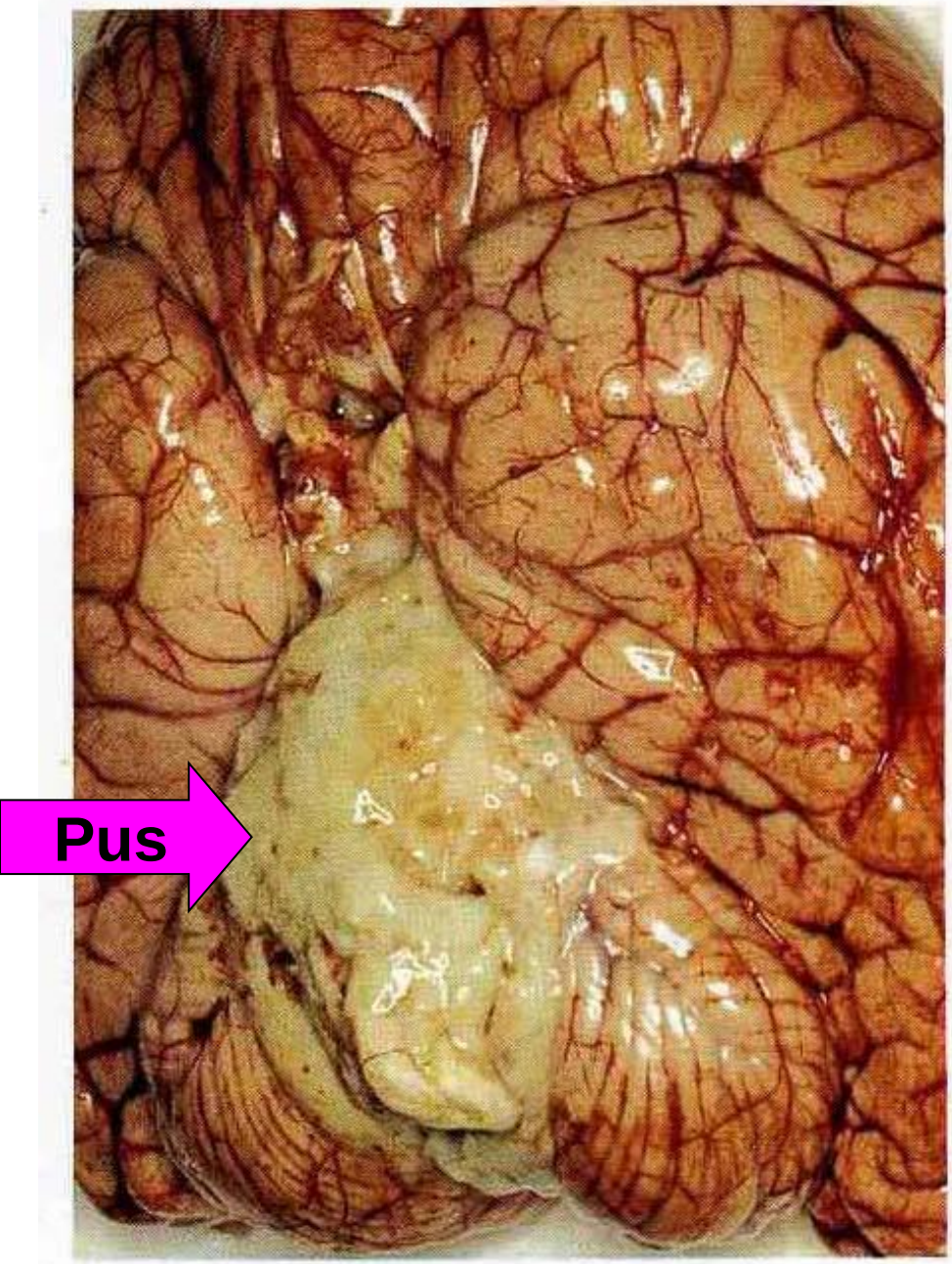
F23-16: **CNS Bacterial infections.**

A, Pyogenic meningitis.

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

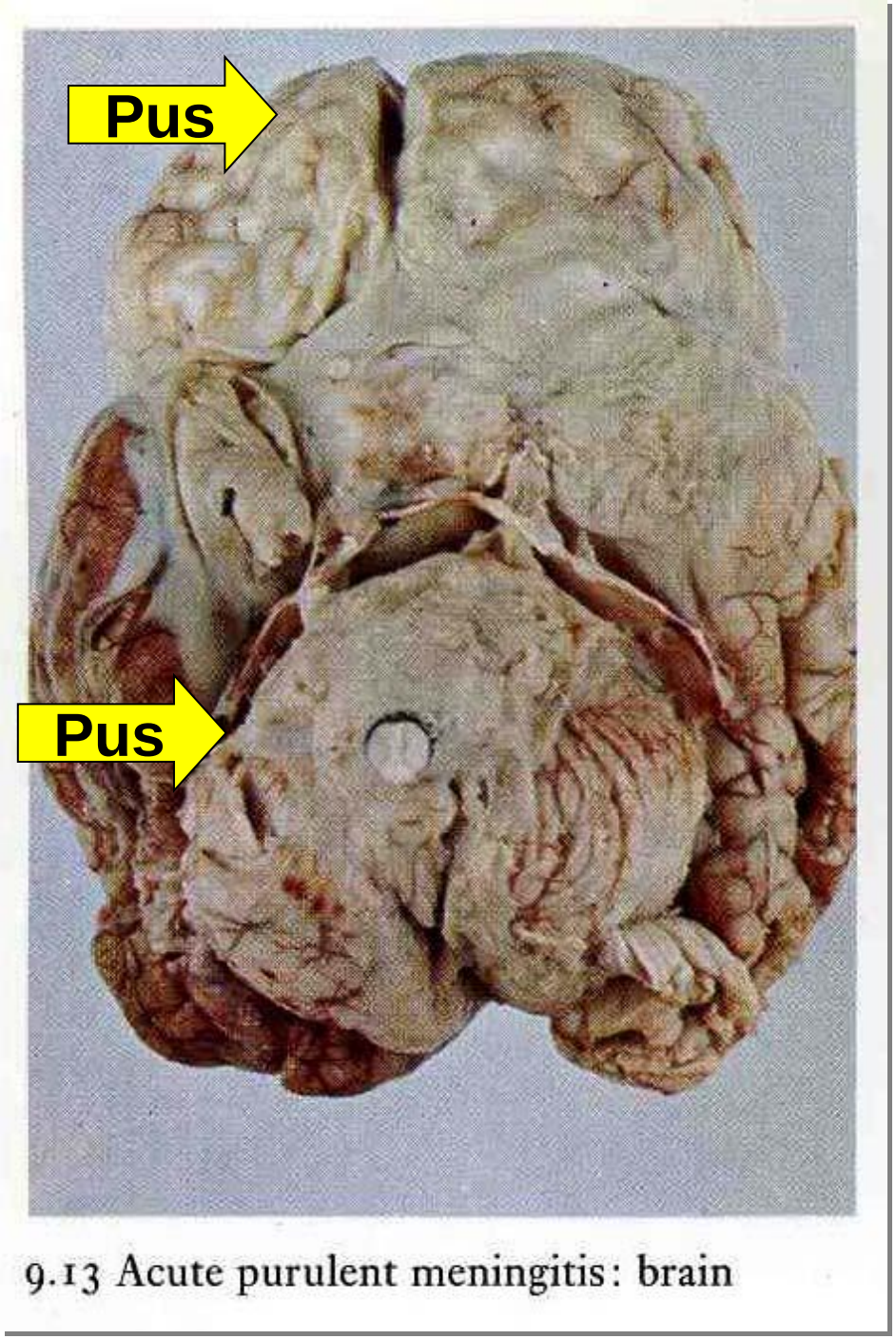
B, Two cerebral abscesses in the frontal white matter (arrows) .

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.

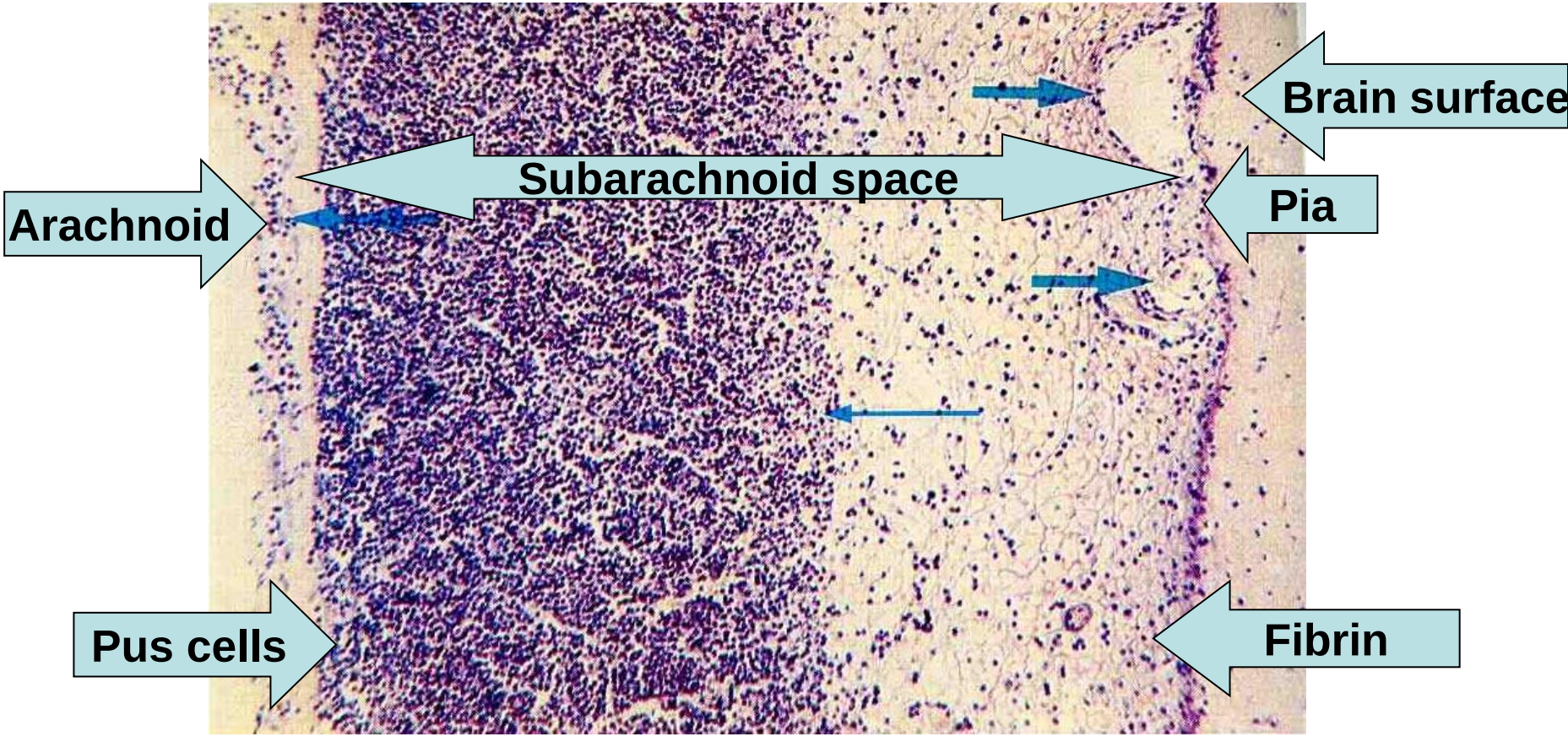
★**CSF** shows • ↑ lymphocytes, • moderate protein elevation, • **NORMAL glucose content &** • **NO bacteria.**

▼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.

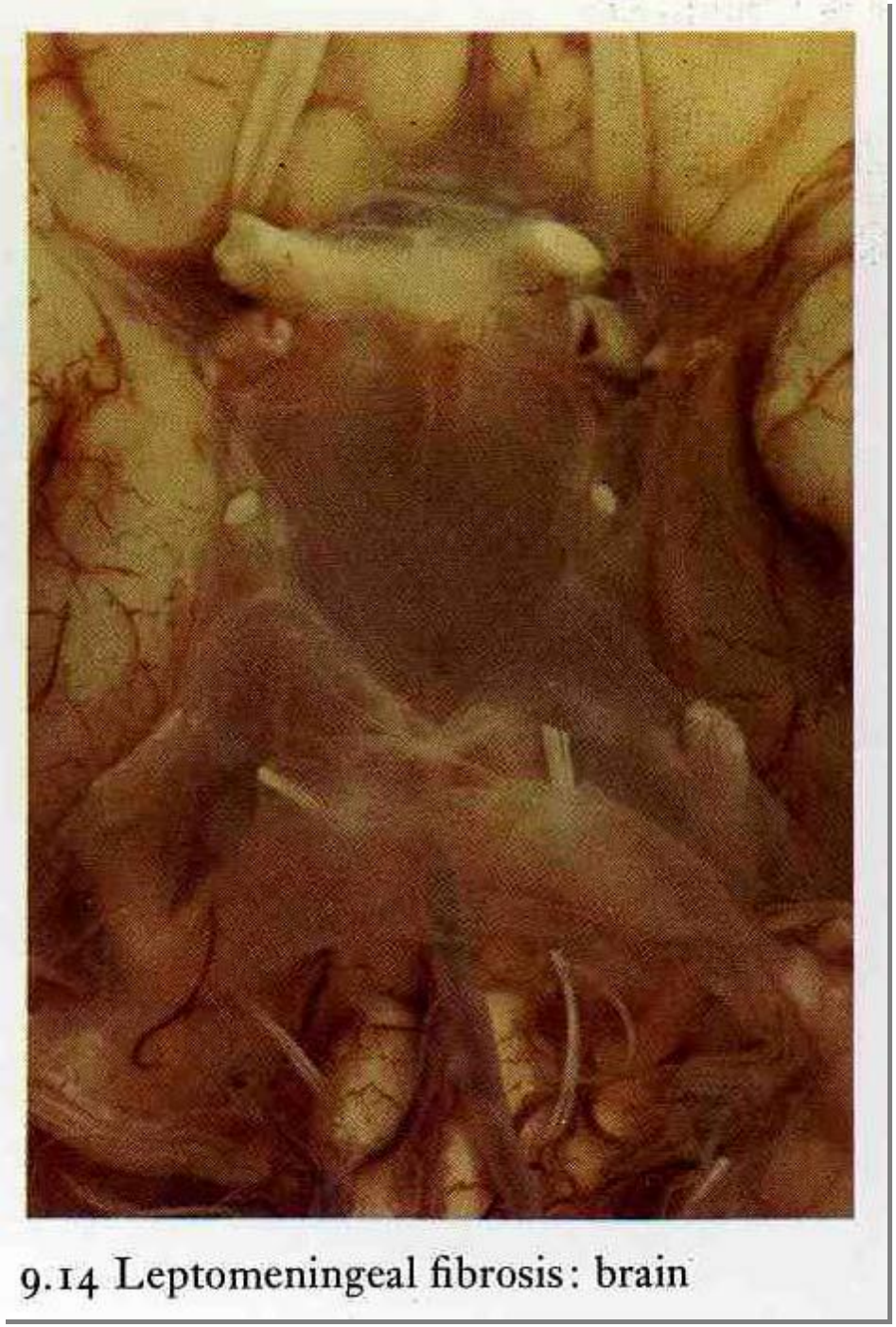
Neurosyphilis

★ 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 &**

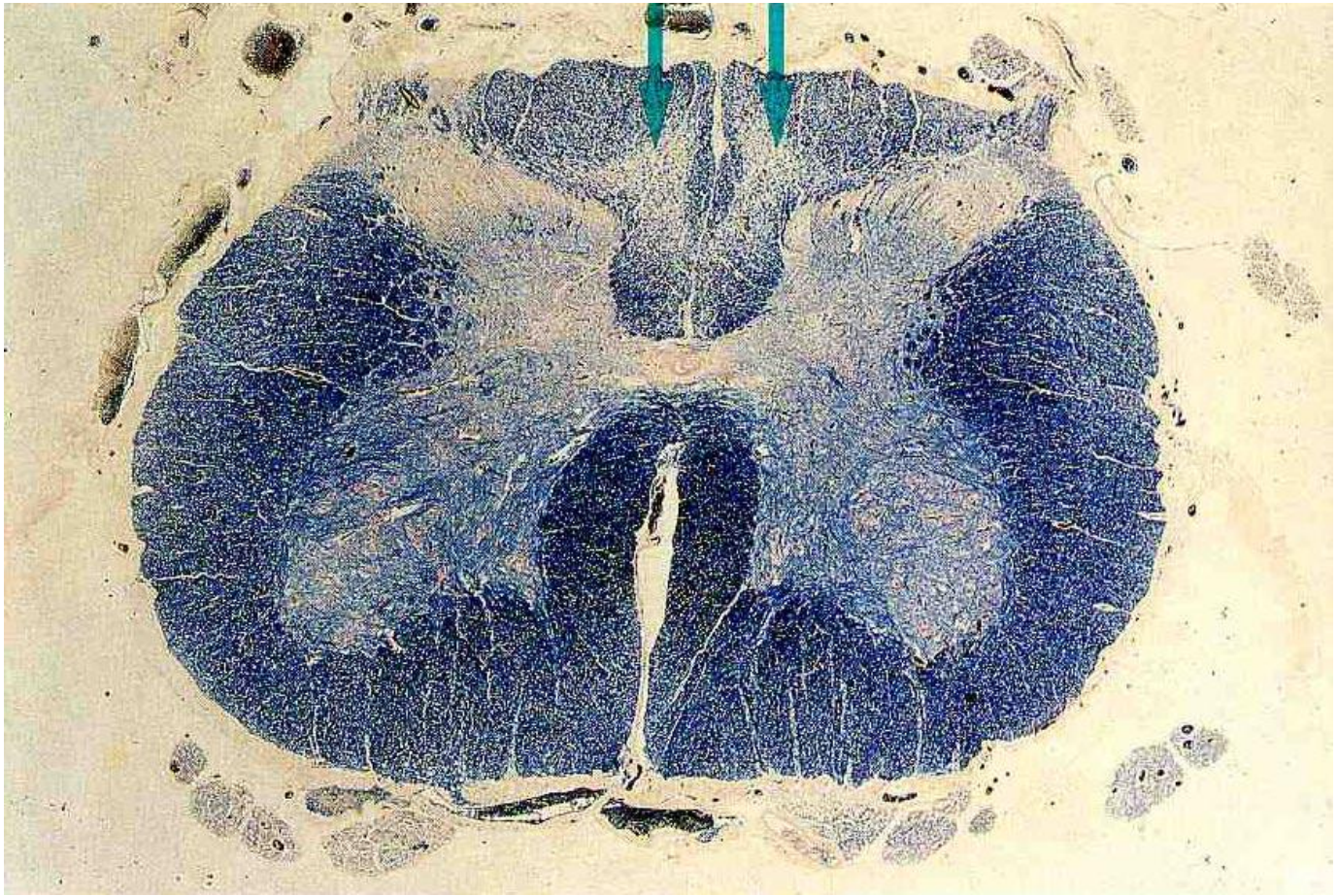
(3) **absence of deep tendon reflexes.**

◘ 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**.



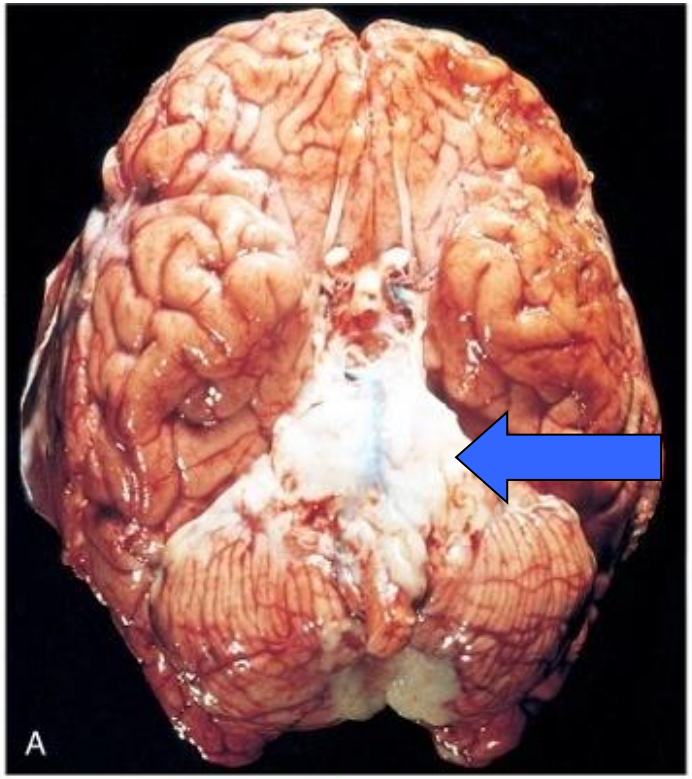
Parenchymal Infections

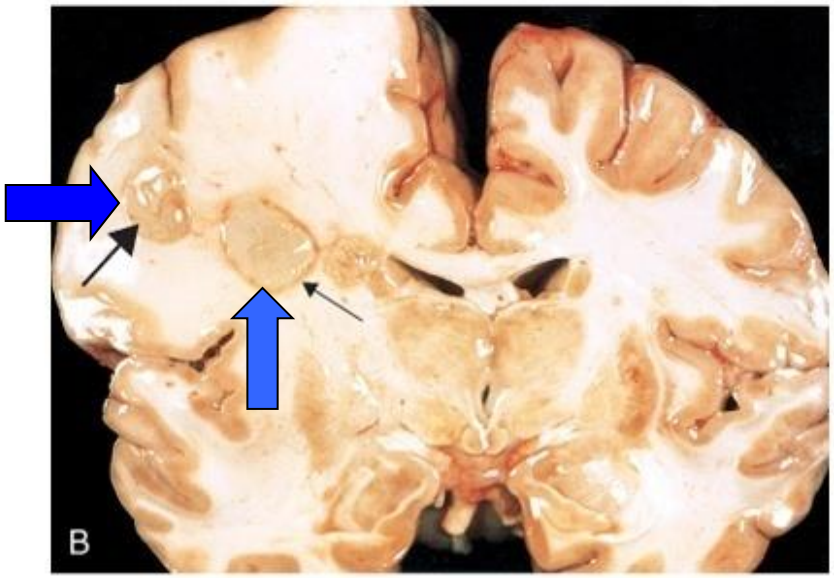
★Most microbes (virus to parasites) can potentially infect the brain. Different pathogens have different patterns of involvement (although the distinctions are not absolute).
In general, **viral infections produce the most diffuse involvement, *bacteria*** (when not associated with meningitis) produce 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.

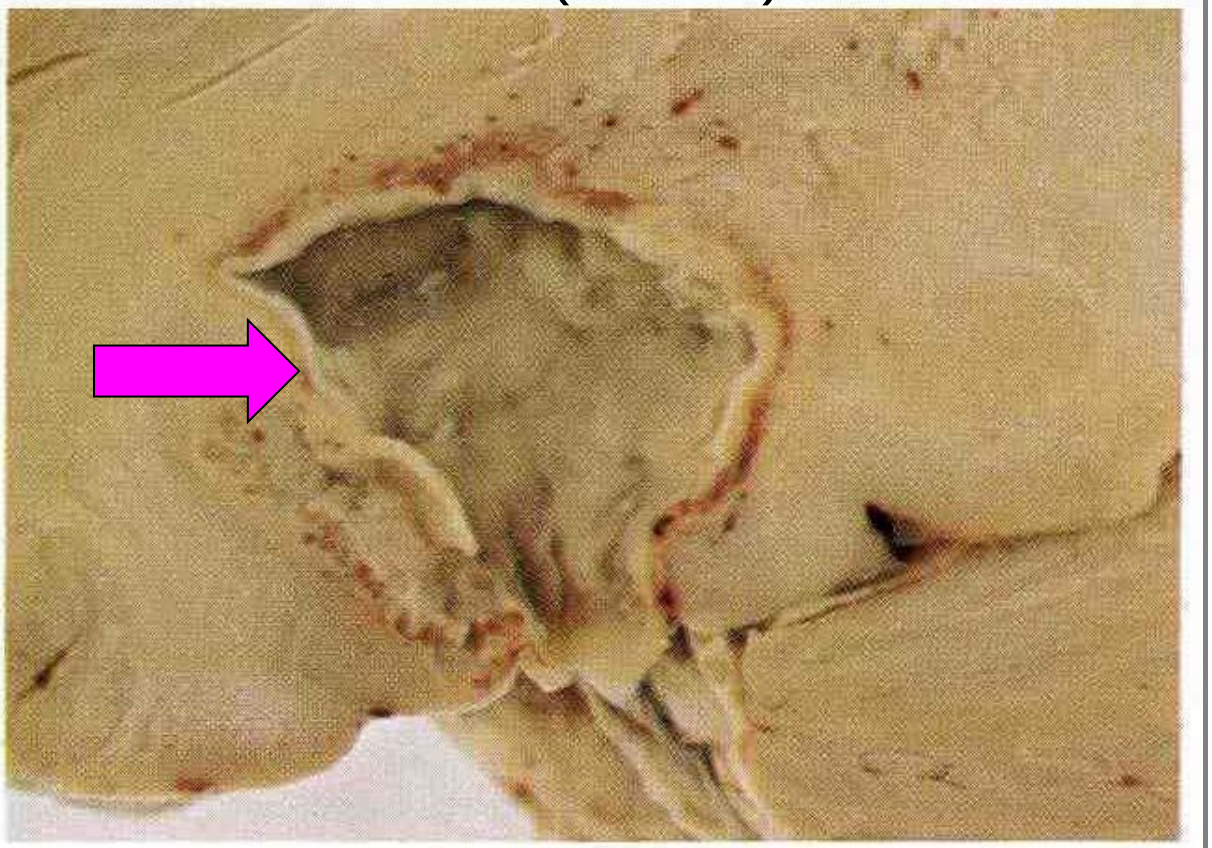
Effects & complications:

☹ **(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.



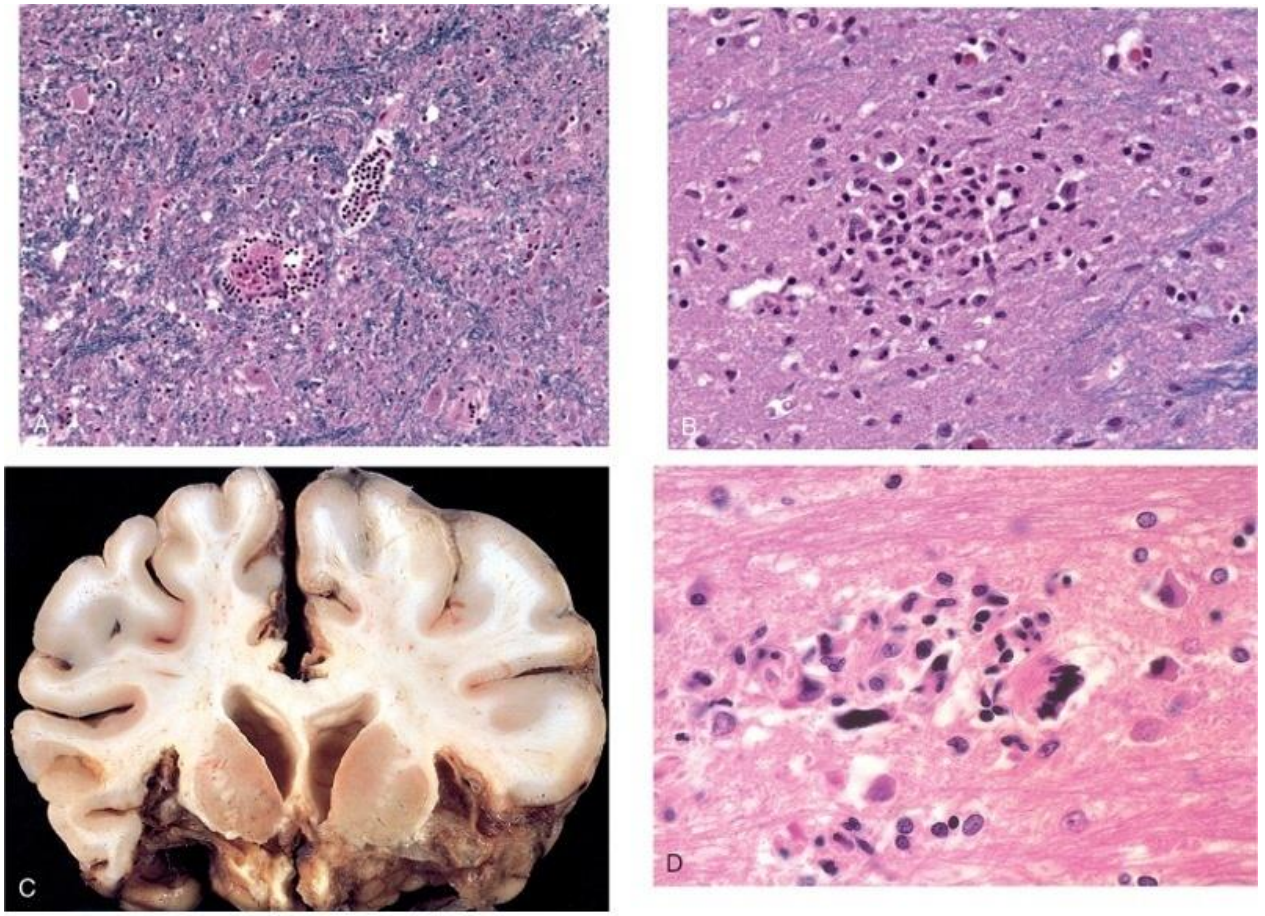
9.11 Chronic abscess: brain

►**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 <u>frontal & temporal lobes.</u>

►**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 <u>to women with</u> <u>active primary HSV Type 2 genital infections.</u>**

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.**

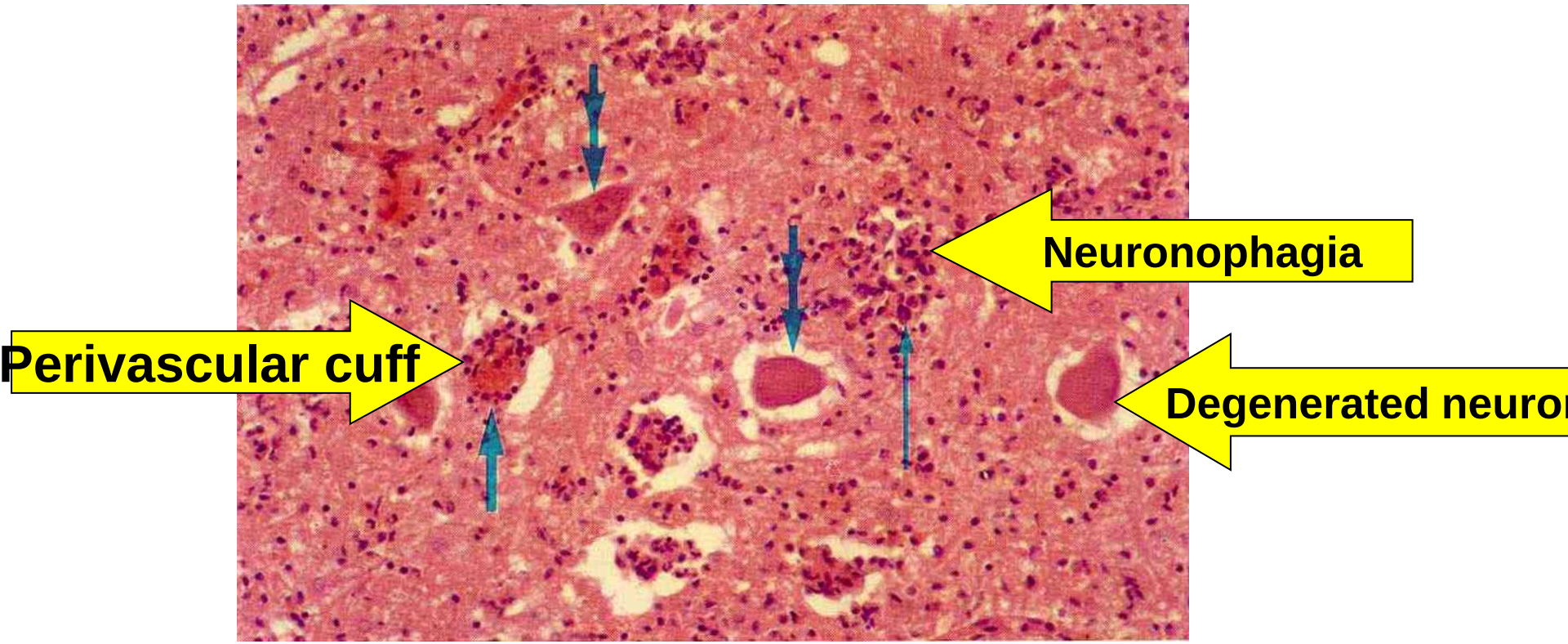
◘ **H, subacute CMV encephalitis is associated with inclusion-bearing cells,** is the most common pattern of involvement in the immunosuppressed patient. Although any type of cell within the CNS can be infected by CMV, there is a tendency for the **virus to localize in the paraventricular subependymal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

Poliovirus (◘ 4.19 & 20)

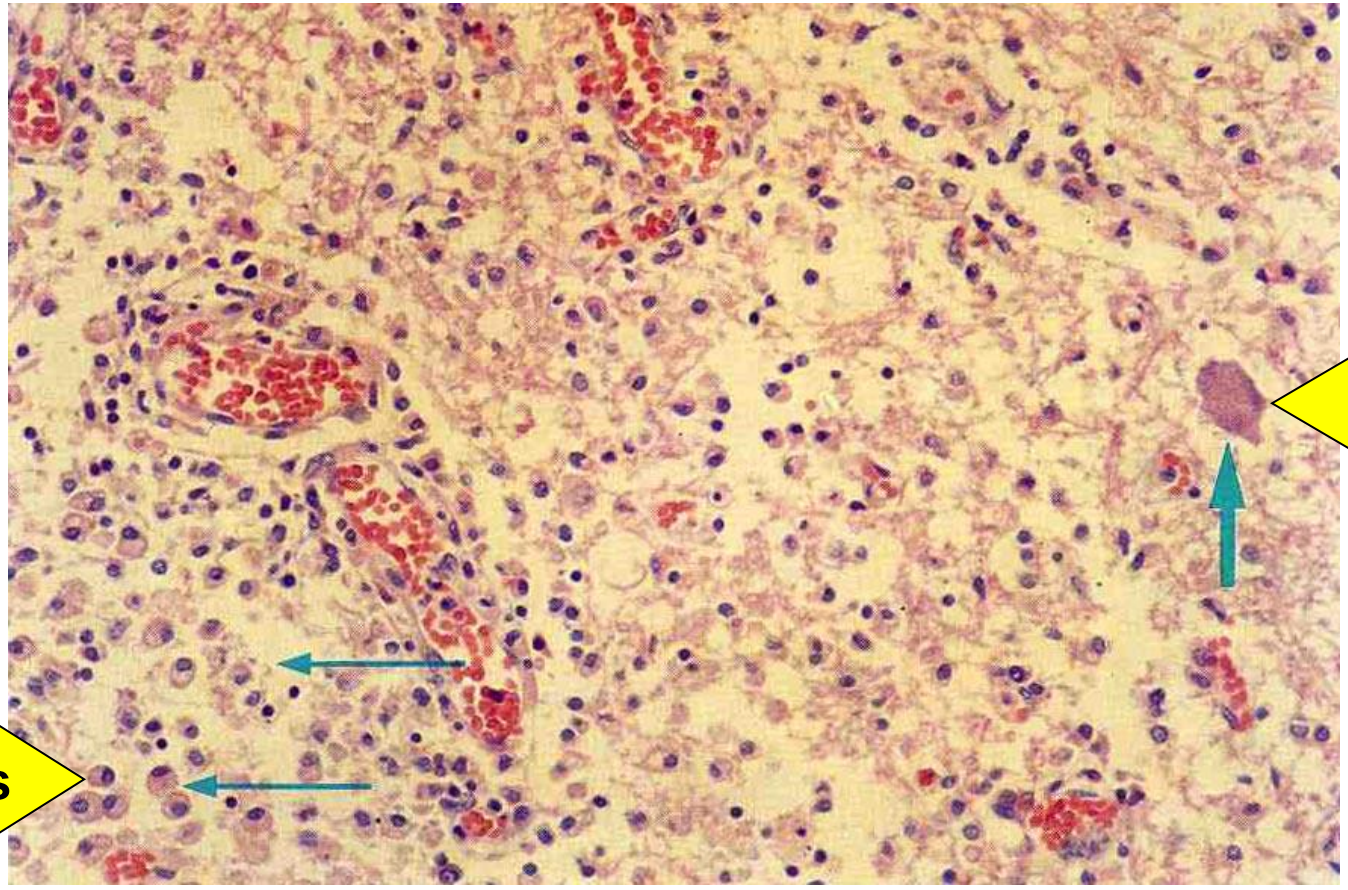
- Is an enterovirus that causes **paralytic poliomyelitis**.
- It has been **eradicated by immunization** in many parts of the world, but there are still many affected regions.
- Infection with poliovirus most often causes a subclinical or mild gastroenteritis; but
- **In few (1%) of cases it secondarily 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.**

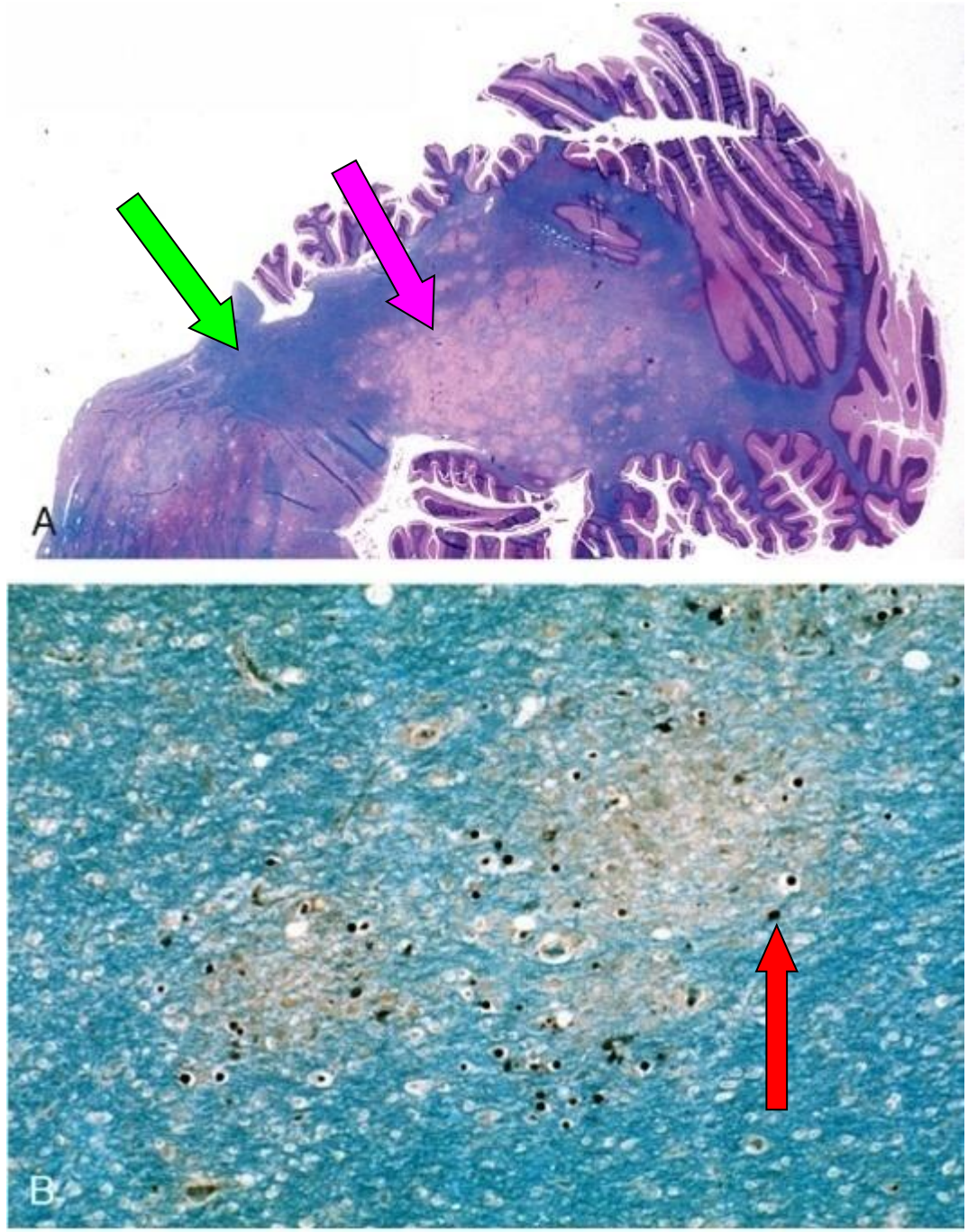
★ The disease occurs invariably in **immunosuppressed** individuals.

★ 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.

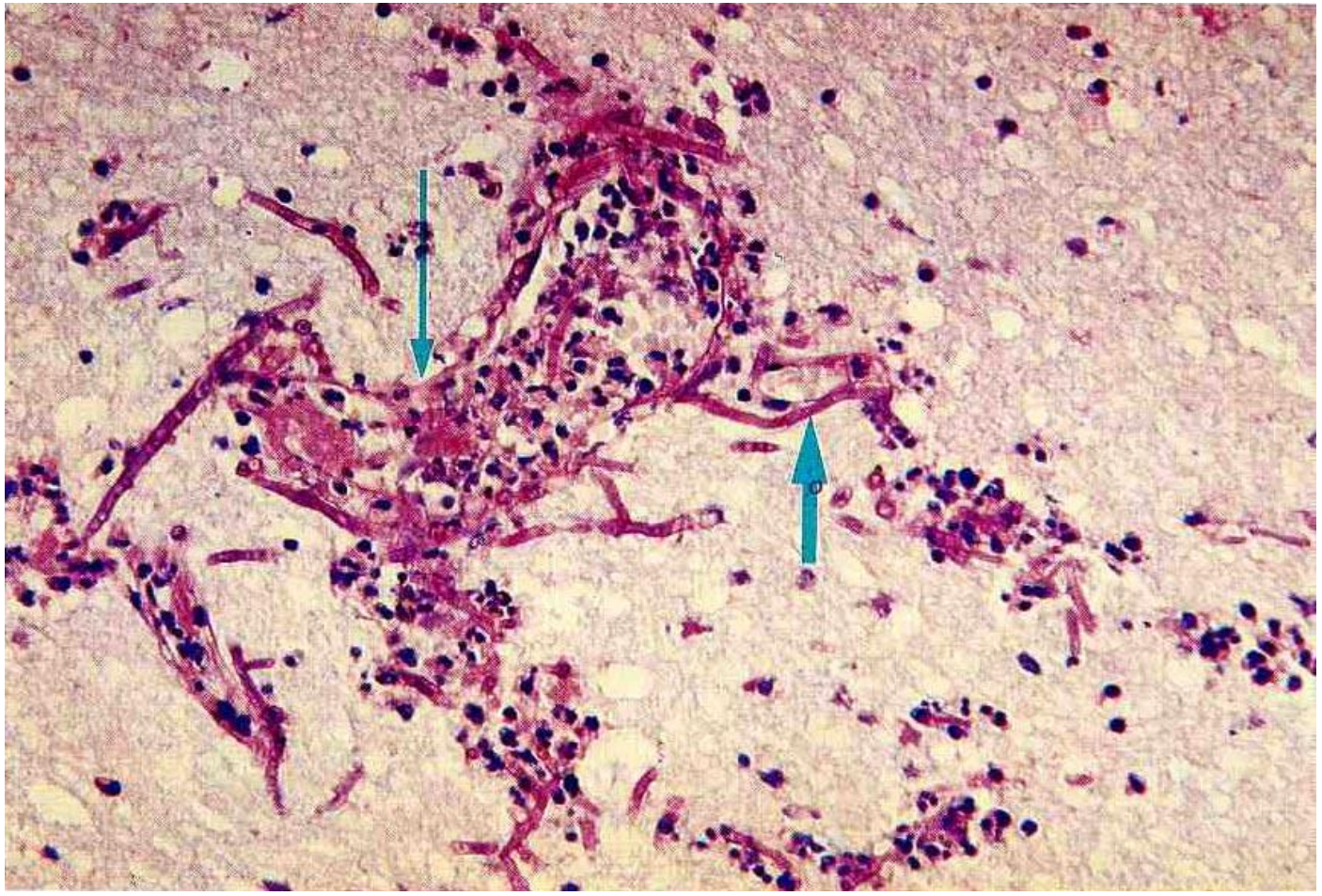
★*Parenchymal invasion,* usually in the form of **granulomas or abscesses,** can occur with most of the fungi & often coexists with meningitis. *Candida* usually produces multiple microabscesses, with or without granuloma formation.

• 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

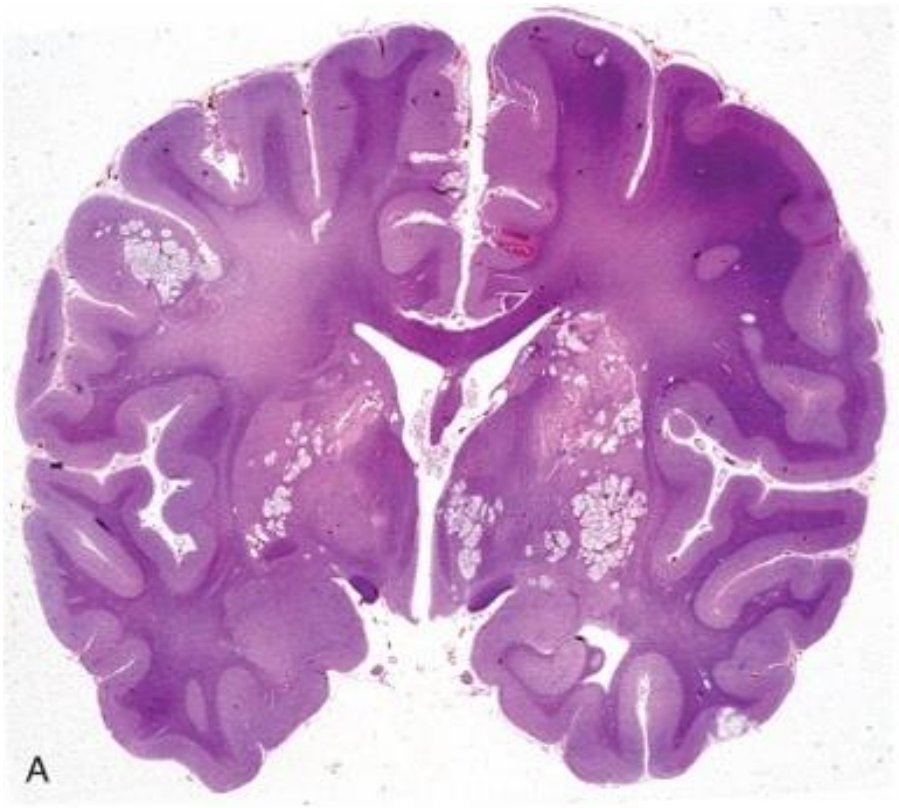
★ Group of diseases includes • sporadic, • familial, • iatrogenic & • variant forms (vCJD) of ➔Creutzfeldt-Jakob disease& Kuru

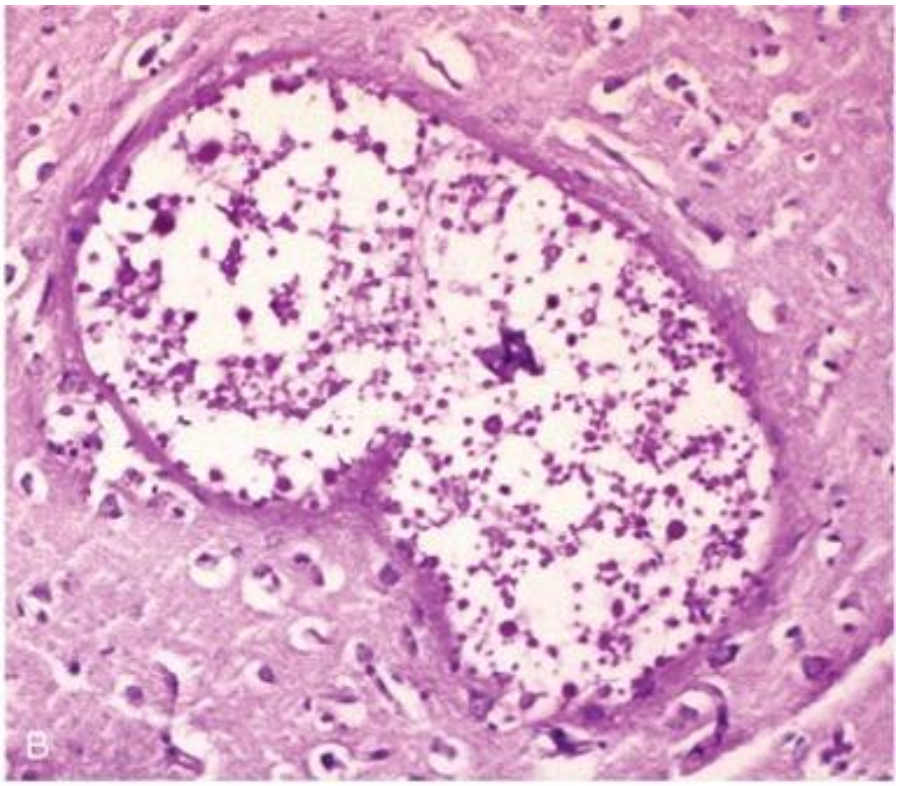
★ Several animal diseases from this group are also known, including **scrapie in sheep & goats; & bovine spongiform encephalopathy in cattle ("mad cow" disease).**

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

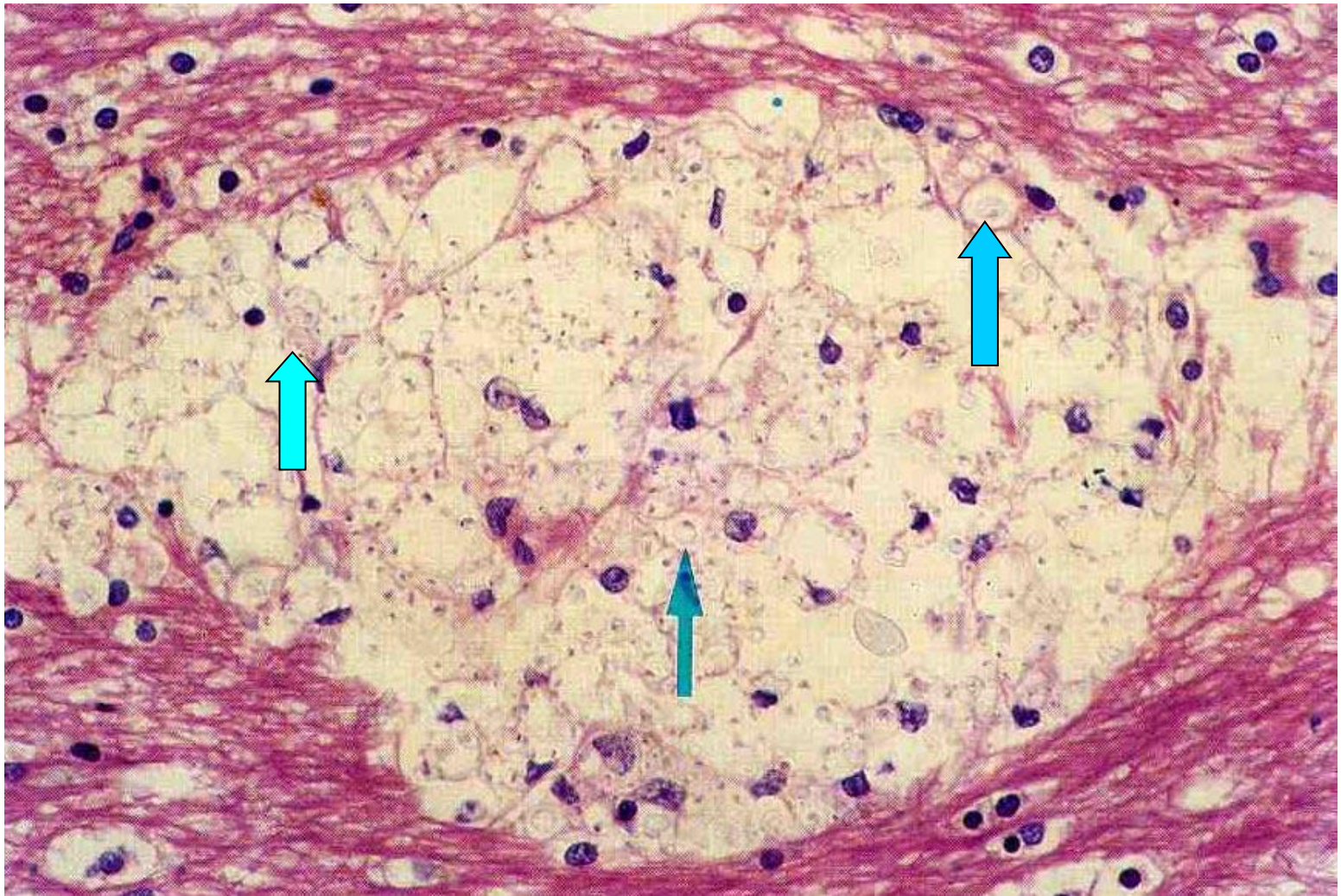
★All these disorders are associated with abnormal forms of a normal cellular protein, termed {**prion protein (PrPc)}.**

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!



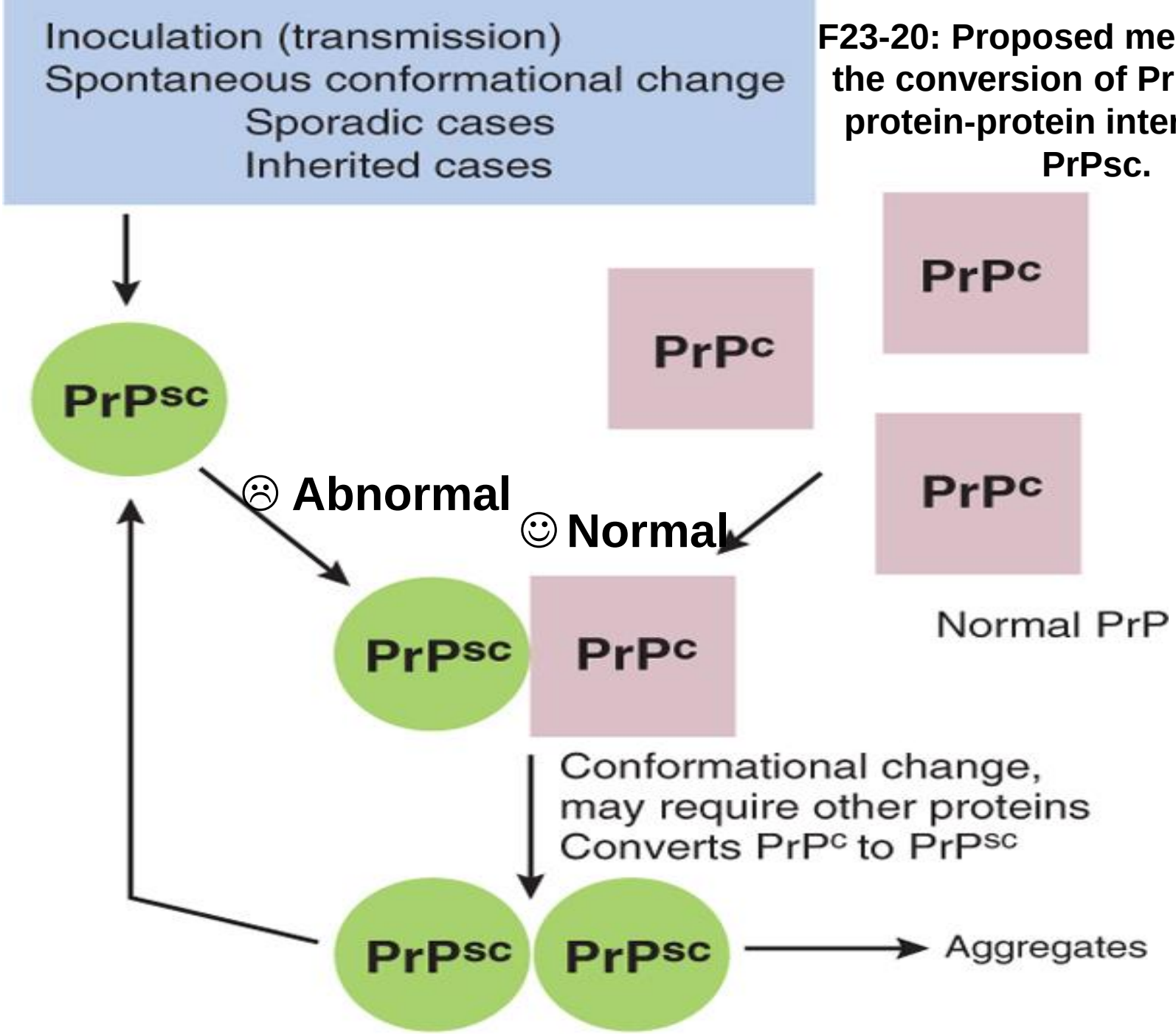
➔**The abnormal form of this protein can act as an infectious agent,** since it propagates itself & injures the cells in which it is present. Most cases of prion disease are either sporadic or associated with mutations in the gene that encodes PrPc.

➔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 *scrapie*) or **PrPres** (for **P**rotease ***resi****stant*) (F23-20).

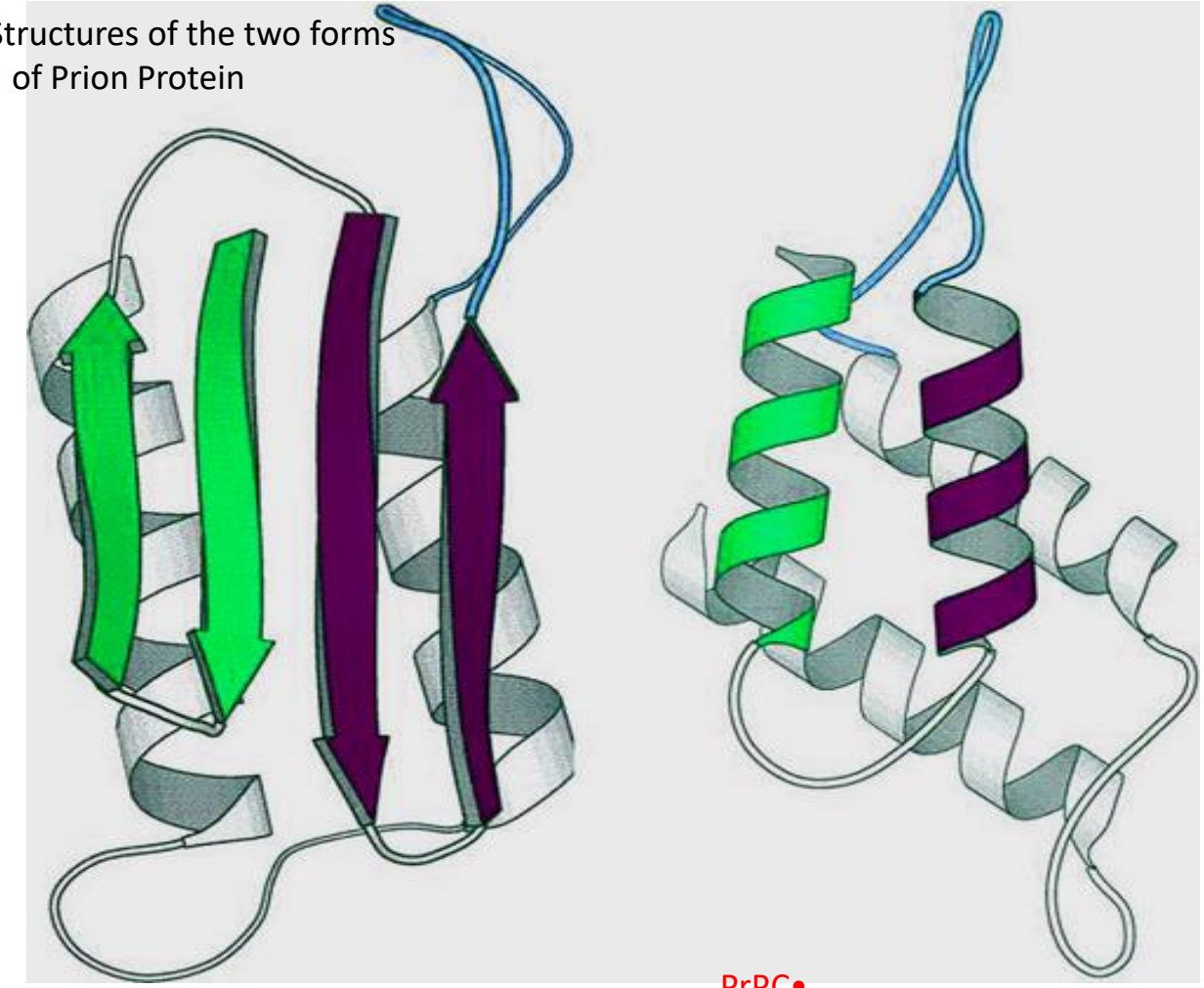
★ In the abnormal conformation, the prion protein becomes **resistant to protease digestion**. Once formed, PrPsc can then initiate comparable transformation of other PrPc molecules.

☹ 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

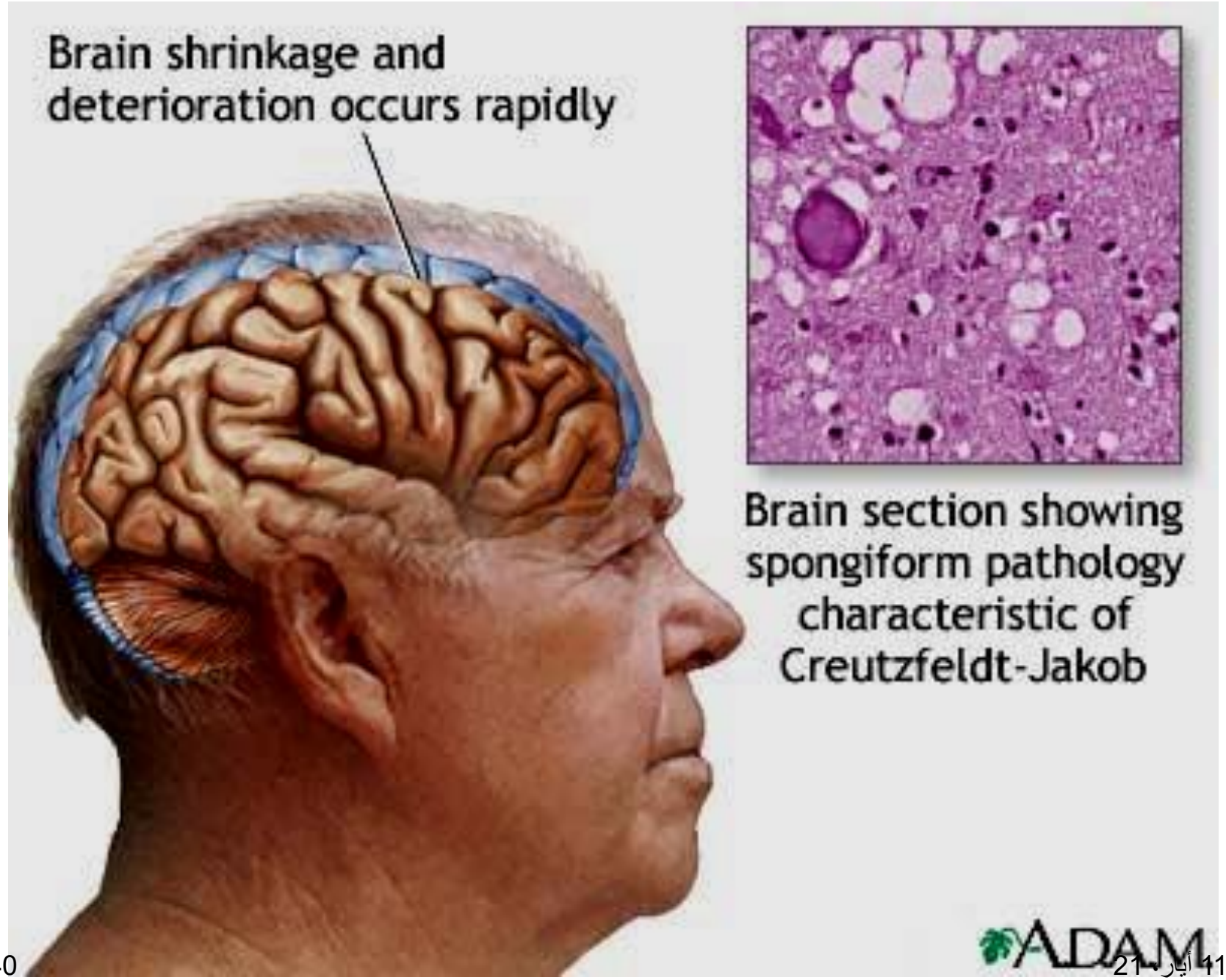
Infectious form(normal form of protein folded incorrectly)..

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).

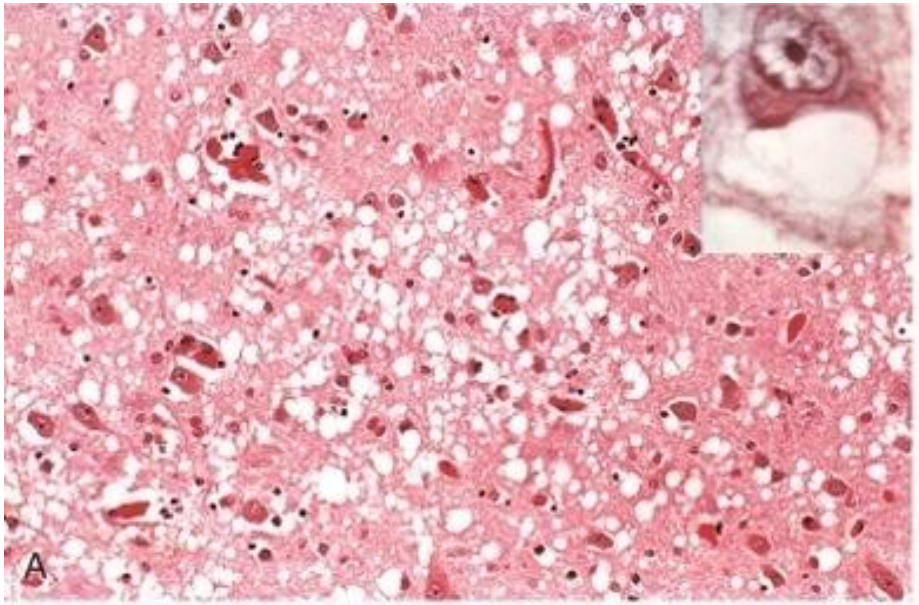
▼**Western blotting of tissue extracts** after partial protease digestion allows detection of diagnostic PrPsc.

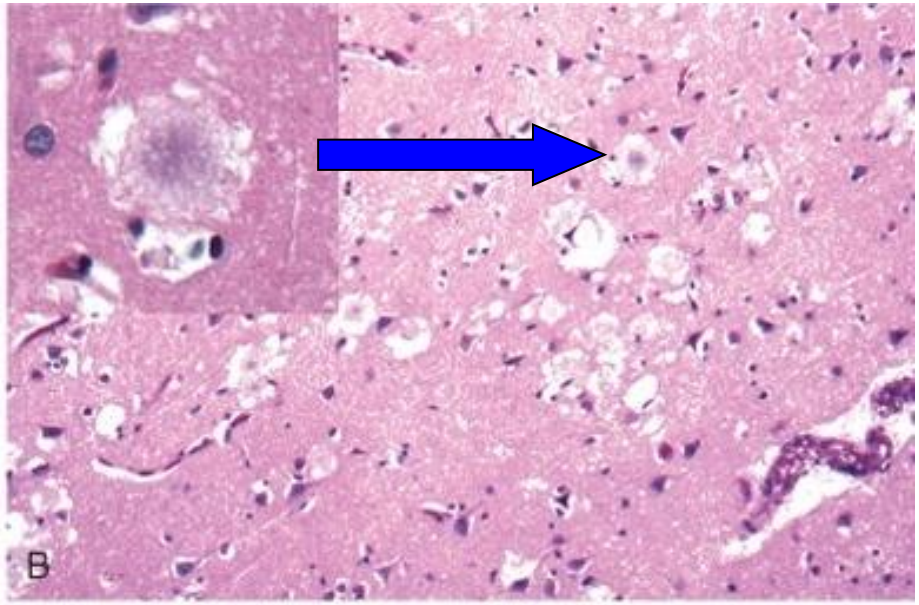
F 23-21: **Prion disease.**

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

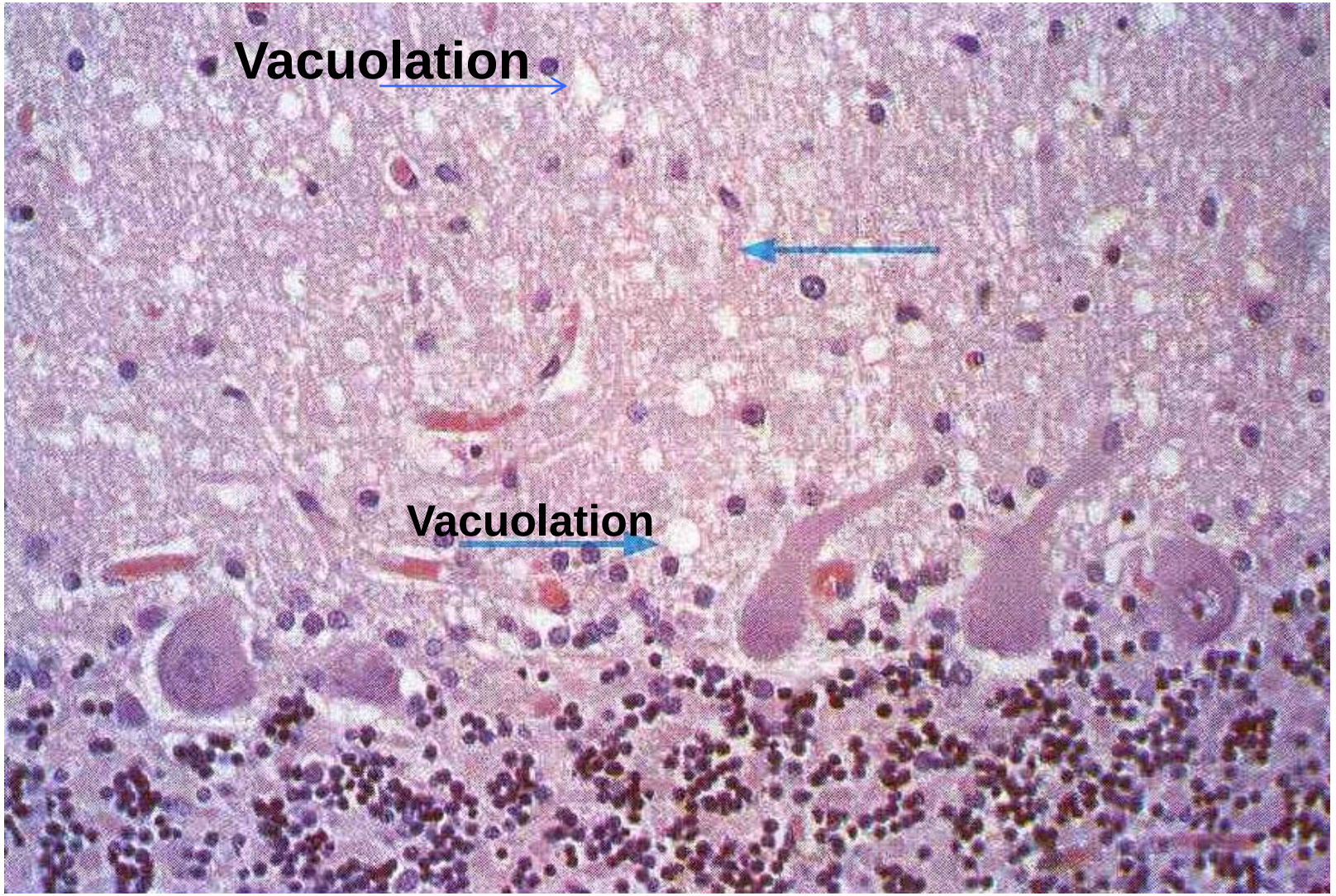
Inset, High magnification of neuron with vacuoles.

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

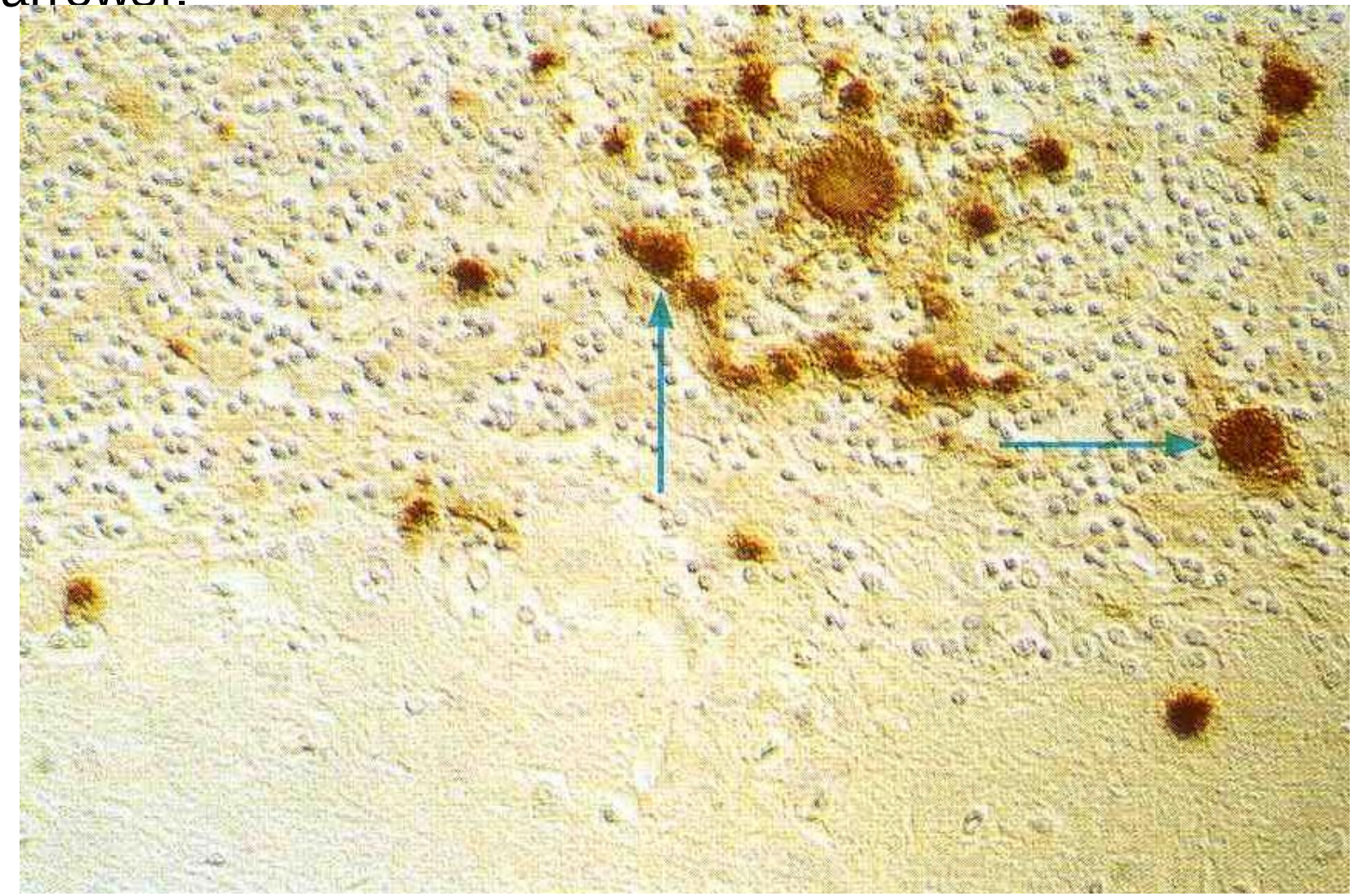




◘ 4.17: **Creutzfeldt-Jakob disease: Brain.** The main features are **loss of neurons**, **demyelination** & spongiform change (confluent **vacuolation** {thin arrow} of the cerebral white matter "neuropil"). However there is **no inflammatory reaction!**



◘ 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).