Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY

DONE BY : Volunteer

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*).

and poliomyelitis.

★ Damage of the infectious agents to nervous tissue may be the consequence of:

→ MO attacks neuron or glia cells.

(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.**

hypersensitivity mechs like herpes infection.

necrosis, Edema, swelling...

infl. response to the organism.

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

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

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

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

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

Epidural (extradural) & Subdural Infections

Both can occur, usually through **direct local spread** to cause:

(I) **Epidural abscess**, commonly associated with **OM**, arises from an adjacent focus of infection, such as sinusitis or a surgical procedure (e.g., craniotomy).

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

(II) **Subdural abscess**, which can produce **mass effect**.

😐 The underlying arachnoid & subarachnoid spaces are usually unaffected. ↑intracranial pressure. + surrounding tissue

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

*subdural abcess → Thrombophlebitis → venous occlusion → infarction of brain
through Bridging vein

★ 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. meningitis.

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

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.

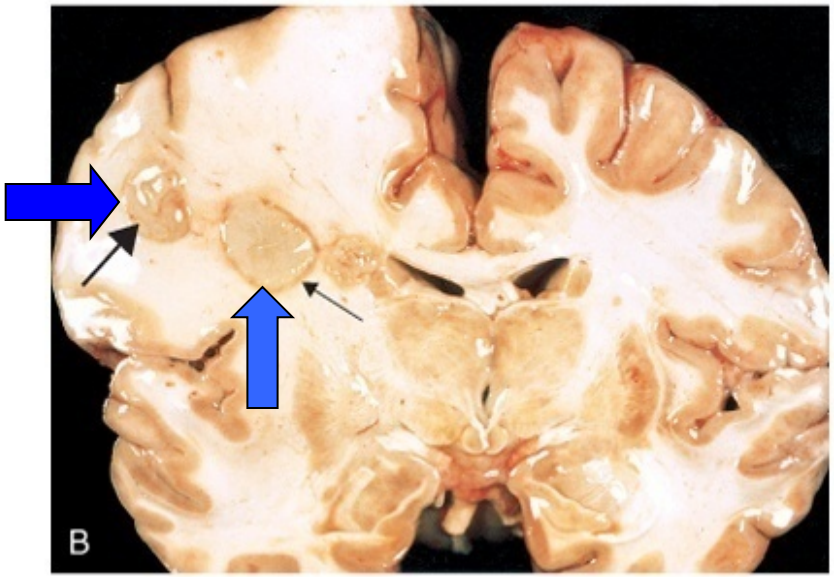
►All patients typically show (1) **systemic signs of infection** superimposed on clinical evidence of (2) **meningeal irritation** & neurologic impairment-including, headache, **neck stiffness**, photophobia, irritability, & clouding of consciousness. → confusion

▼**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). → in the under surface of the brain
(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**. → very severe.



مع الدب.

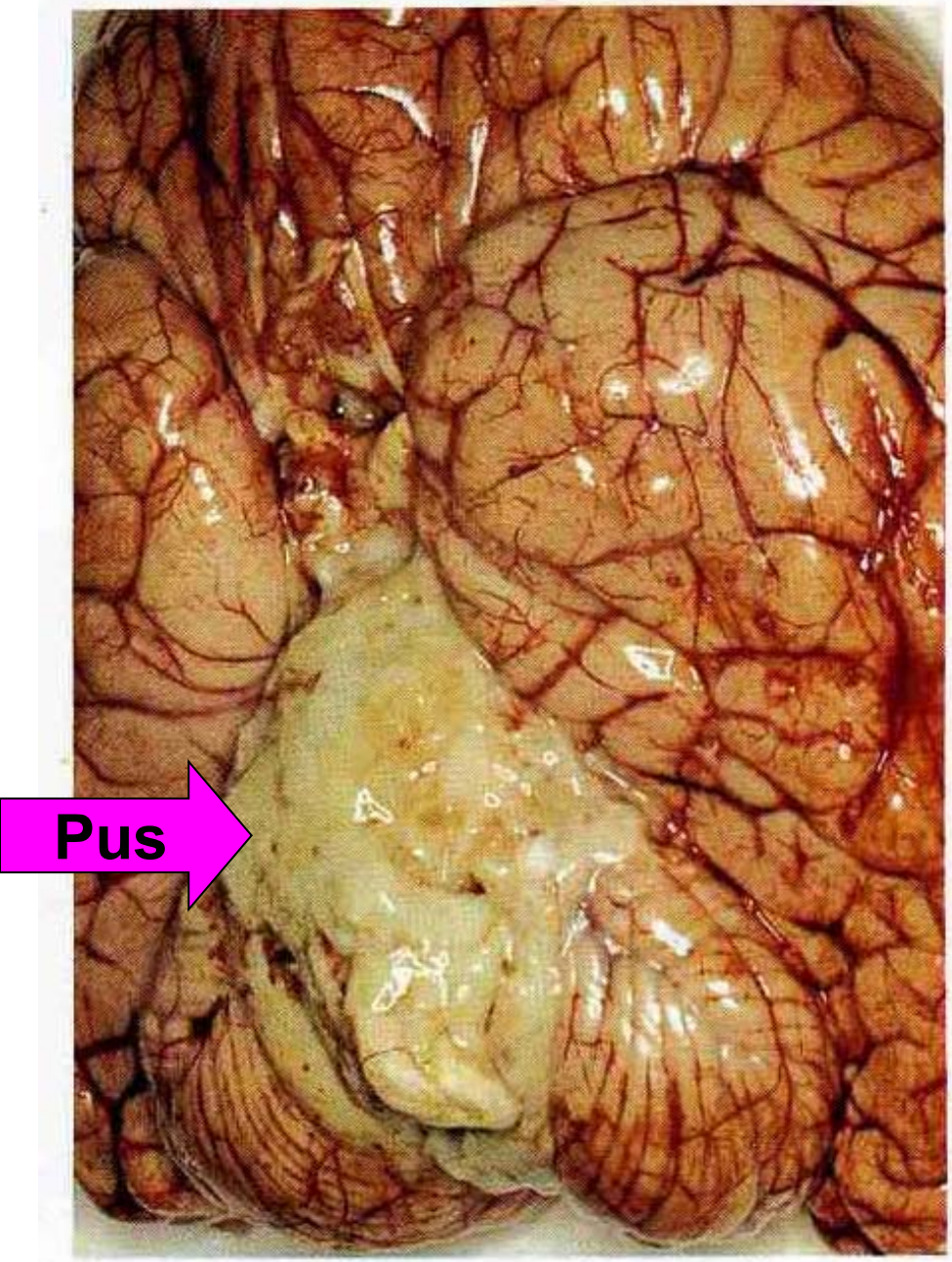
F23-16: **CNS Bacterial infections.**

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? Blood



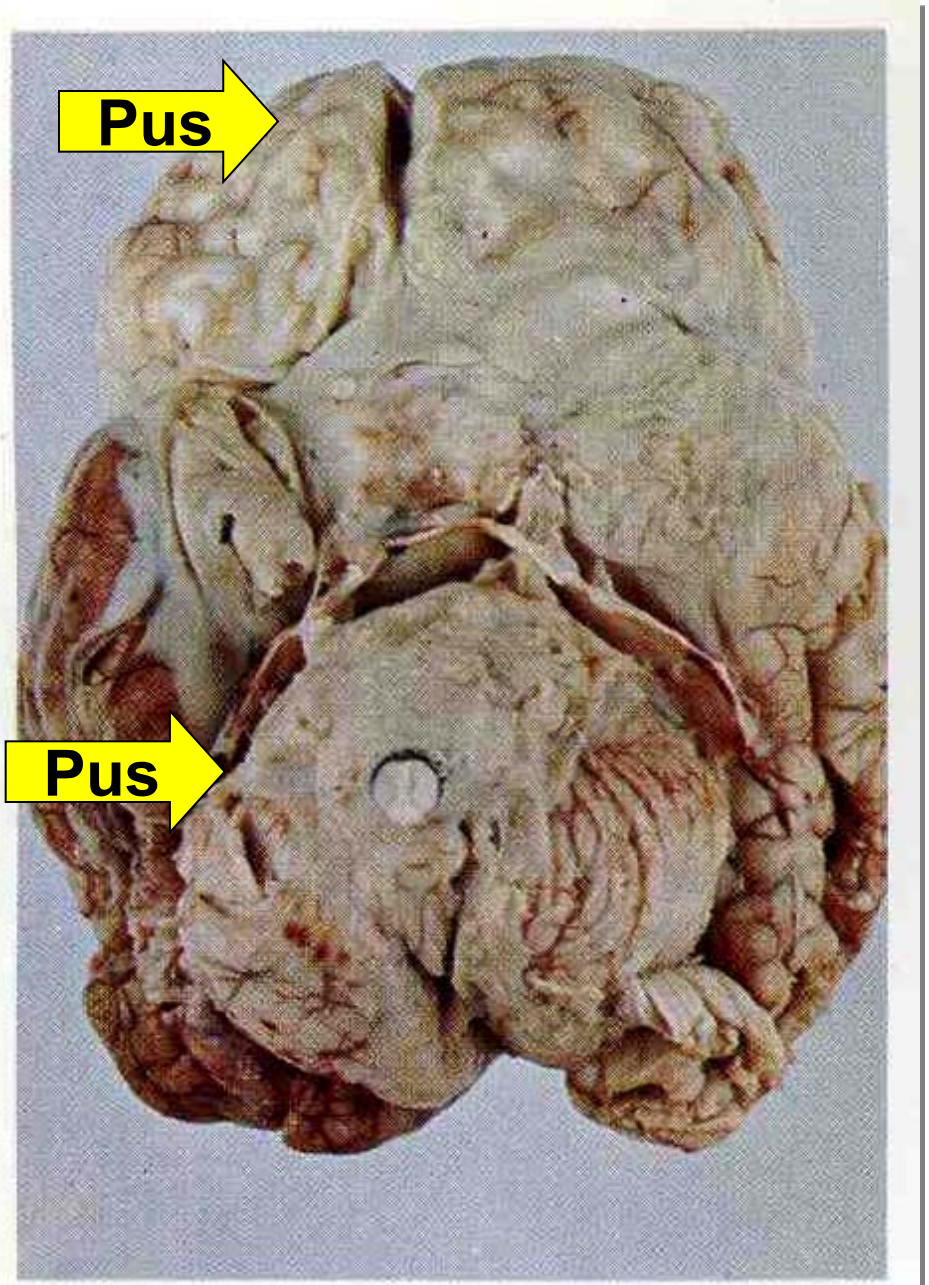
1.6 Purulent meningitis

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

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

دائماً تبدو على ال pus في ال inferior (under) surface of the brain.

✱ 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. more than 80% of the brain is covered by pus.

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

① craniopharyngio hydrocephalus → to the ② right atrium
③ septic meningitis
hydrocephalus

◘ 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.

injury to the endothelium → مباشرة thrombosis.

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. → علاجي أدوية

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

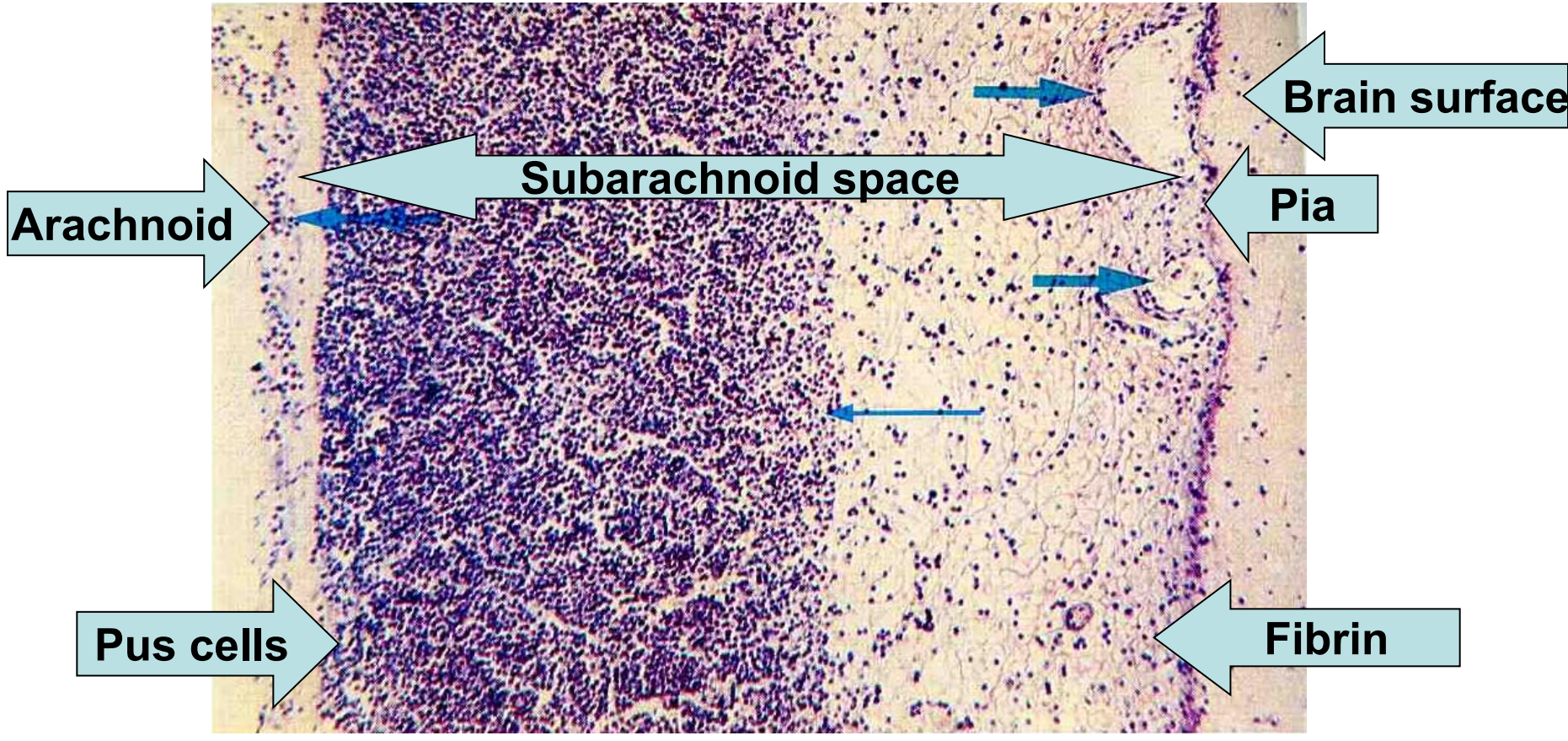
▼ In **70% of cases**, a virus can identified, most commonly an **enterovirus**.

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

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

عكس الـ pyogenic

◘ 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.

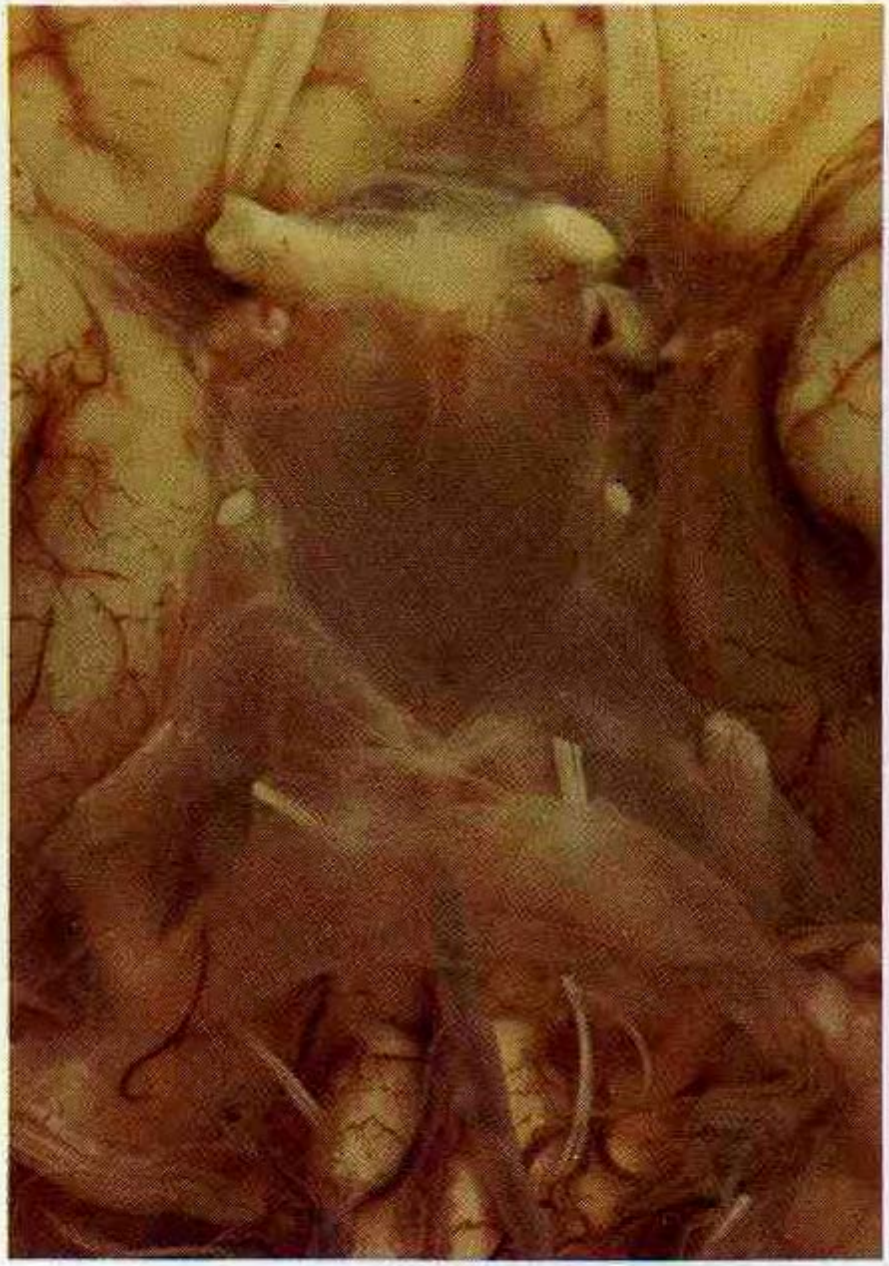
Neurosyphilis

★ 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.** أوهام العظمة

◘ 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

archanoid + pia only

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.

not cerebellum.

☹ **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 (1) **loss of pain & sensation**, leading to skin & joint damage (**Charcot joints**); &

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

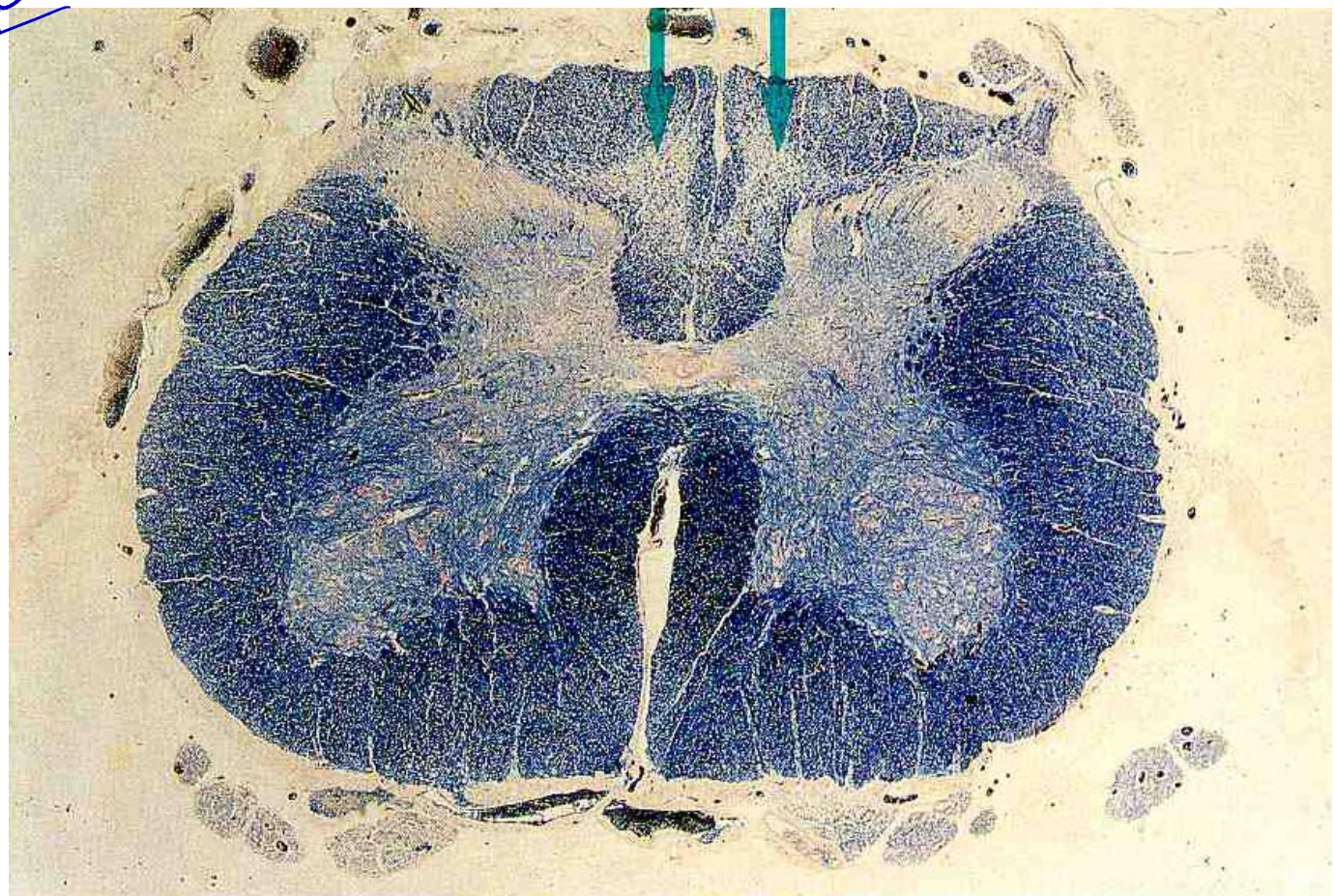
(3) **absence of deep tendon reflexes**.

◘ 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.** (Thickening of the intima).

(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**.



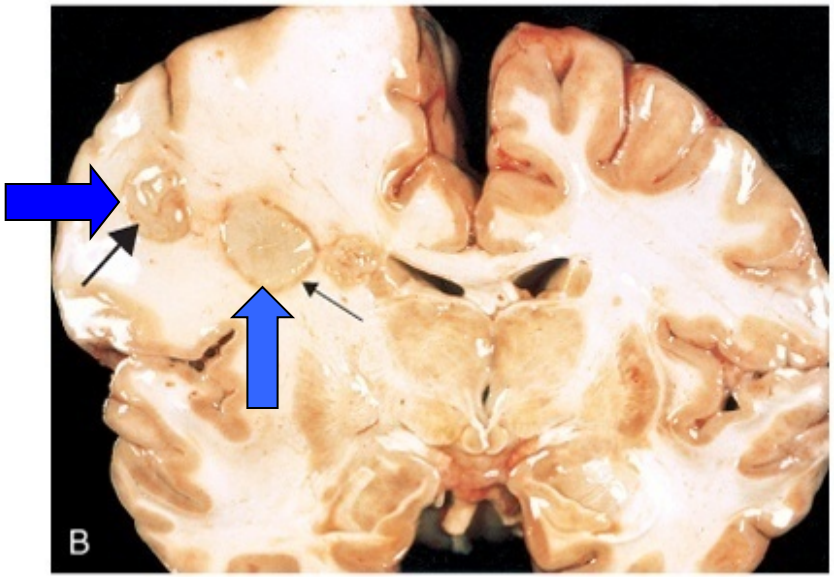
Parenchymal Infections

★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? Hematogenous (Blood)

from heart, lung or OM.

☹ 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 في المنطقة اللي تصورت
(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.

By polmunary veins to left atrium → left ventricle → aorta to brain.

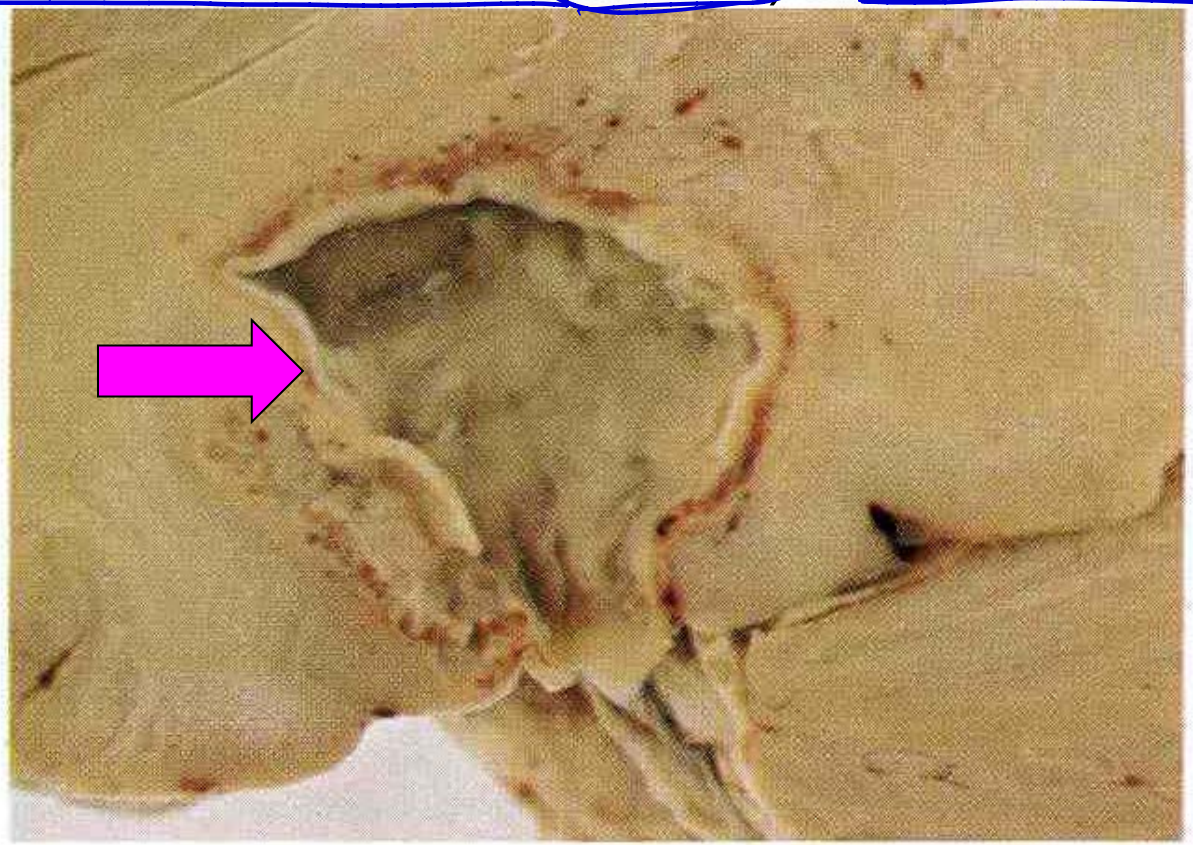
Effects & complications: معلومة إضافية

☹ **(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.

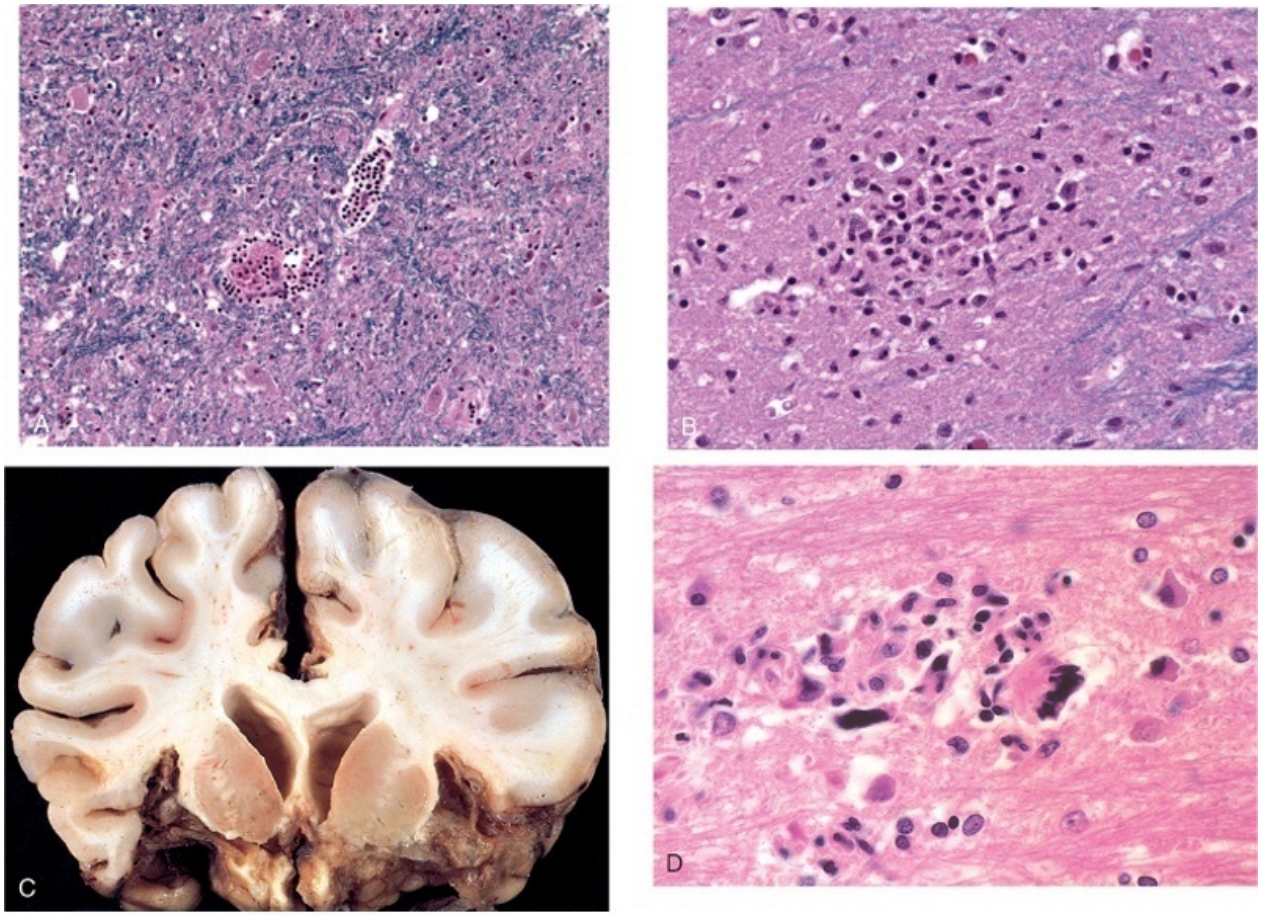
Viral Encephalitis

• 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**. الحصبة الألمانية.

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**. نفس الـviral meningitis.

◘ 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.** يعني الأغلبية ما كانوا مطاعيم

Only some patients have previous oral herpetic lesions.

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

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

Herpes Simplex Virus Type 2

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

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

يعني إذا انولد بعملية قيصرية طارح يصيبه الـ virus.

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.**

ضرر في الدماغ.

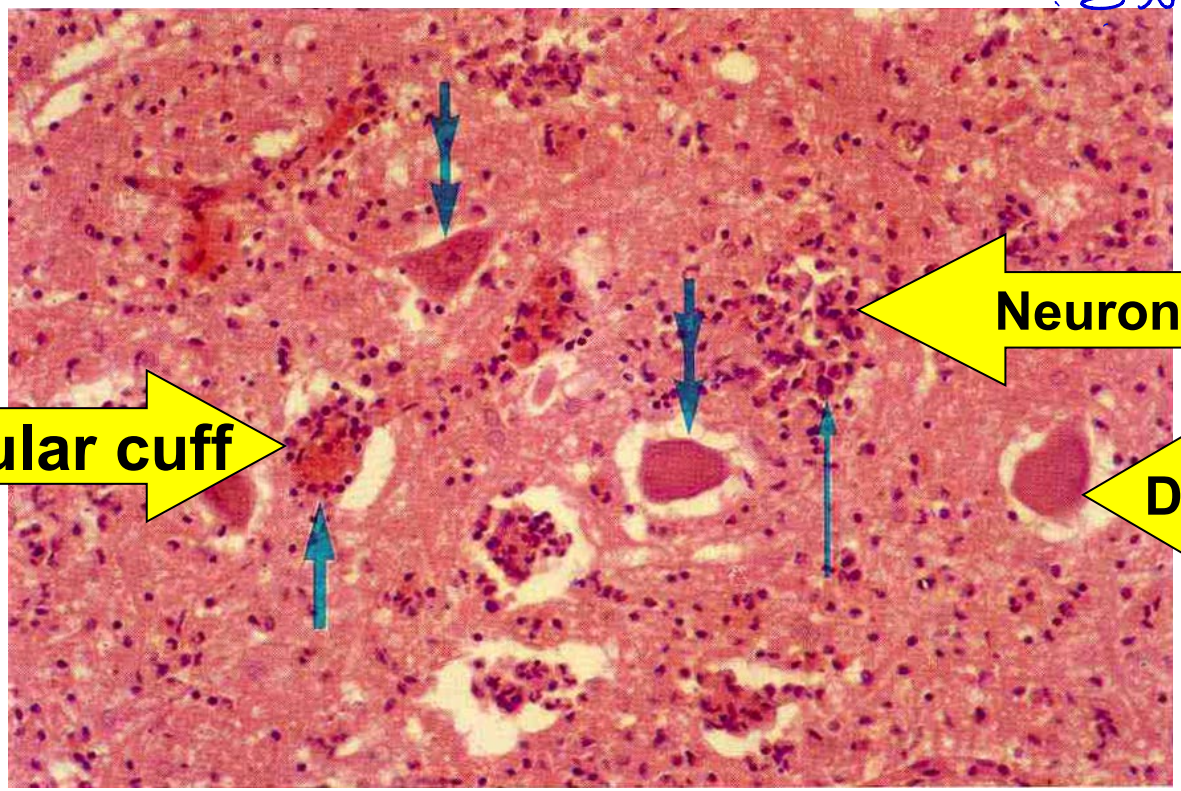
◘ **H, subacute CMV encephalitis is associated with inclusion-bearing cells,** is the most common pattern of involvement in the immunosuppressed patient. Although any type of cell within the CNS can be infected by CMV, there is a tendency for the **virus to localize in the paraventricular subependymal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

Poliovirus (◘ 4.19 & 20)

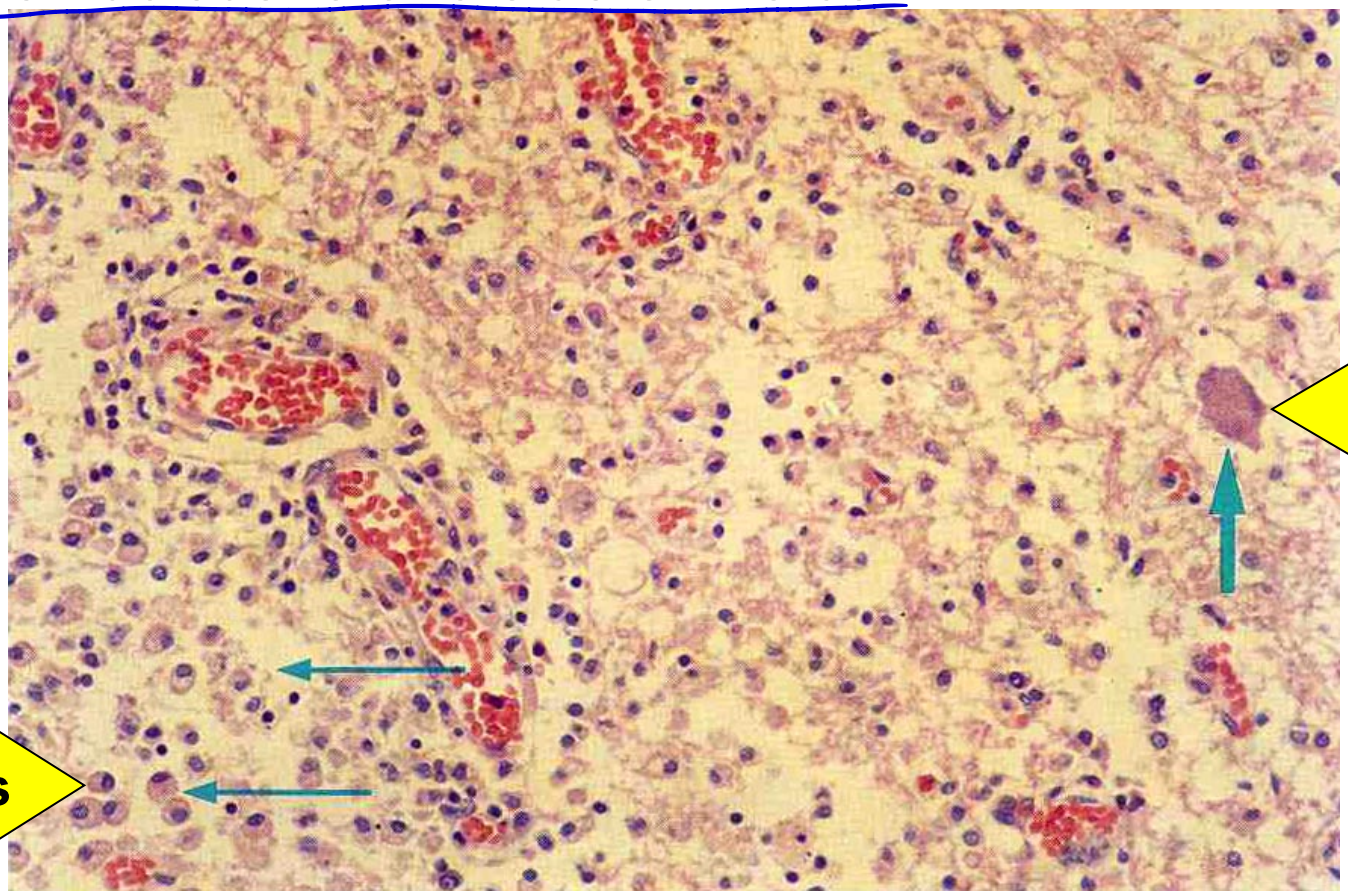
- Is an enterovirus that causes **paralytic poliomyelitis**.
- It has been **eradicated by immunization** in many parts of the world, but there are still many affected regions.
- Infection with poliovirus most often causes a subclinical or mild gastroenteritis; but
- **In few (1%) of cases it secondarily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

➔ 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: هي

(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.

هذا المرض سببه الرئيسي ↓ هو نقص الـ vit. B12 . ولكن هنا الـ vit. مع يكون طبيعي.

Progressive Multifocal Leukoencephalopathy (PML)

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

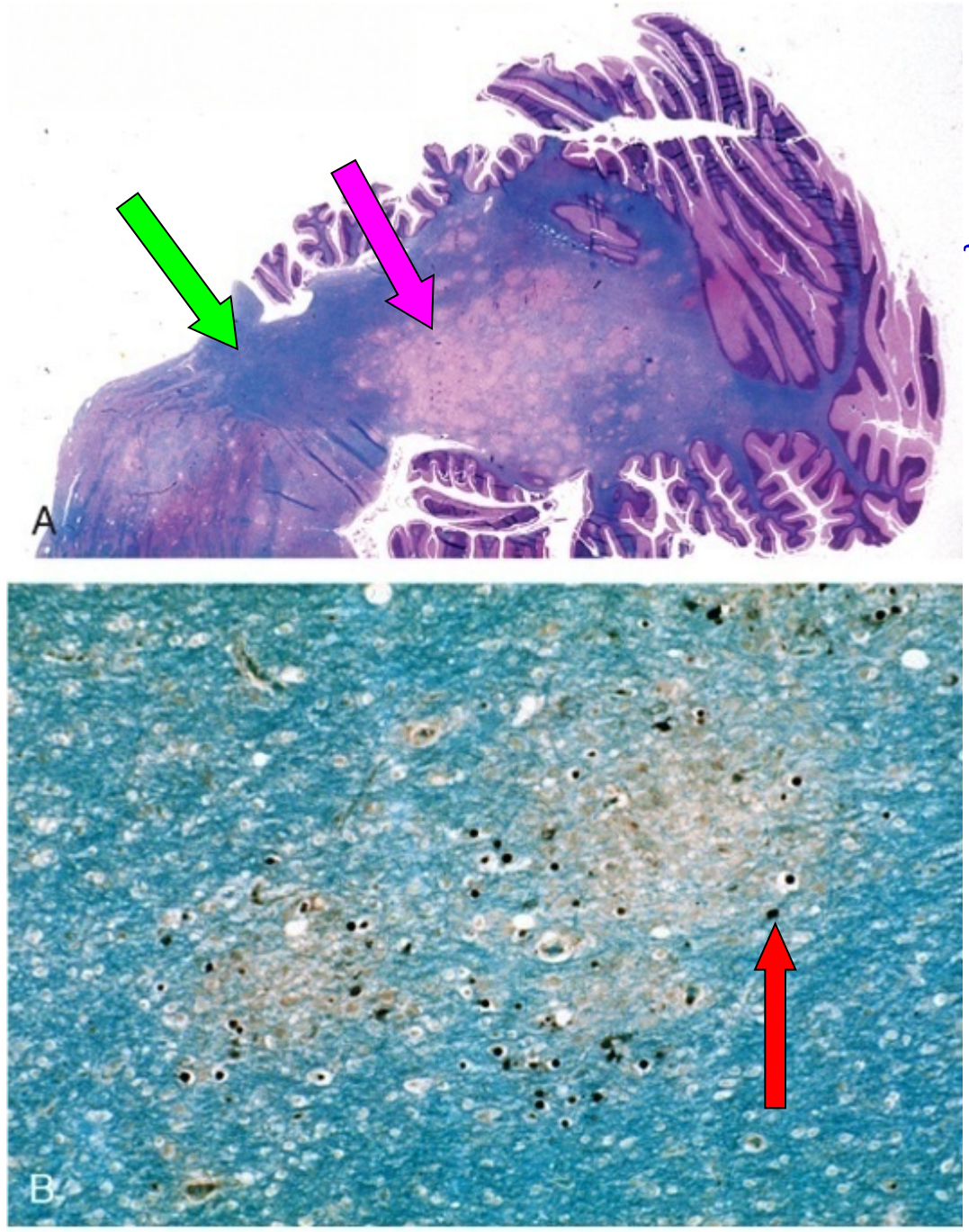
★ The disease occurs invariably in **immunosuppressed** individuals.

★ 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.

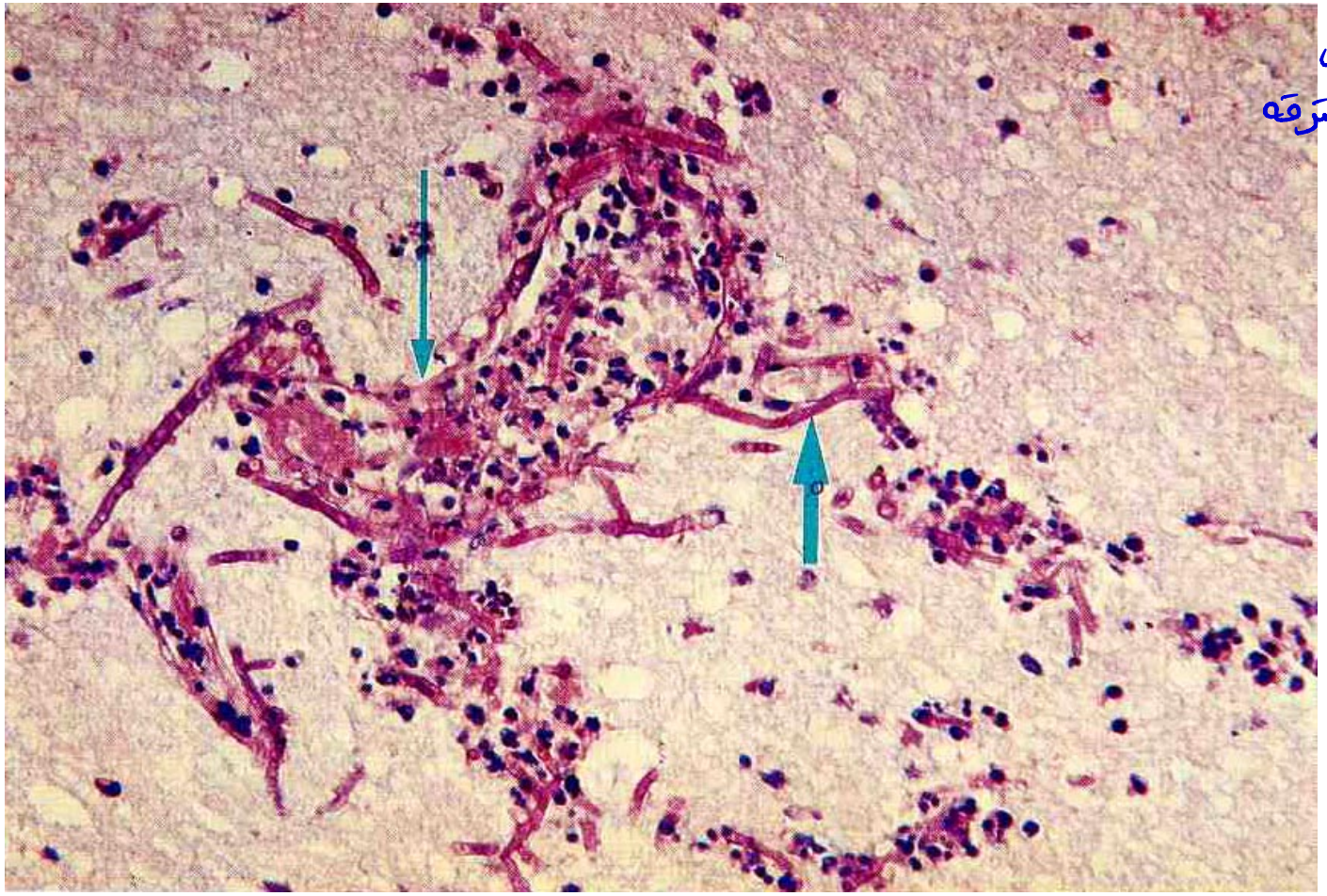
• Although most fungi invade the brain by **blood dissemination**,

• 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**.

يعني بركب عالـ embolus وبنتقل إلى أماكن أخرى.

◘ 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.



بتعيش داخل
ال vein و بتخرقه

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

Prion Diseases

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

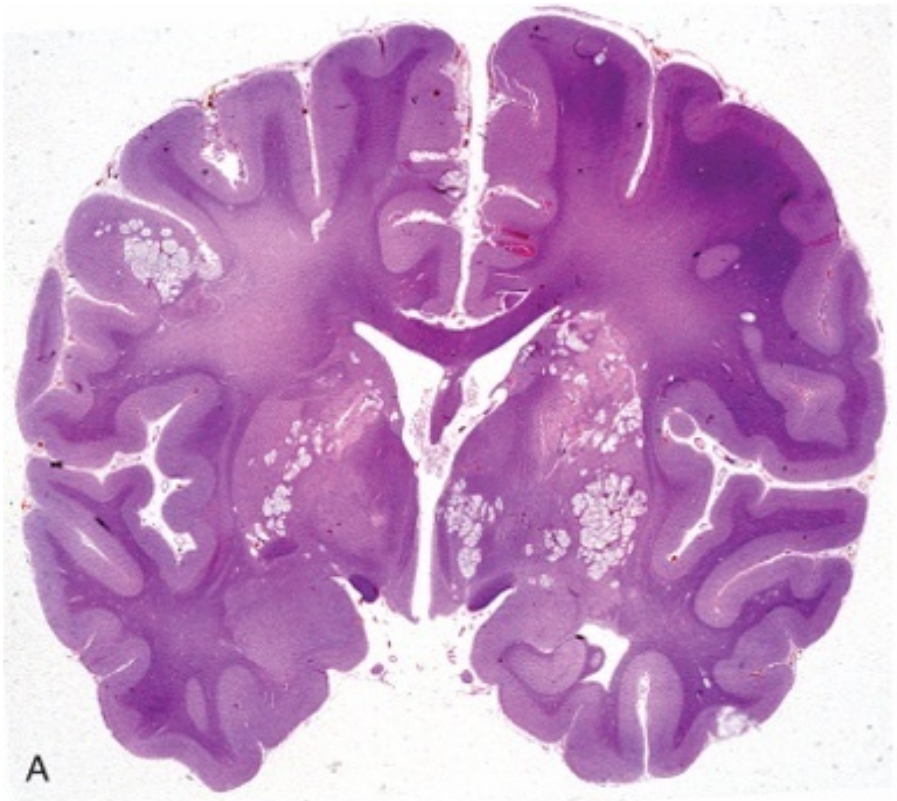
★ Several animal diseases from this group are also known, including **scrapie in sheep & goats; & bovine spongiform encephalopathy in cattle ("mad cow" disease).**

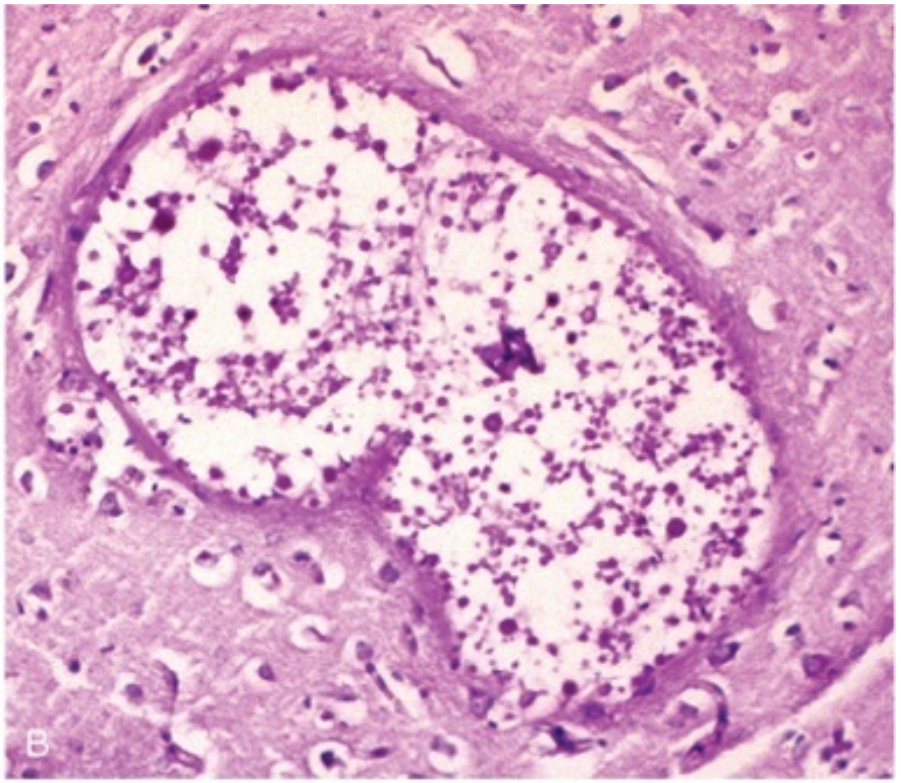
★Prion disease represents a form of protein-induced transmissible disease that is unique to the CNS.

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

F23-19: **Cryptococcal infection.** Inhalation of the yeast from the environment (pigeon droppings) may produce lesions in the lung, which in immune depressed patient may spread to the CNS, causing meningo-encephalitis.

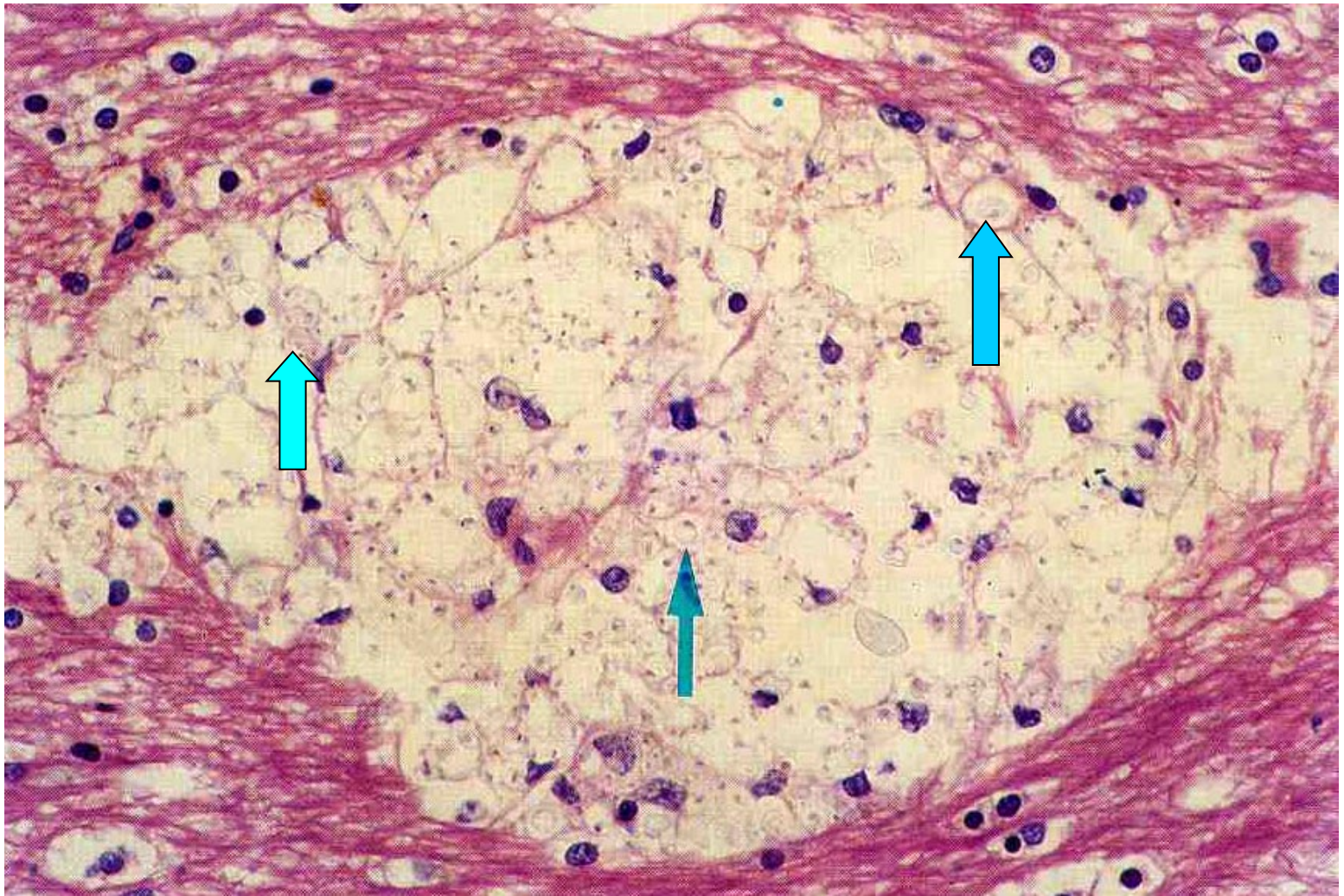
A, Brain section showing many areas of tissue destruction associated with the spread of organisms in the perivascular spaces. **B, Cryptococci** in the lesions at higher magnification.





◘ 4.11: **Cryptococcosis (neoformans) : brain X360.**

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



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

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

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

☹ The **infectious nature** of PrPsc protein comes from this ability to propagate the pathologic conformational change.

★ The conformational change can occur:

(I) **spontaneously** at an extremely low rate & accounts for **sporadic cases** of prion disease **(1per million person).**

(II) If there is a **mutation** in the gene encoding PrPc, then the change can occur at a higher rate; this results in **familial forms** of prion disease.