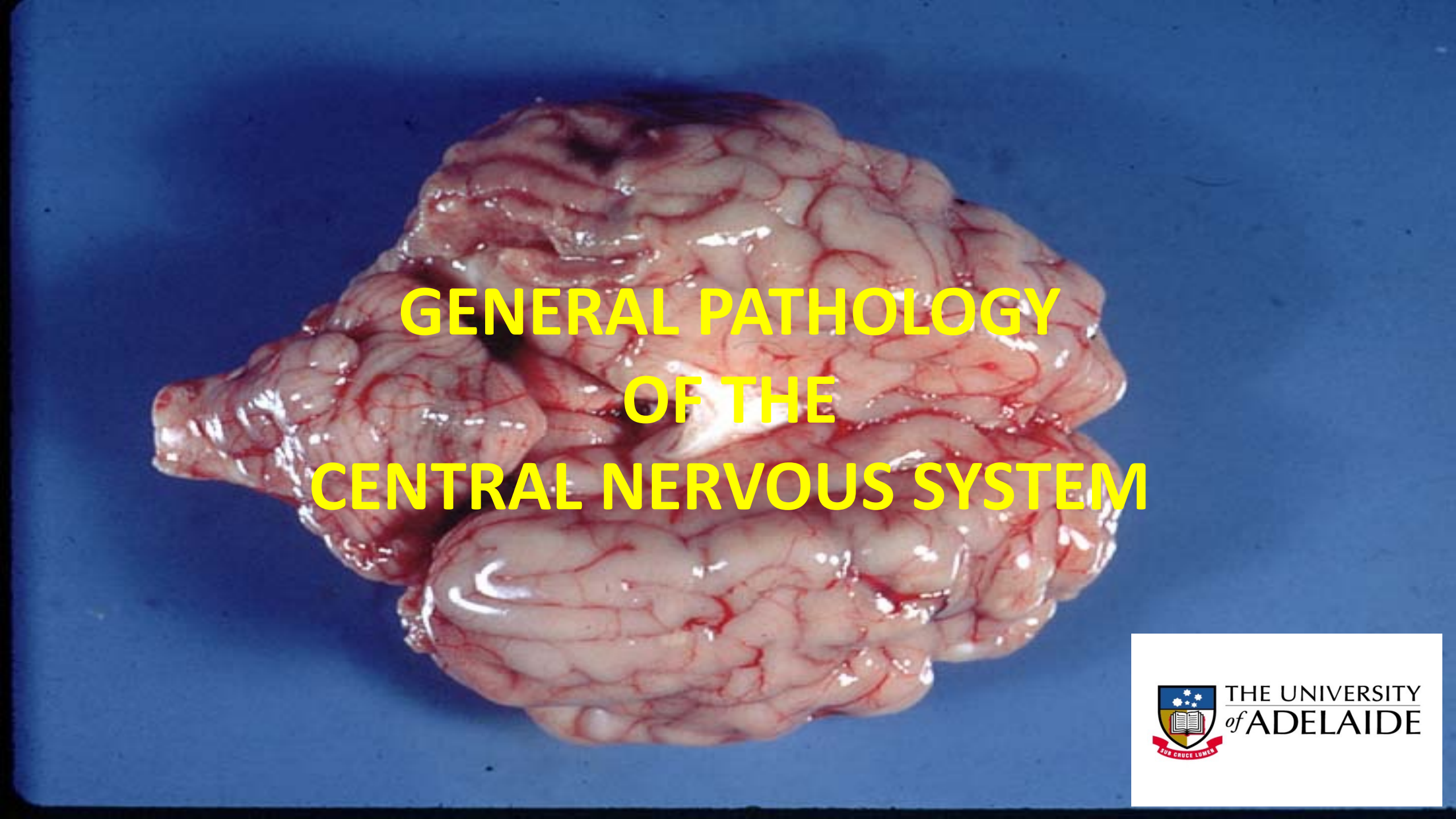

GENERAL PATHOLOGY OF THE CENTRAL NERVOUS SYSTEM

THE UNIVERSITY of ADELAIDE

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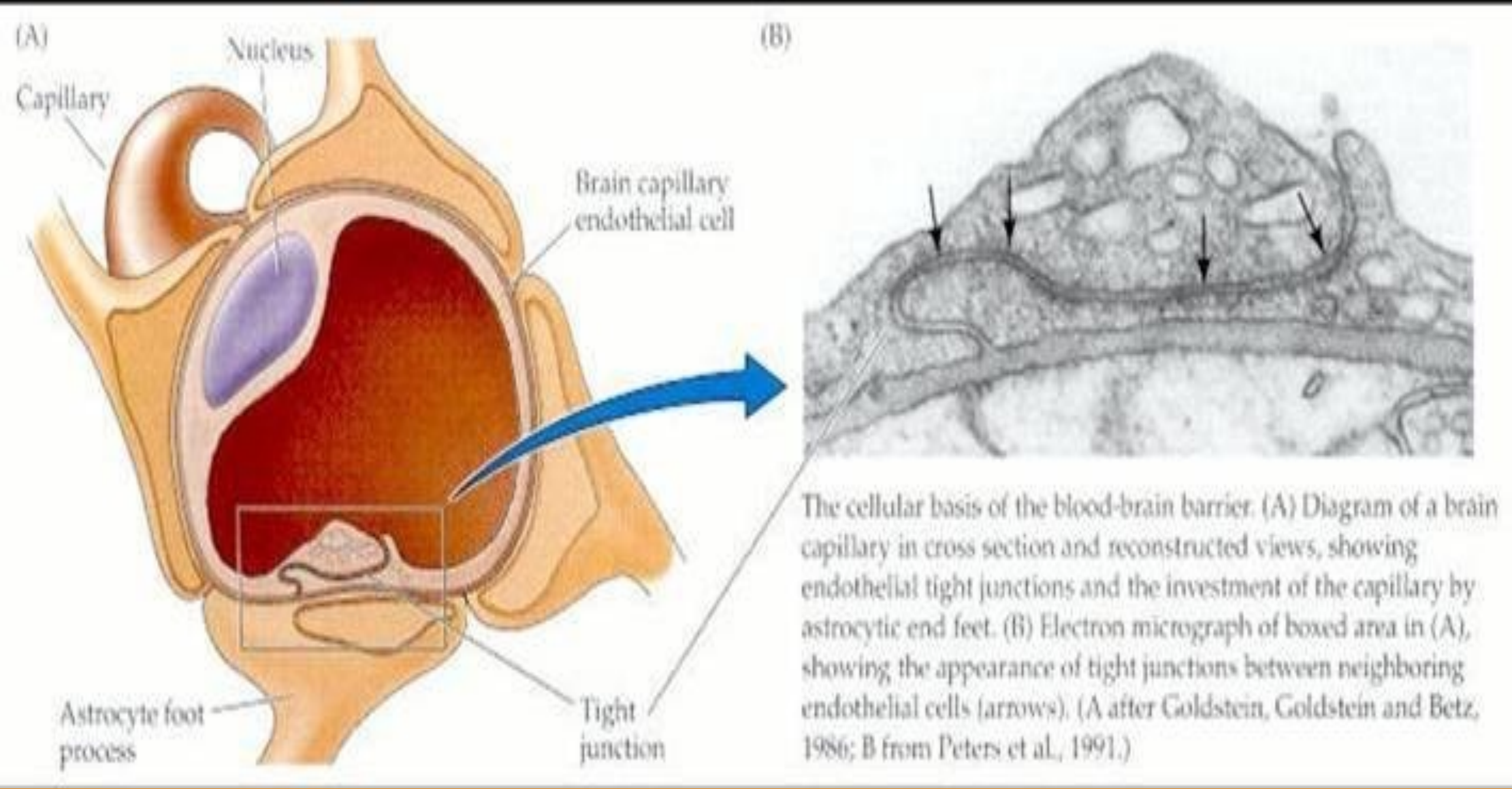
Blood-Brain Barrier (BBB)

Dynamic interface between blood and brain, maintaining homeostasis in the CNS

Permeability properties due to the capillary endothelium – especially interendothelial tight junctions + lack of micropinocytotic vesicles + astrocytic end-feet which cover most of the capillary surface (differ from endothelia elsewhere)



The cellular basis of the blood-brain barrier. (A) Diagram of a brain capillary in cross section and reconstructed views, showing endothelial tight junctions and the investment of the capillary by astrocytic end feet. (B) Electron micrograph of boxed area in (A), showing the appearance of tight junctions between neighboring endothelial cells (arrows). (A after Goldstein, Goldstein and Betz, 1986; B from Peters et al., 1991.)


Astrocytic foot processes completely
cover surface of capillaries and form part of
BBB regulation

BBB

Small molecules (O_2, CO_2) and lipophilic agents (barbiturates, ethanol) diffuse freely through BBB

Specific transport systems regulate transendothelial traffic of small hydrophilic molecules

<u>Neurogliovascular units</u> – complex signalling permits neuronal activity to be signalled to endothelium (directly or via astrocytes) to regulate blood flow and increase efficiency of nutrient supply/waste excretion and maintain optimum ionic composition for synaptic and axonal function

Ischaemia-hypoxia

Energy to sustain high CNS metabolic rate is oxidative to form high energy phosphates needed to maintain ion gradients, axoplasmic transport, and synthesis of cellular components and neurotransmitters

Significant dysfunction occurs when hypoxia is combined with blood perfusion failure (ischaemia) = ISCHAEMIC-HYPOXIC ENCEPHALOPATHY

Ischaemia is especially damaging – oxygen/nutrient deprivation + failure to remove toxic metabolic wastes

Ischaemia-hypoxia

Ischaemic-hypoxia is the commonest cause of cerebral necrosis

Usually related to perfusion failure, which can be:

focal (especially when the collateral circulation is incomplete) or global (e.g. cardiac failure)

Ischaemia-hypoxia

Reduced substrate delivery (especially oxygen, glucose) causes reduced ATP, leading to membrane pump failure, influx of Ca ions (neurotoxic), cellular swelling, and death by necrosis or apoptosis (the latter particularly when ischaemia is brief)

Ca ions are essential messengers in many cellular processes, but are often also a common pathway to cell death, impeding nearly all anabolic and metabolic cell functions when in excess

Free radical and excitotoxic amino acid (glutamate and aspartate) release is also damaging

Ischaemia-hypoxia

Global cerebral ischaemia (e.g. cardiac arrest) occurs when cerebral perfusion pressure (mean arterial BP minus ICP) falls below a certain threshold due to increased ICP or decreased arterial BP

Cerebral oedema is an important sequel to ischaemia-hypoxia and raises ICP

Ischaemia-hypoxia

If the circulation is restored after protracted ischaemia-hypoxia, further neural damage can occur (termed ischaemia reperfusion injury)

Spectrum of damage occurs from ischaemia-hypoxia, ranging from selective neuronal necrosis (type of excitotoxic injury 2º to excess glutamate) to pannecrosis (infarction)

Selective vulnerability

Expression of ischaemia-hypoxia very variable because:

Brain is not uniformly affected

Certain regions (cerebral & cerebellar cortices, hippocampus, & caudate-putamen) are more sensitive

GM more vulnerable than WM

Selective vulnerability to ischaemia-hypoxia

Sensitivity (in descending order):

Neurons

Oligodendrocytes

Astrocytes

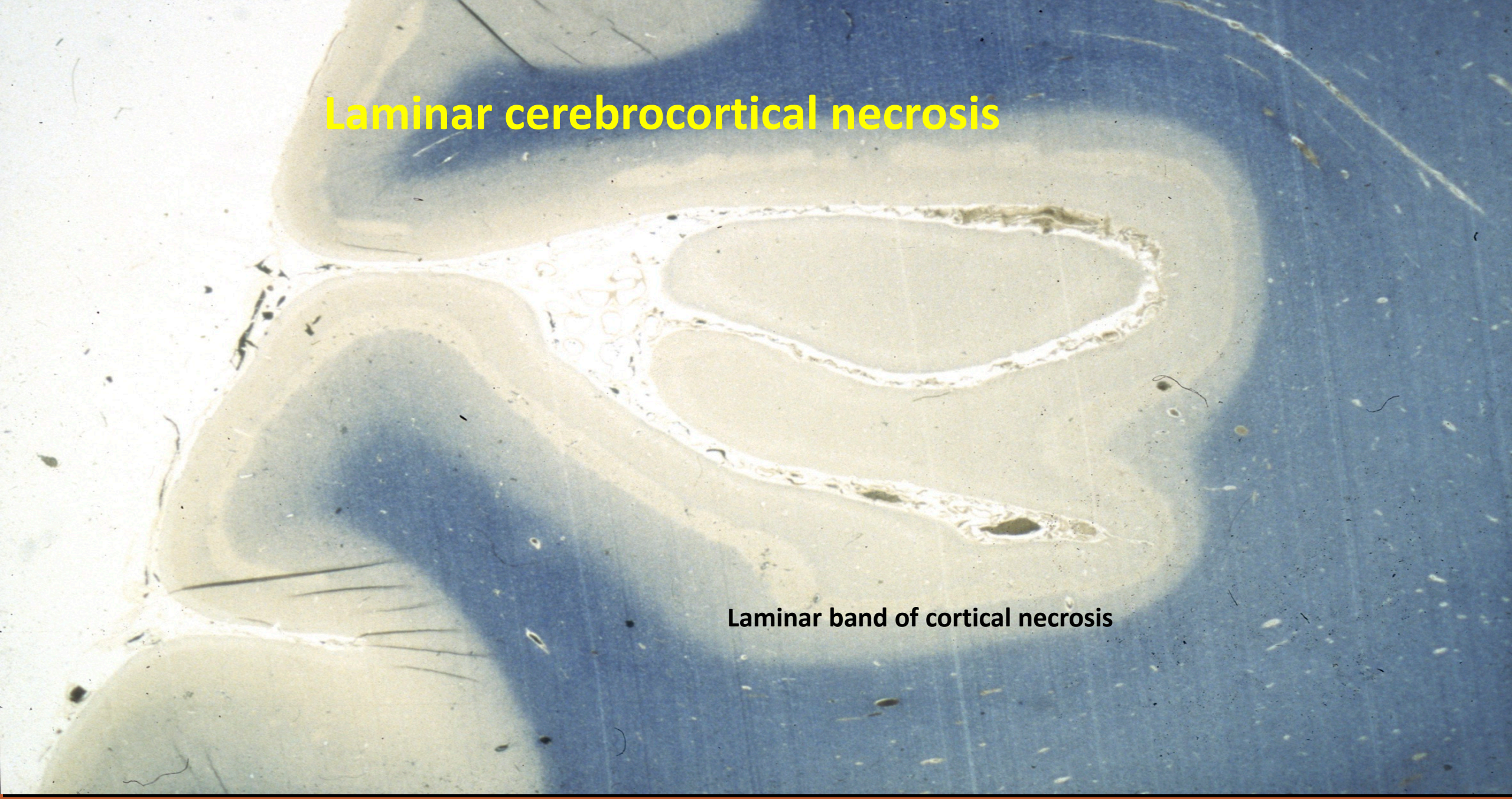
Microglia and vascular endothelium

Sensitivity to ischaemia-hypoxia

Middle laminae of cerebral cortex more vulnerable = laminar cortical necrosis (in fact, usually pseudolaminar as >1 lamina affected)

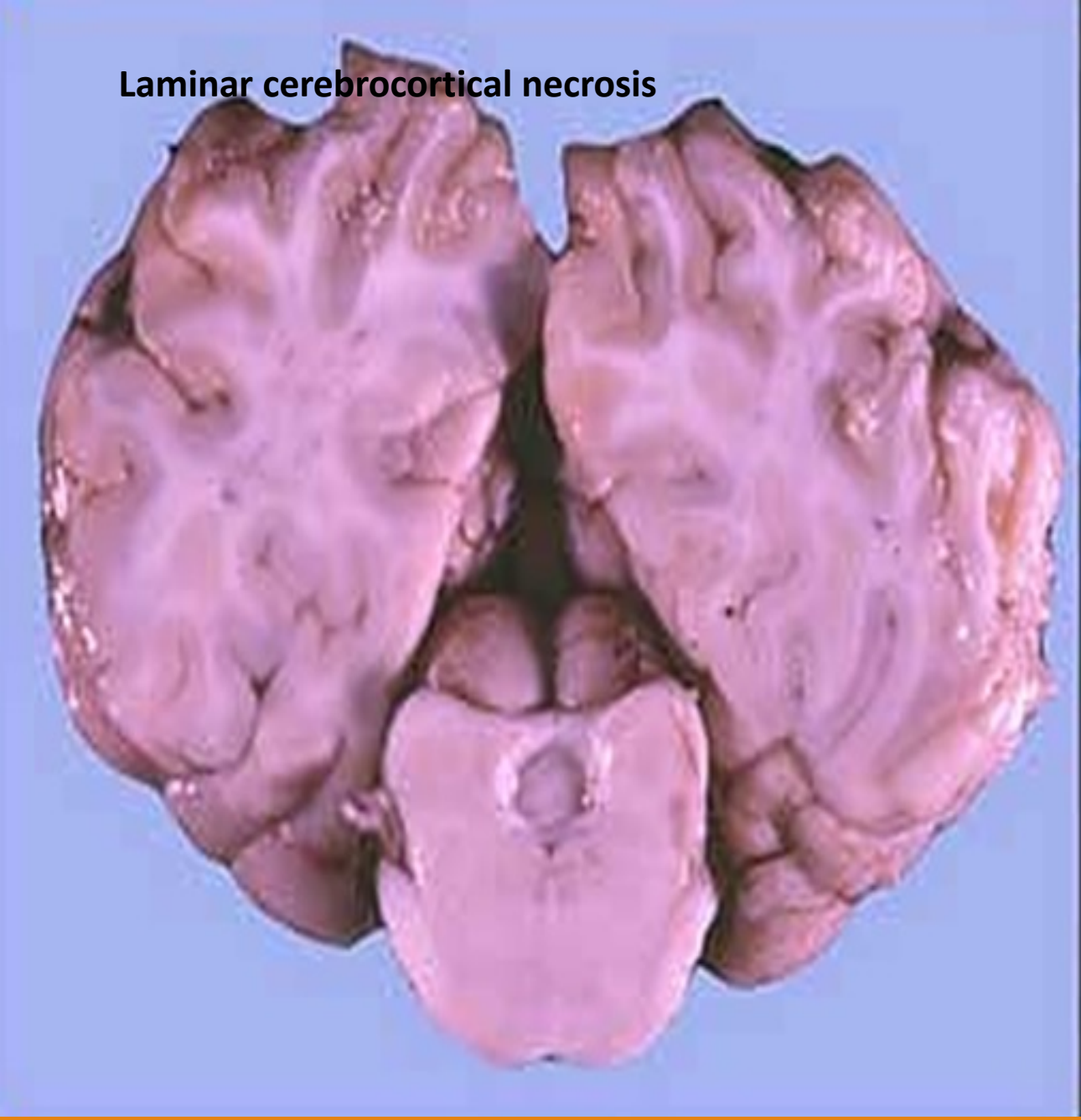
Also cerebellar Purkinje cells and hippocampal pyramidal layer + central grey matter (caudate-putamen and thalamus)

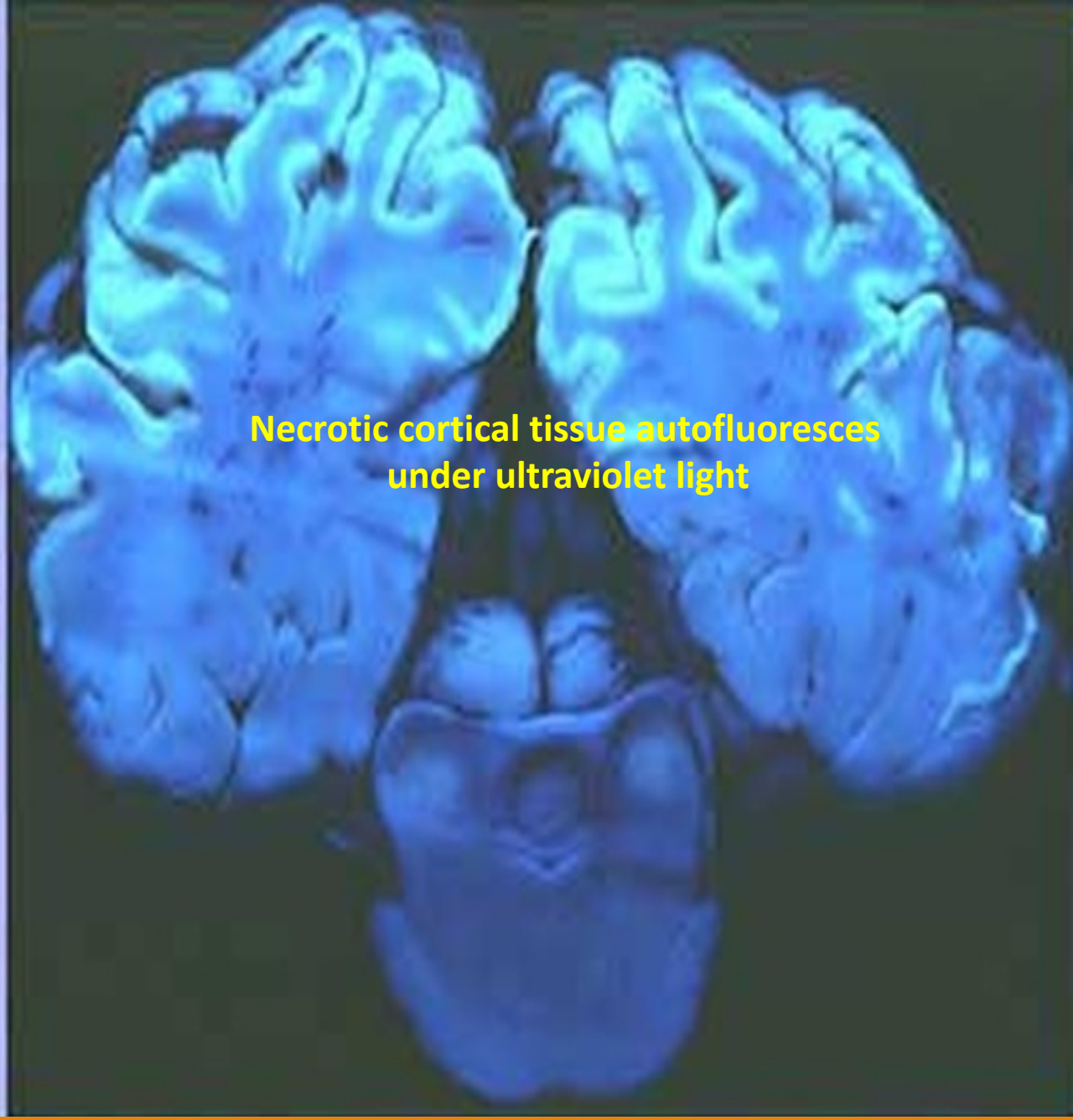
Laminar cerebrocortical necrosis



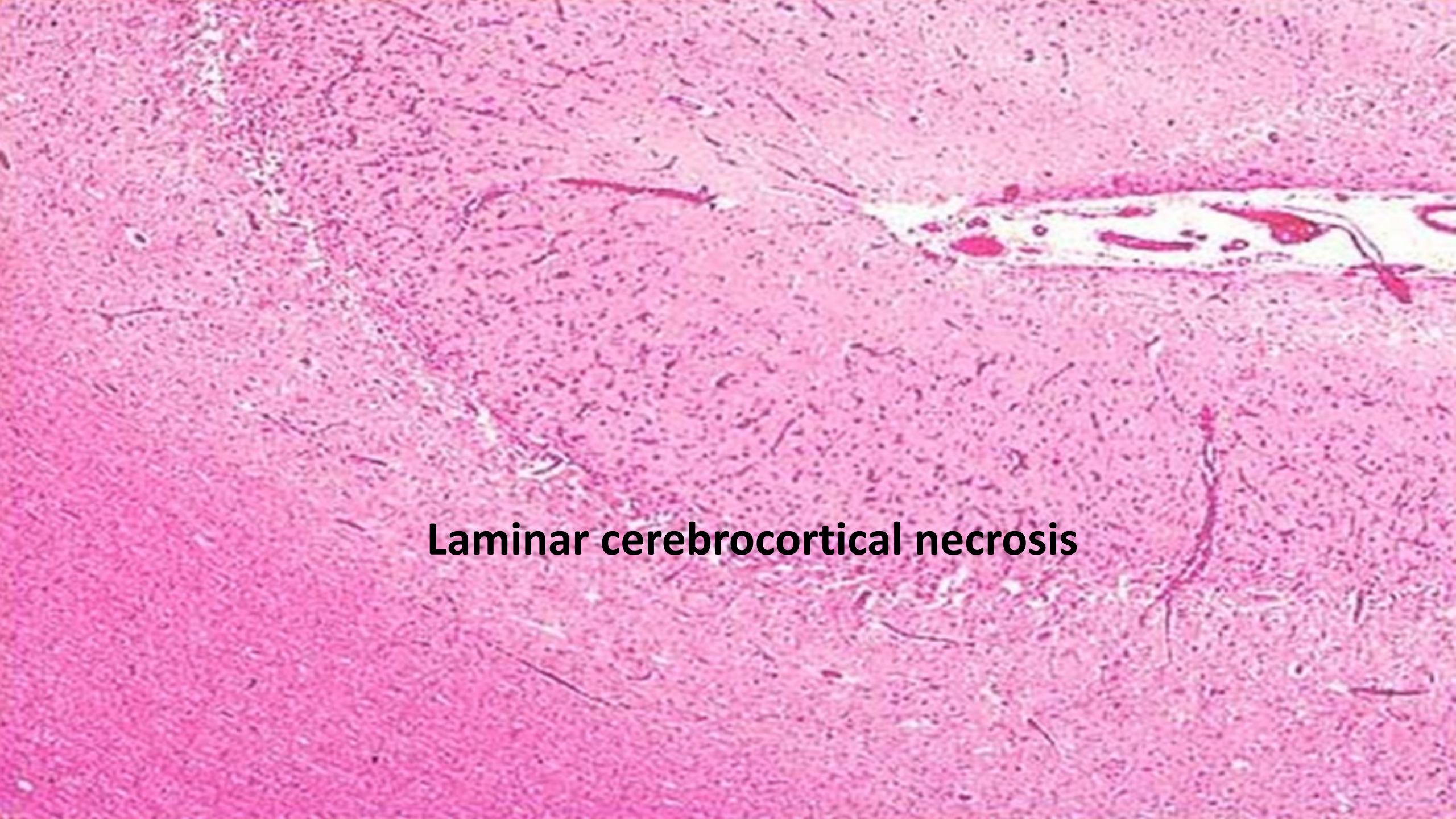
Laminar band of cortical necrosis

Laminar cerebrocortical necrosis

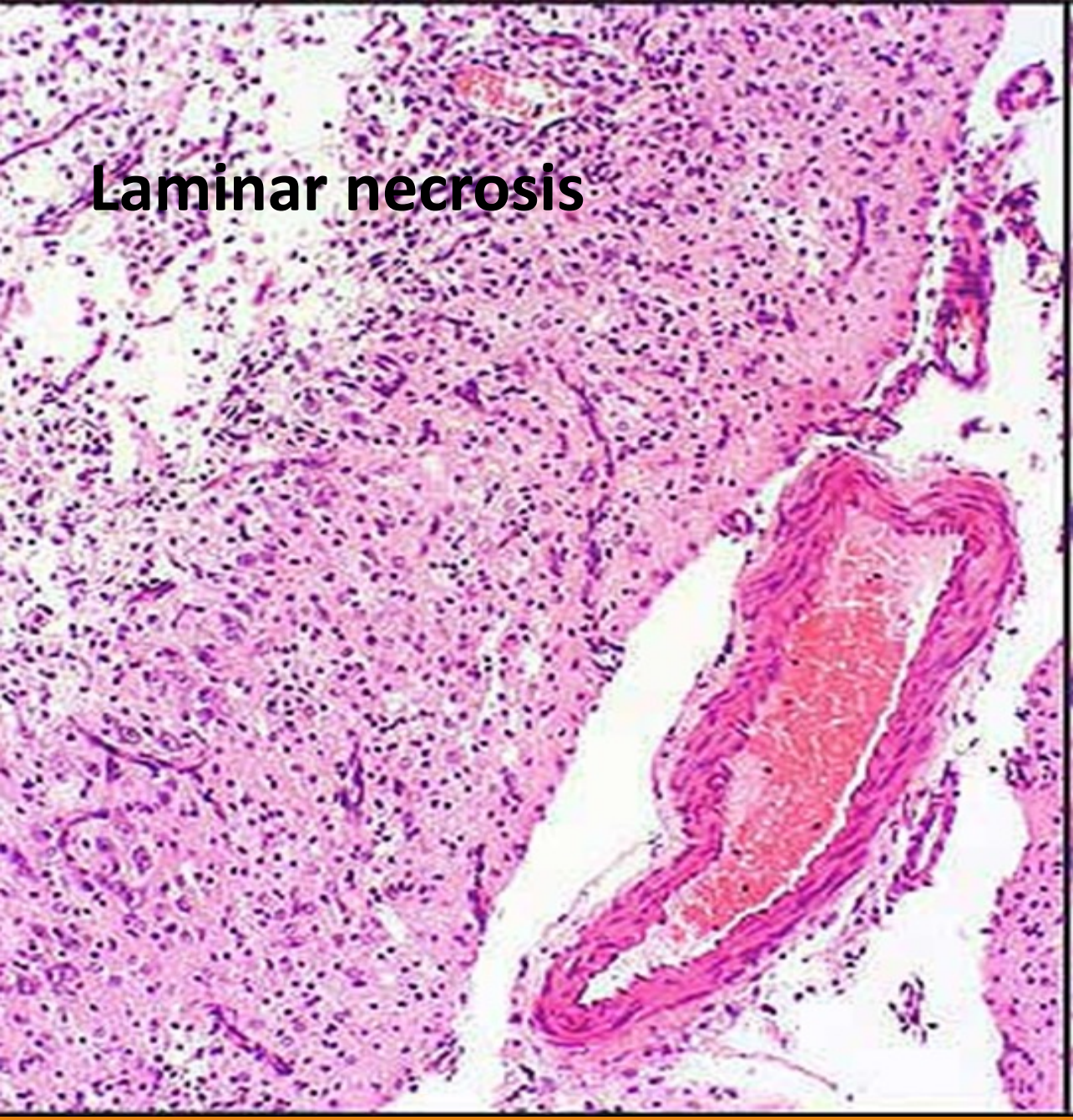




Necrotic cortical tissue autofluoresces under ultraviolet light



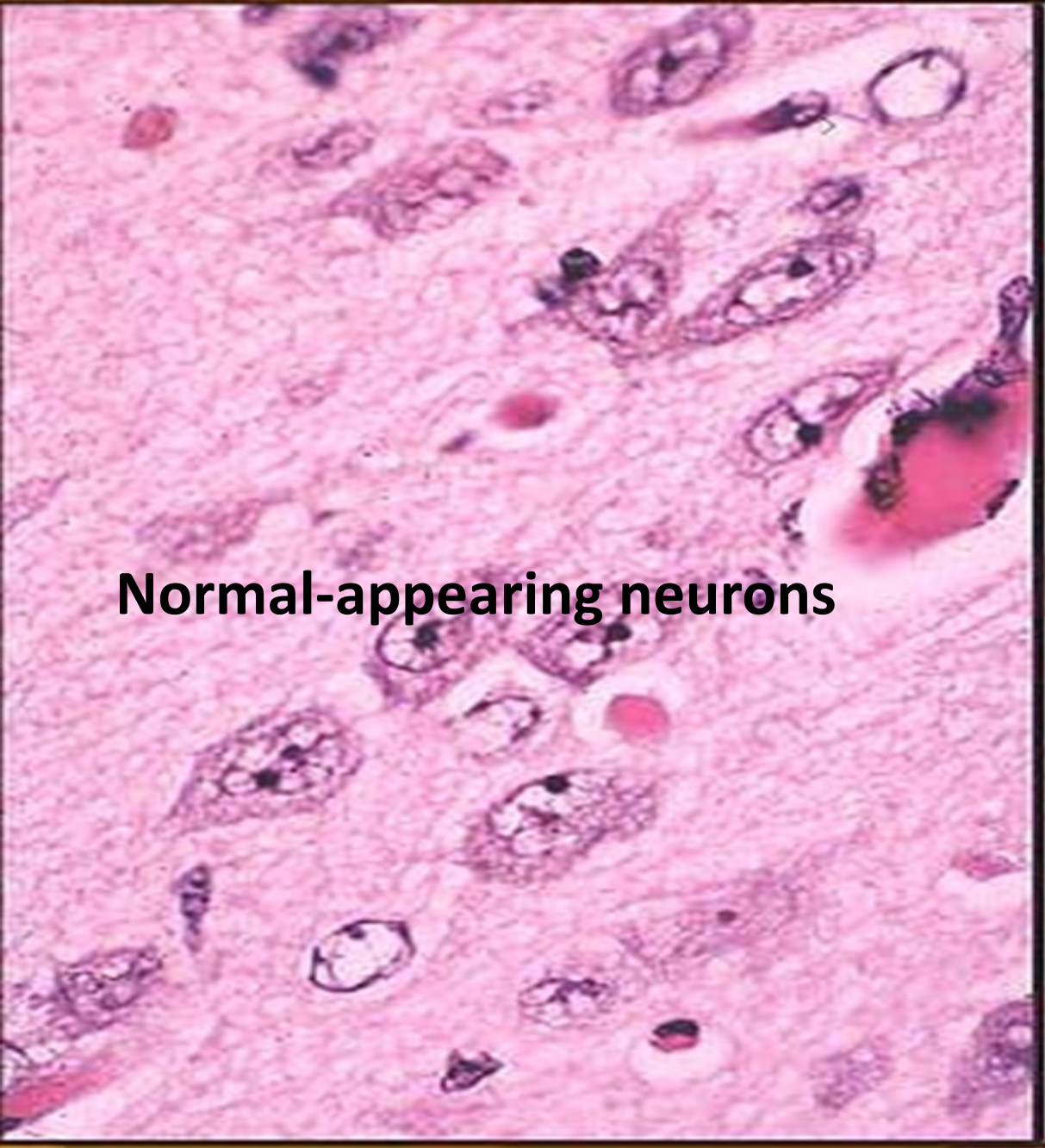
Laminar cerebrocortical necrosis

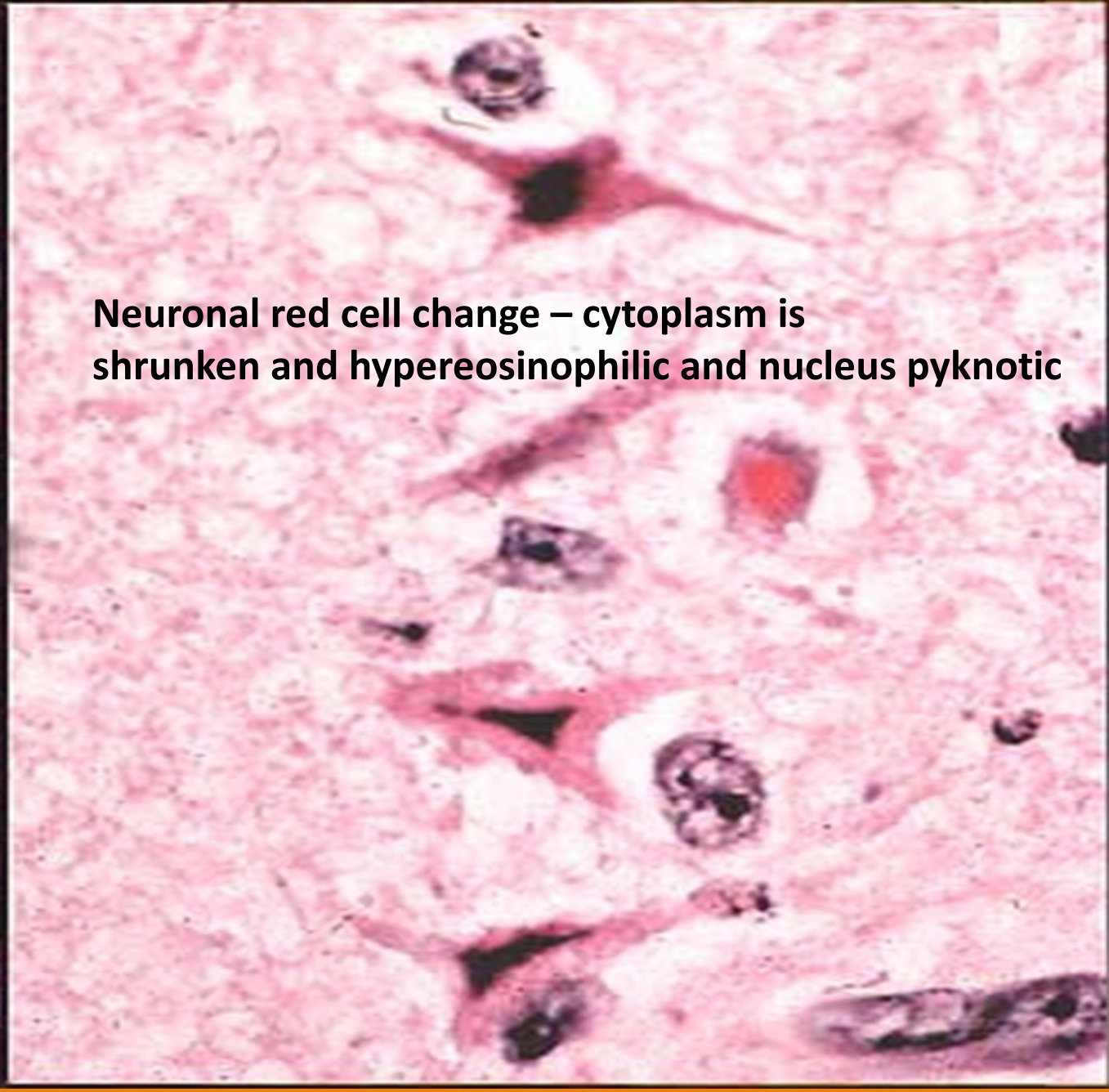

Laminar necrosis


Macrophages containing necrotic debris

Ischaemic-hypoxic neuronal change

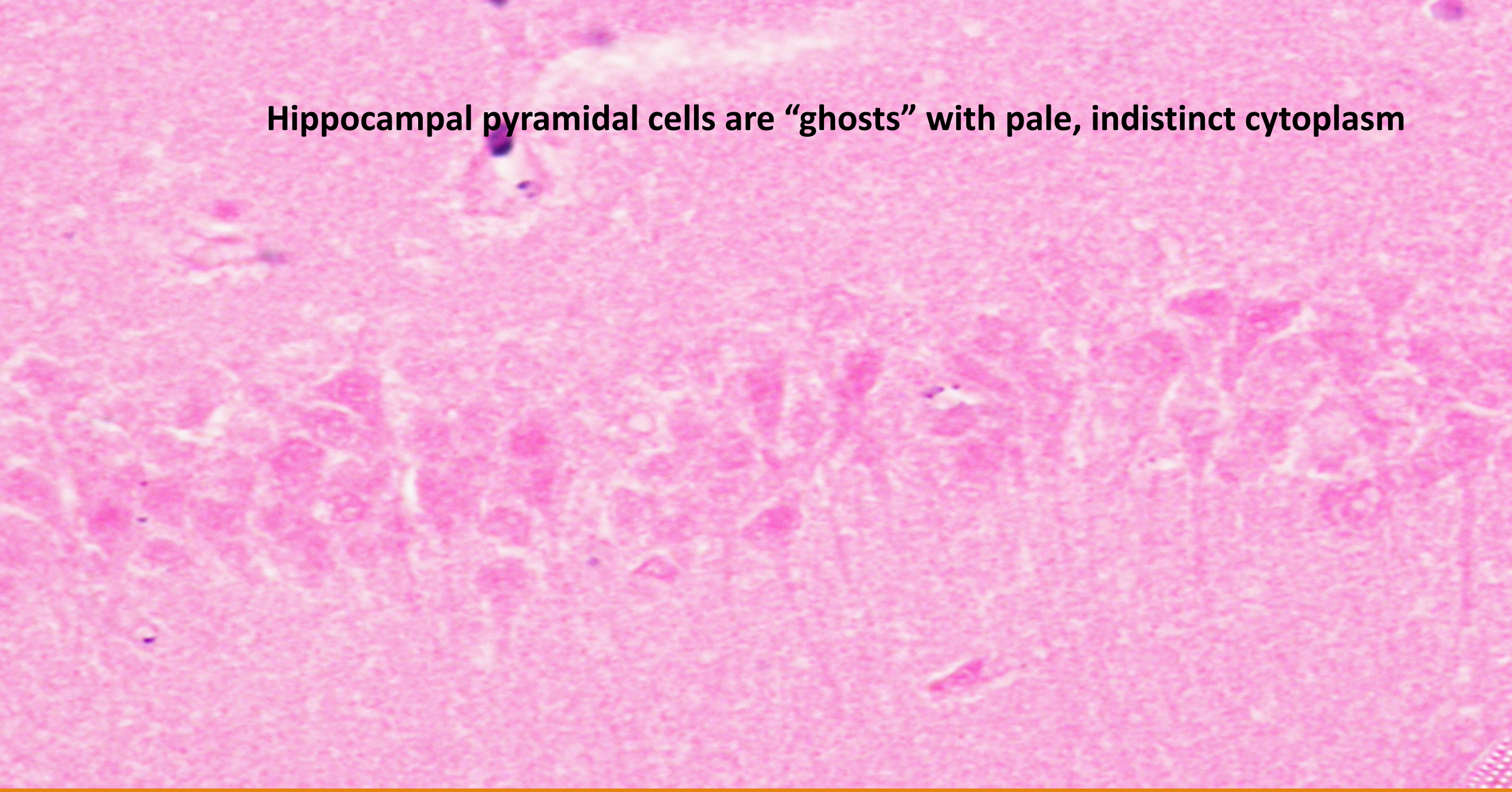
Produces tinctorial changes in neuronal cytoplasm (hypereosinophilia) = neuronal red cell change (acidophilic or eosinophilic change or ischaemic cell change, the latter best avoided since this neuronal change is not restricted to ischaemic insults)


Normal-appearing neurons


Neuronal red cell change – cytoplasm is
shrunken and hypereosinophilic and nucleus pyknotic

Ischaemic-hypoxic neuronal change

Red neurons eventually develop into homogenising cell change with homogeneous cytoplasmic staining and progressive loss of staining intensity, the latter resulting eventually into "ghost cells"



Hippocampal pyramidal cells are “ghosts” with pale, indistinct cytoplasm

Ischaemia-hypoxia

Global ischaemia eventually compromises vital brainstem centres, causing cardiorespiratory arrest + cerebral oedema (which raises ICP)

Space-occupying lesions

Haematomas, tumours and abscesses often cause BBB breakdown and severe cerebral oedema

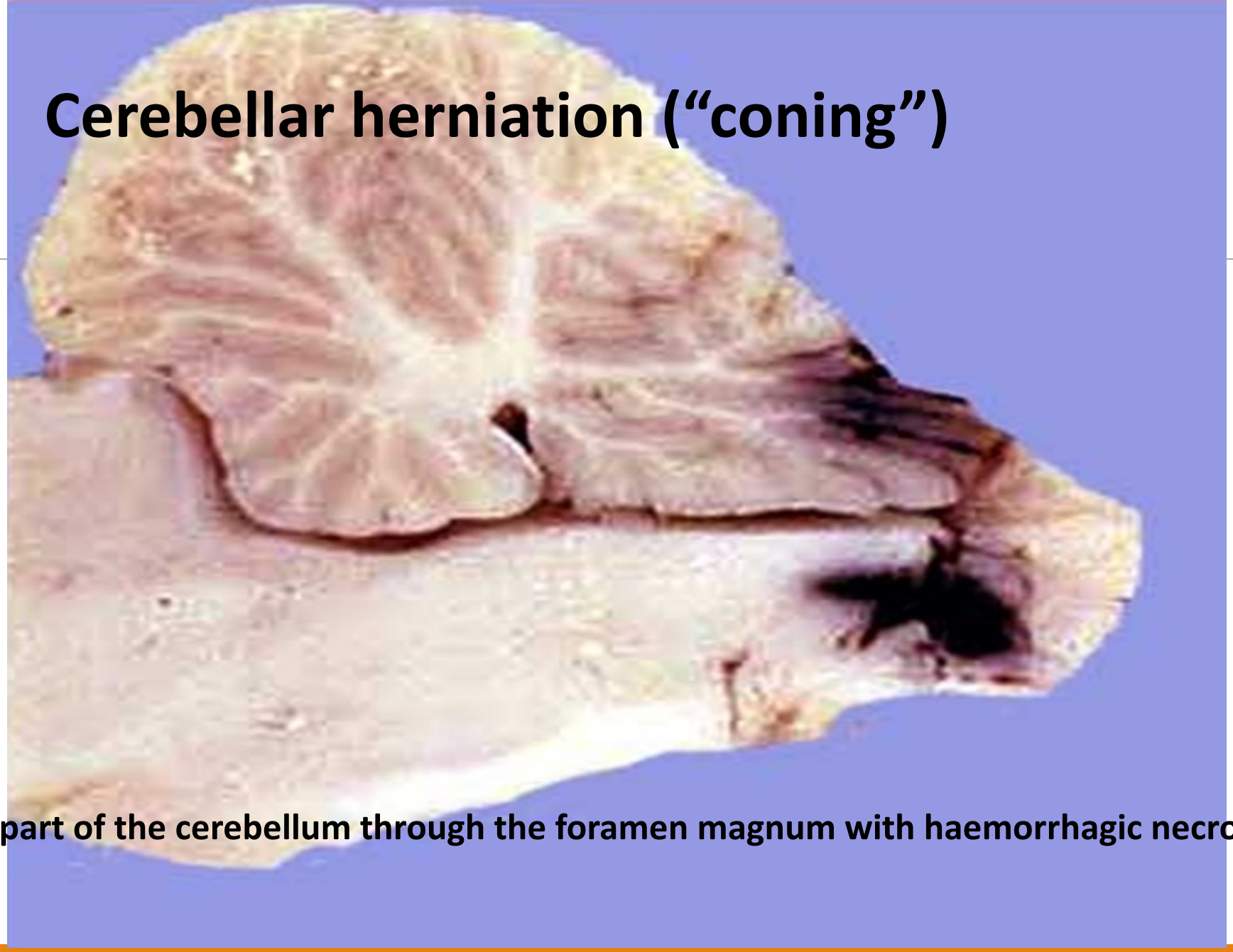
Mass effect of lesion + oedema (+/- CSF obstruction and hydrocephalus) causes increased ICP, one of main factors determining clinical outcome

Monro-Kellie doctrine

Because the brain is encased in a rigid bony skull, any volumetric change to one of intracranial constituents (brain, CSF, blood) must be compensated for by a reciprocal and equivalent decrease in other constituents

Eventually, raised ICP causes marked reduction in cerebral blood perfusion of brain, brainstem compression, and herniation (movement of brain from one compartment to another), commonly downward protrusion and impaction of cerebellar tonsils, which descend through foramen magnum into cervical canal (cerebellar coning)

Cerebellar herniation (“coning”)



Protrusion of part of the cerebellum through the foramen magnum with haemorrhagic necrosis

NEOPLASIA (TUMOURS, CANCER)

Hallmarks of cancer

Sustaining proliferative signalling

Evading growth suppressors

Activating invasion and metastasis

Induction of new blood vessel formation

Enabling replicative immortality

Resisting cell death

Reprogamming energy metabolism

Evading immune destruction

Tumour nomenclature

The nomenclature reflects the cell of origin, either mesenchymal or epithelial

Mesenchymal tumours arise in cells of embryonic mesodermal origin, benign tumours given the suffix *–oma* (e.g. fibroma) and malignant tumours the suffix *–sarcoma* (e.g. fibrosarcoma). Tumours arising from circulating blood cells or their precursors = *leukaemias*

With epithelial tumours, benign have suffix *–oma*, while those arising from glandular epithelium are termed *adenomas*. Malignant tumours of epithelial origin = *carcinomas*, and *adenocarcinomas* if expressing a glandular pattern

Tumour nomenclature

Carcinoma *in situ* is a pre-invasive form of carcinoma restricted to its normal site

When the histological appearance of tumours gives no clue as to their cell of origin = undifferentiated neoplasms

Hamartomas are tumour-like lesions showing disorganised proliferation, but composed of mature cells in their normal location (especially common with blood vessels)

Choristomas are composed of normal tissue occurring at an ectopic site

Benign tumours

Well-differentiated with a similar structure to the tissue of origin

Little or no anaplasia (cellular atypia)

Slow progressive expansion

Mitotic figures rare

No invasion, but cohesive, expansile growth

Often encapsulated

No metastasis

Malignant tumours

Lack some differentiation and their structure is often atypical

Variable anaplasia

Slow-to-rapid, erratic growth

Mitotic figures often numerous and sometimes atypical

Local infiltration; usually not encapsulated

Often contain necrotic areas (where growth exceeds the capacity of the blood supply to sustain tumour cells)

Frequent metastasis (but those of the CNS very rarely metastasise, but are notably invasive)

Neoplasia

Anaplastic cells are poorly differentiated and show cellular and nuclear pleomorphism (variation in size and shape). Nuclei are often hyperchromatic (dark staining) due to increased DNA content, are generally larger, and often have prominent nucleoli

Most carcinomas metastasise via lymphatics, while sarcomas favour the haematogenous route

Metastasis requires invasion of the extracellular matrix (ECM), entry into lymphatics/blood vessels, extravasation, and colonisation at a distant site

Neoplasia

Once lymphatic/vascular invasion has occurred, tumour cells aggregate as emboli and the ultimate site of lodgement is determined by the pattern of vessel distribution and ability to interact with adhesion molecules on endothelial cells + metastatic sites must provide a suitable microenvironment for tumour cell growth

Astrocytoma showing nuclear pleomorphism with a large nucleus (arrowed) and an abnormal mitotic figure (double arrow)

Neoplasia

Some tumours preferentially metastasise to specific tissues (e.g. prostatic carcinomas to bone)

Tumour cells are supported by non-neoplastic extracellular connective tissue (stroma) and they interact with the stroma in a complex manner via signalling molecules to control growth and differentiation. When stroma contains excessive amounts of collagen = scirrhous or desmoplastic response

Tumour-associated fibroblasts may also differentiate into myofibroblasts with contractile properties

Tumour neovascularisation

In tumours up to ~1-2 mm diameter, diffusion from pre-existing host vessels provides oxygen and nutrients and eliminates waste products of tumour metabolism – steady state between tumour cell proliferation and apoptosis (avascular or dormant phase)

But, due to rapid tumour proliferation and vascular insufficiency, tumours eventually become hypoxic and necrotic, precipitating a vascular phase, which is largely driven by hypoxia

New blood vessel formation (neovascularisation) is critical to continued tumour growth and dissemination and controlled by pro-angiogenic factors such as VEGF (vascular endothelial growth factor)

Brain tumours

Relatively rare in adults, but often rapidly fatal

Second leading cause of cancer-related death in children and young adults

Most primary brain tumours arise in glial cells

WHO grading system for brain tumours

Grade I – slow growing, well-differentiated, often long-term survival

Grade II – relatively slow growing, less well-differentiated, may invade contiguous parenchyma, and sometimes recur

Grade III – faster growing, rather poorly differentiated, infiltrative and recurring

Grade IV – rapid growth, very poorly differentiated; necrotic areas, incites neovascularisation to promote growth

Brain tumours in adults

Astrocytoma – Grade I or II (low grade); III (high grade, anaplastic); IV (glioblastoma or glioblastoma multiforme)

Oligodendroglioma – grades II or III

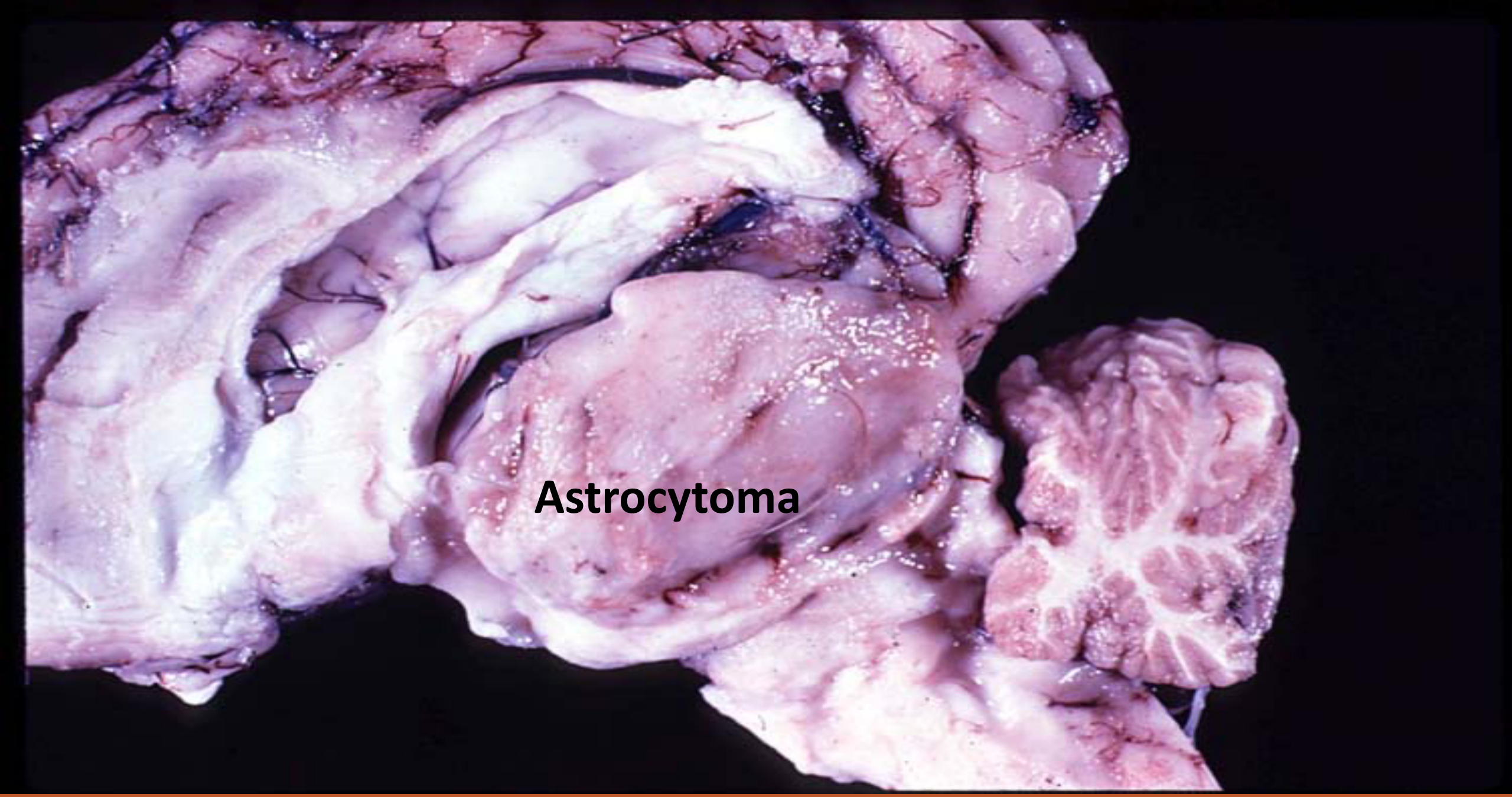
Meningioma – grades I-III; usually benign and slow growing

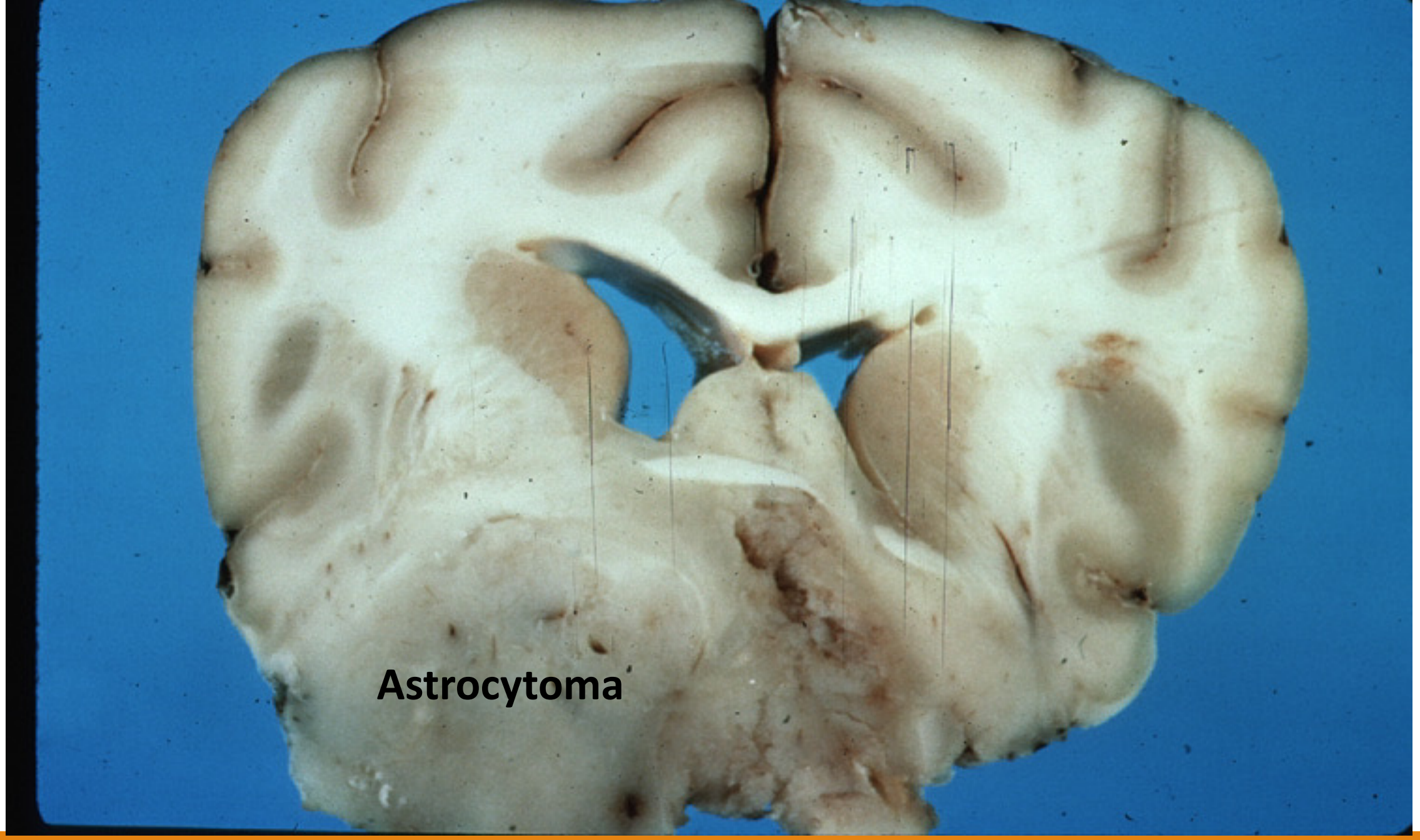
Brain tumours in children

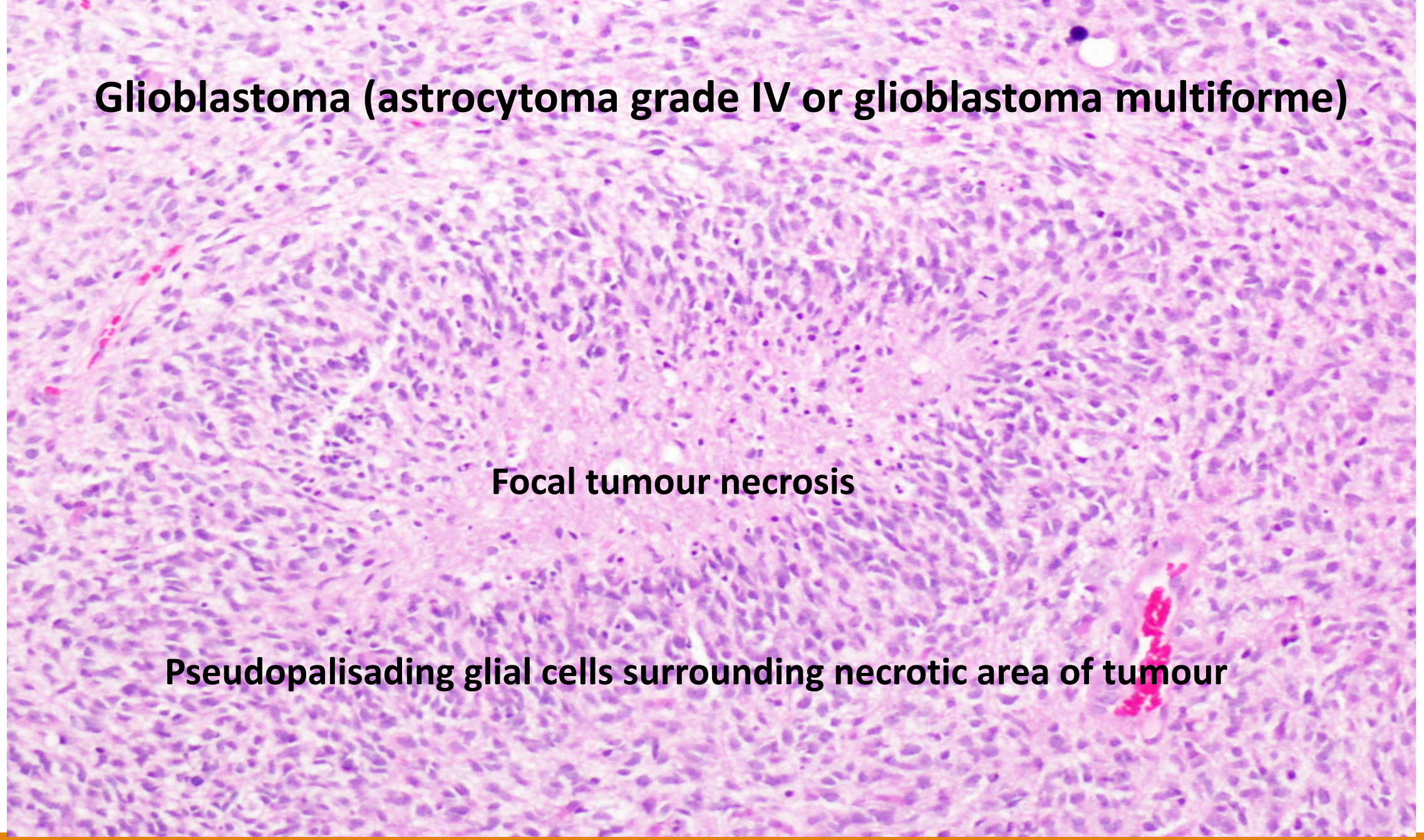
Medulloblastoma (primitive neuroectodermal tumour) - grade IV

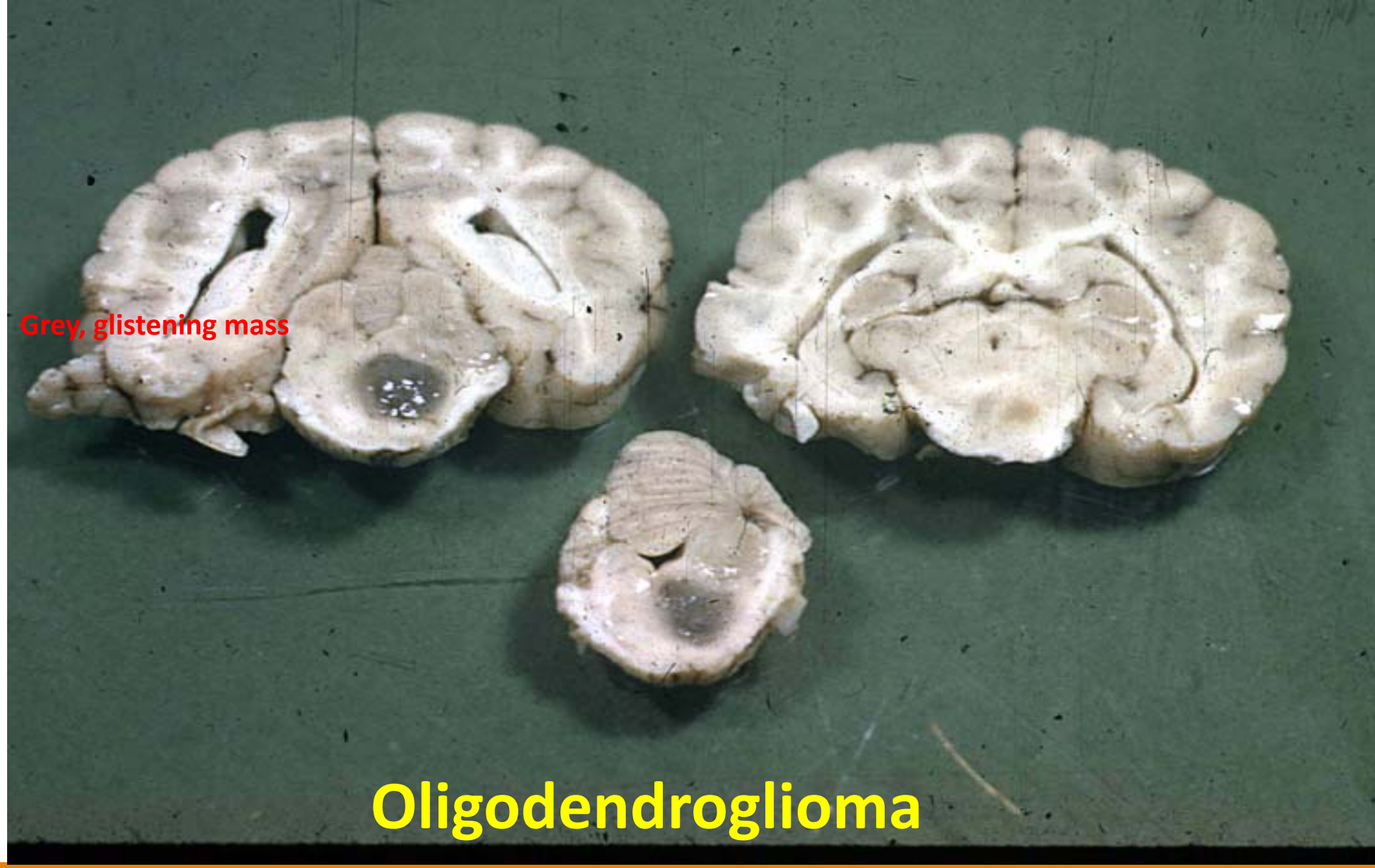
Astrocytoma – usually grades I or II

Ependymoma – from ventricular lining (grades I-III)


Astrocytoma


Astrocytoma


Glioblastoma (astrocytoma grade IV or glioblastoma multiforme)
Focal tumour necrosis
Pseudopalisading glial cells surrounding necrotic area of tumour



Oligodendroglioma

Metastatic brain tumours

Incidence (in decreasing order of frequency):

Lung (up to 50%)

Breast

Genitourinary

Bone

Melanoma

Head and neck

Gastrointestinal tract (especially colorectal and pancreatic)

Lymphoma

Metastatic, pigmented malignant melanoma

(note midline shift and
distortion of the brain)

Adaptive changes in tissues

Adaptive changes to increased/decreased demand or tissue loss due to injury can result in:

Hypertrophy – increase in cell size, not number, due to the synthesis of more organelles. Tends to occur in cells that undergo limited replication (e.g. muscle)

Hyperplasia – increase in cell numbers due to increased mitotic division. Cells resemble normal cells. (e.g. epidermis, hepatocytes, intestinal enterocytes, bone marrow)

Adaptive changes in tissues

Atrophy – decrease in cell and tissue size

Metaplasia is a potentially reversible change in which one adult cell type is replaced by another – usually a specialised epithelium is replaced by a less specialised epithelium

(e.g. respiratory ciliated columnar epithelium is replaced by squamous epithelium in the trachea/bronchi after prolonged irritation)

Cerebral oedema

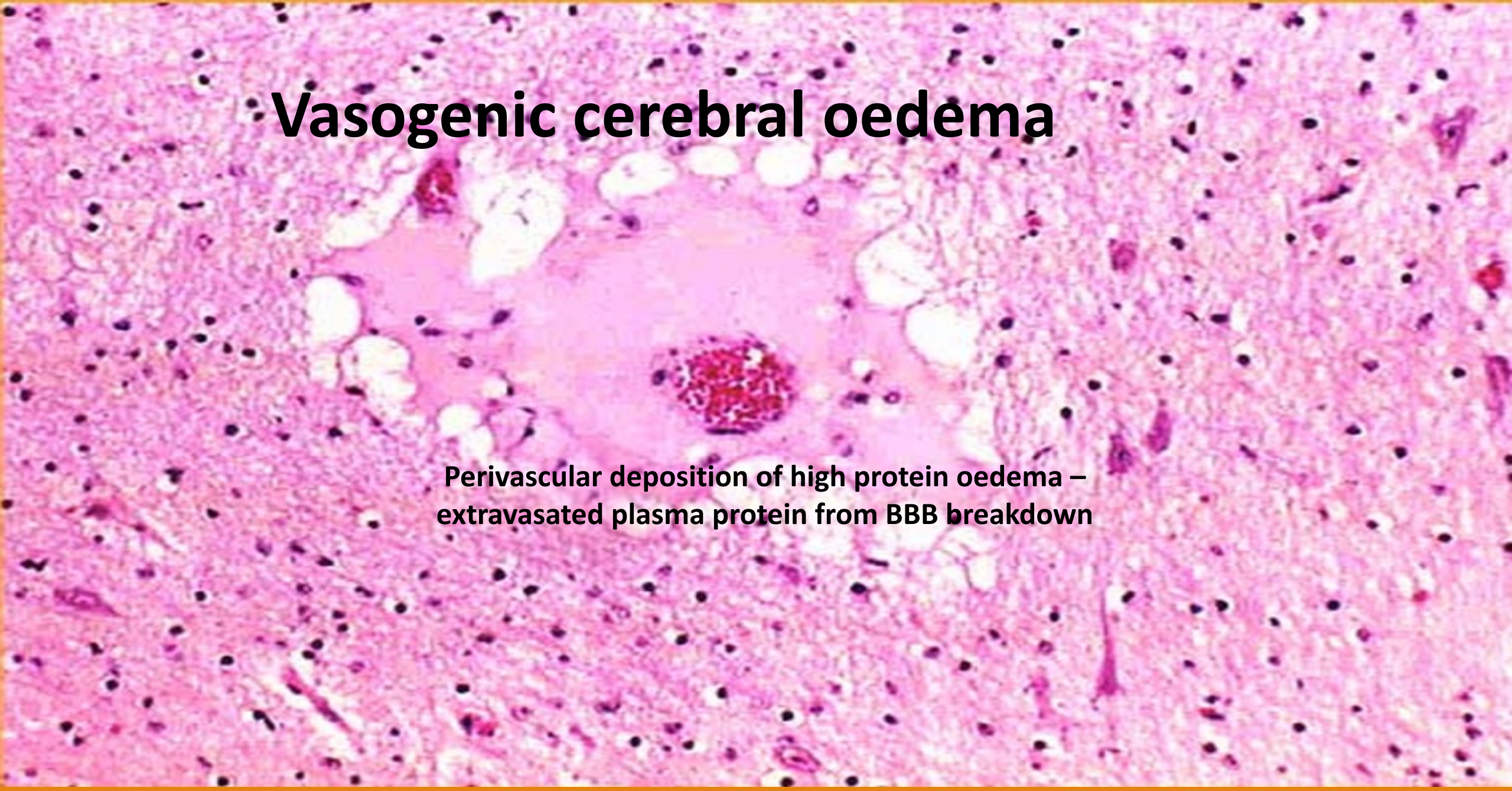
2 main types, both of which are usually present in varying combinations, which can alter over time

Vasogenic (open barrier) oedema – from BBB breakdown, resulting in extravasation of a protein-rich fluid

Cytotoxic (closed barrier) oedema – a transudate, causing intraastrocytic swelling

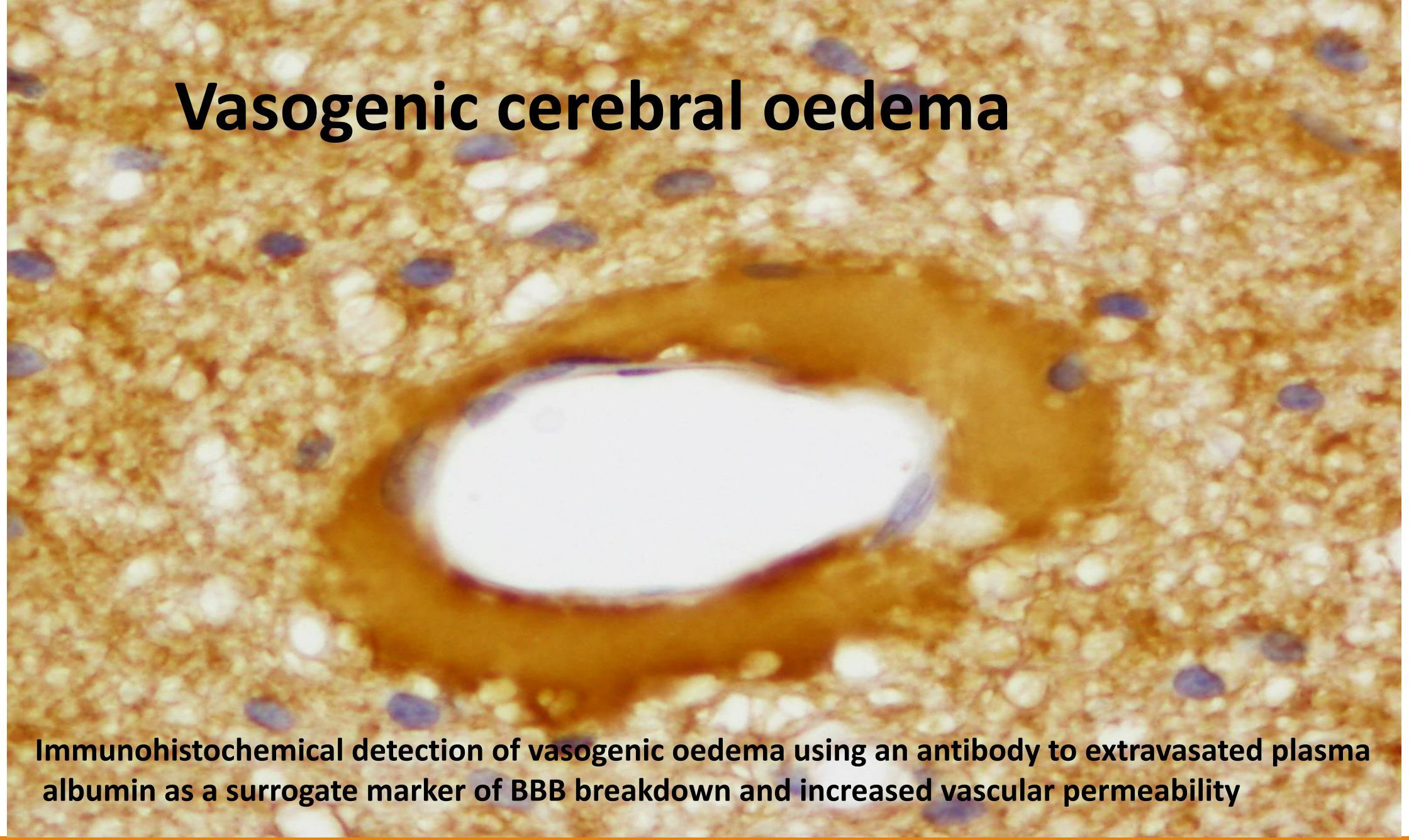
Also obstructive, high-pressure hydrocephalus can cause transependymal seepage of CSF into brain (interstitial oedema)

Vasogenic cerebral oedema



Perivascular deposition of high protein oedema – extravasated plasma protein from BBB breakdown

Vasogenic cerebral oedema



Immunohistochemical detection of vasogenic oedema using an antibody to extravasated plasma albumin as a surrogate marker of BBB breakdown and increased vascular permeability

INFLAMMATION OF THE CNS

Meningo/encephalo/myelitis = inflammation of meninges, brain and spinal cord, respectively

Leptomeningitis = inflammation of pia/arachnoid; **pachymeningitis** = dural inflammation

Ependymitis = inflammation of ependyma (ventricular lining)

Choroiditis = inflammation of choroid plexus

Polio-, leuco, or pan = inflammation of GM, WM, or both

Infectious agents usually produce leucocytic infiltration into perivascular (Virchow-Robin) spaces = **perivascular cuffing**

Type of inflammatory response and likely infectious agent

Neutrophils predominate in bacterial infections (suppurative/fibrinosuppurative)

Lymphocytes predominate in viral infections (non-suppurative), with fewer plasma cells/macrophages

If perivascular cuff contains lymphocytes admixed with plasma cells or other leucocytes, likely to be a response to infection

If perivascular cuff is thick with almost solely lymphocytes, suggests a non-infectious, degenerative disorder

Granulomatous/pyogranulomatous inflammation e.g. systemic mycotic (fungal) infection; granulomatous, e.g. mycobacteria

CNS Inflammation

Combination of compressive perivascular cuffs (+ adventitial proliferation) + endothelial hypertrophy/hyperplasia

Causes luminal stenosis (narrowing), leading to ischaemic-hypoxic injury (focal necrosis)

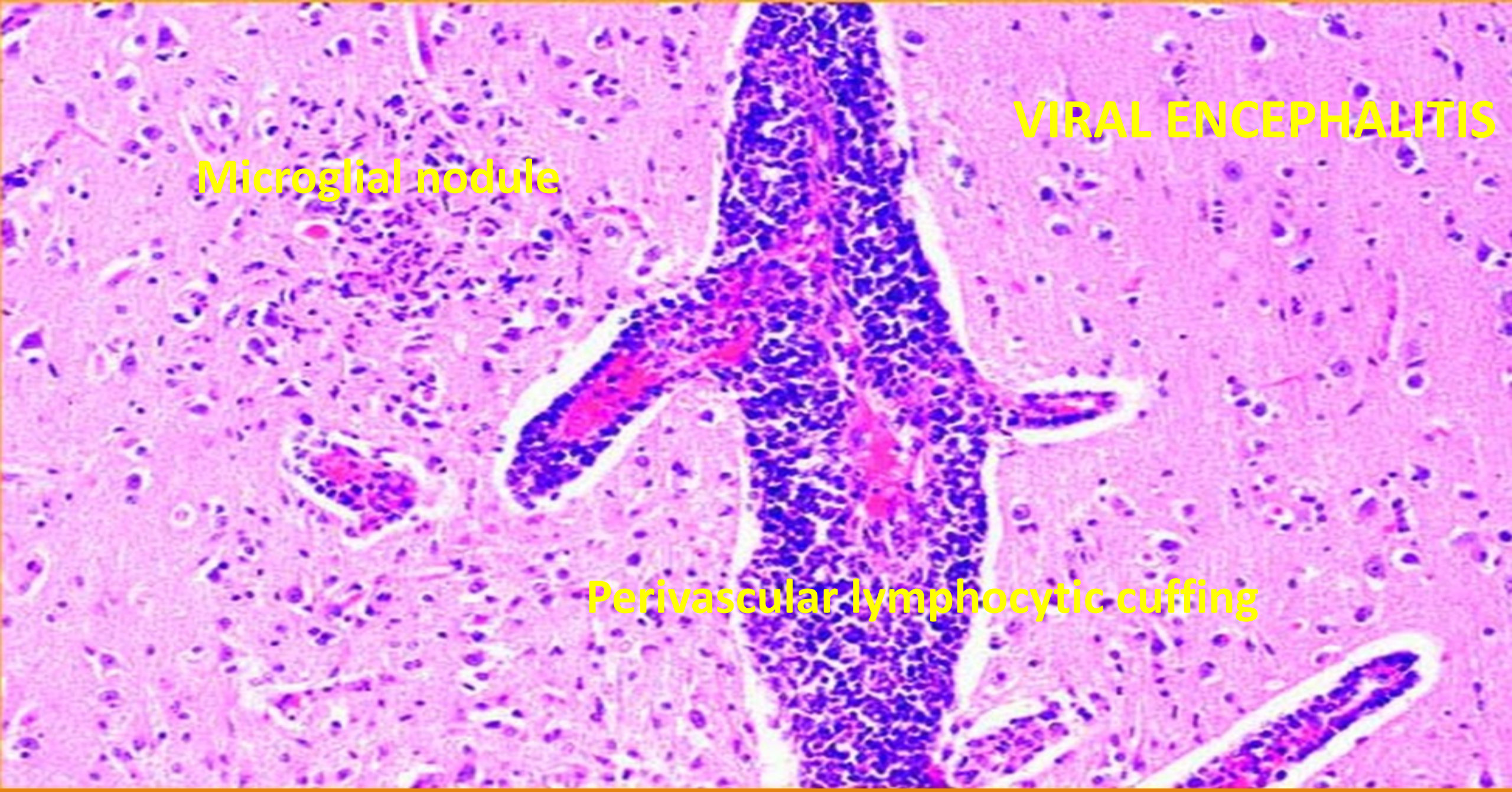
Hallmarks of viral infections

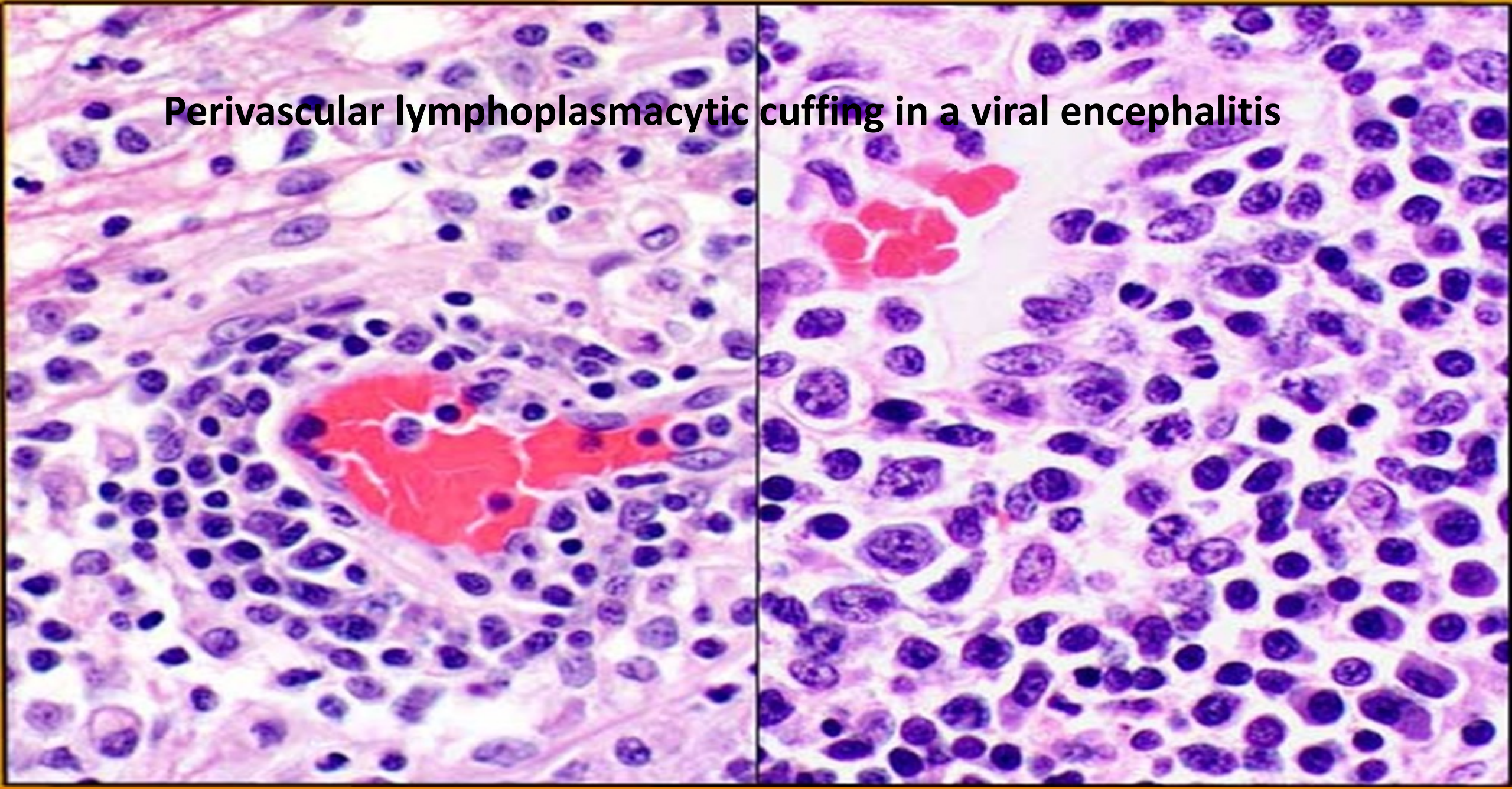
neuronal degeneration

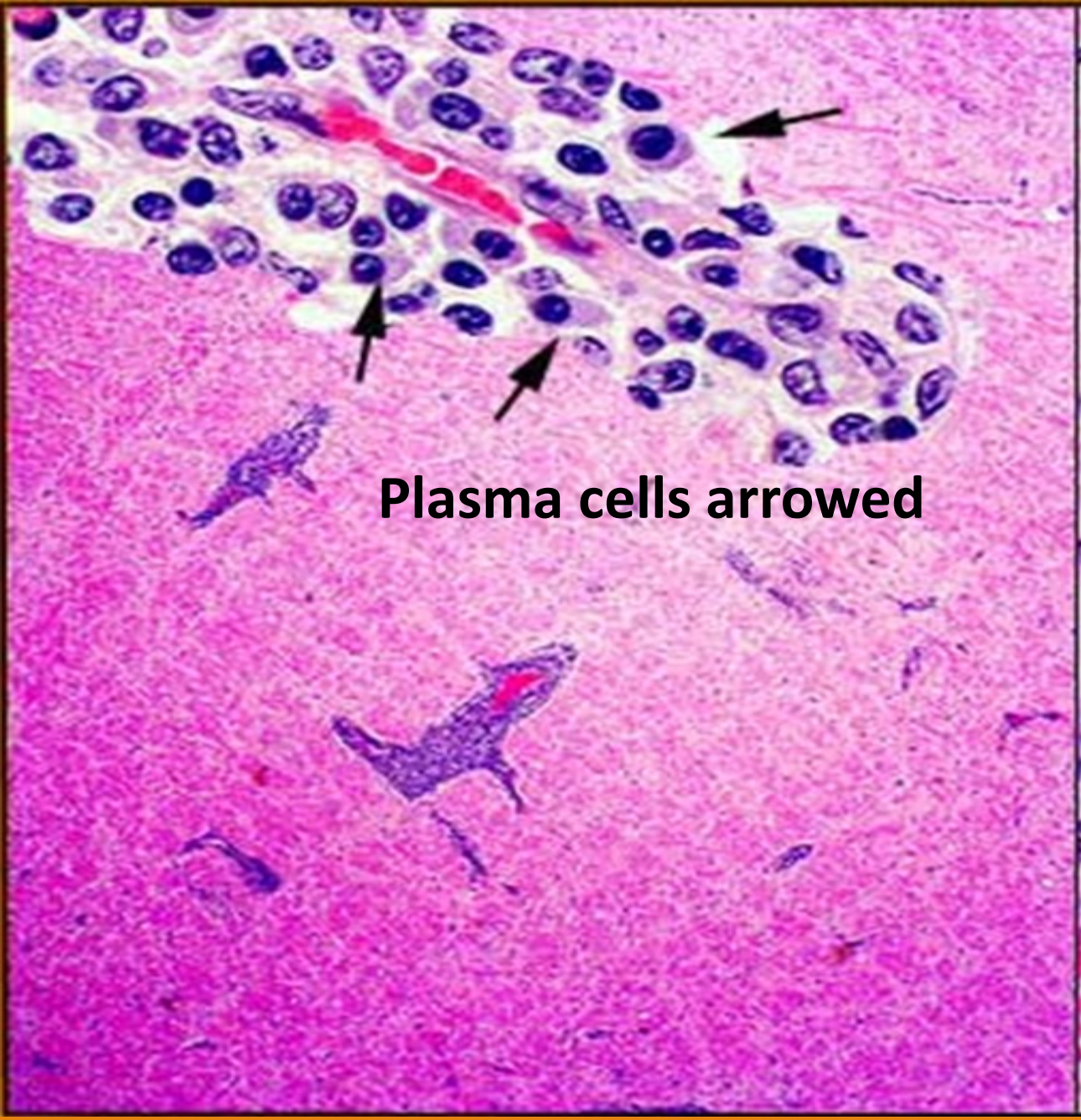
non-suppurative (lymphoplasmacytic)perivascular cuffing

focal microglial nodules or more diffuse gliosis

+/- inclusion bodies


VIRAL ENCEPHALITIS
Microglial nodule
Perivascular lymphocytic cuffing


Perivascular lymphoplasmacytic cuffing in a viral encephalitis


Plasma cells arrowed


Perivascular lymphoplasmacytic cuffing
in a viral encephalitis

Bacterial infections of CNS

CNS is injured in all cases of bacteraemia/septicaemia

Skull, vertebral column and meninges are effective barriers, but

CNS can be invaded by bloodstream, peripheral nerves, through skull fractures/penetrating wounds, through cribriform plate, or via inner ear

Bacteria incite inflammation, increased BBB permeability, and cerebral oedema, which may spread the infective process

Bacterial infections of CNS

Unyielding bony skull favours increased ICP (major determinant of clinical outcome) with cerebral oedema, decreasing blood perfusion, and ischaemic-hypoxic injury

CNS infections often cause death after brief clinical course

Pathogenic profile of bacterium: (1) success in entering brain; (2) finding unique niche; and (3) avoiding host protective mechanisms and multiplying

Bacterial infections of CNS

Once pathogenic bacteria enter CNS (e.g. breach the BBB) , host defences are suboptimal and some (e.g. inflammation) may exacerbate injury

CSF low in protein (including antibodies and complement) and is good growth medium for bacteria

Failure of immune transfer to neonates is an important predisposing factor

Acute meningitis

Most common bacterial infection of CNS

Aetiological agents are age-related

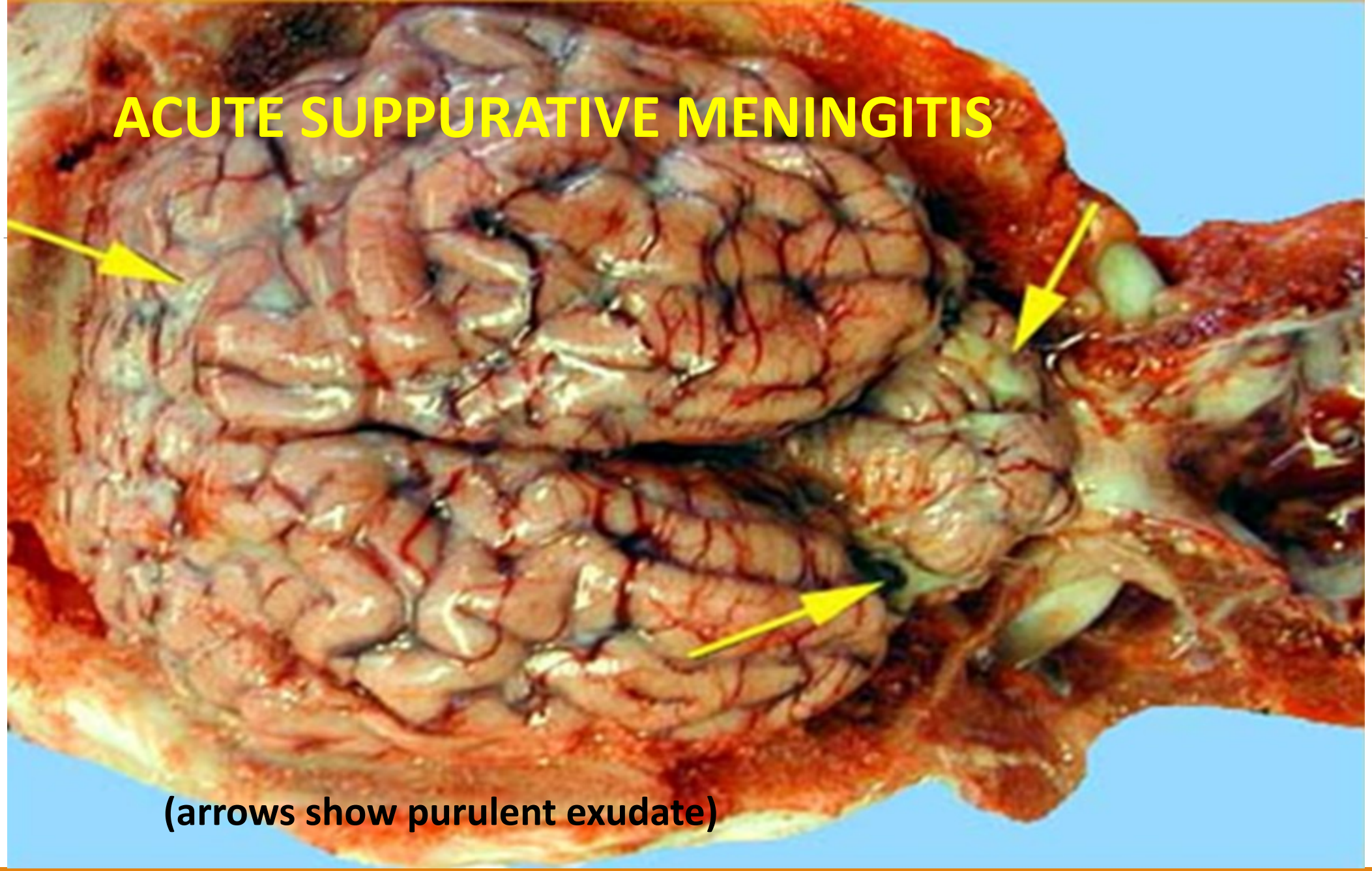
In neonates, Gram-negatives are most common, especially *E. coli*; 10-12 MO, *Neisseria meningitidis* (meningococcus), *Strep. pneumoniae* (pneumococcus), and *Haemophilus influenzae*; in adolescents, *N. meningitidis*; and, in adults, *Strep. pneumoniae*

Acute meningitis

Meninges initially cloudy, the exudate (mainly neutrophilic) accumulates (yellow-grey pus), especially over the base of the brain

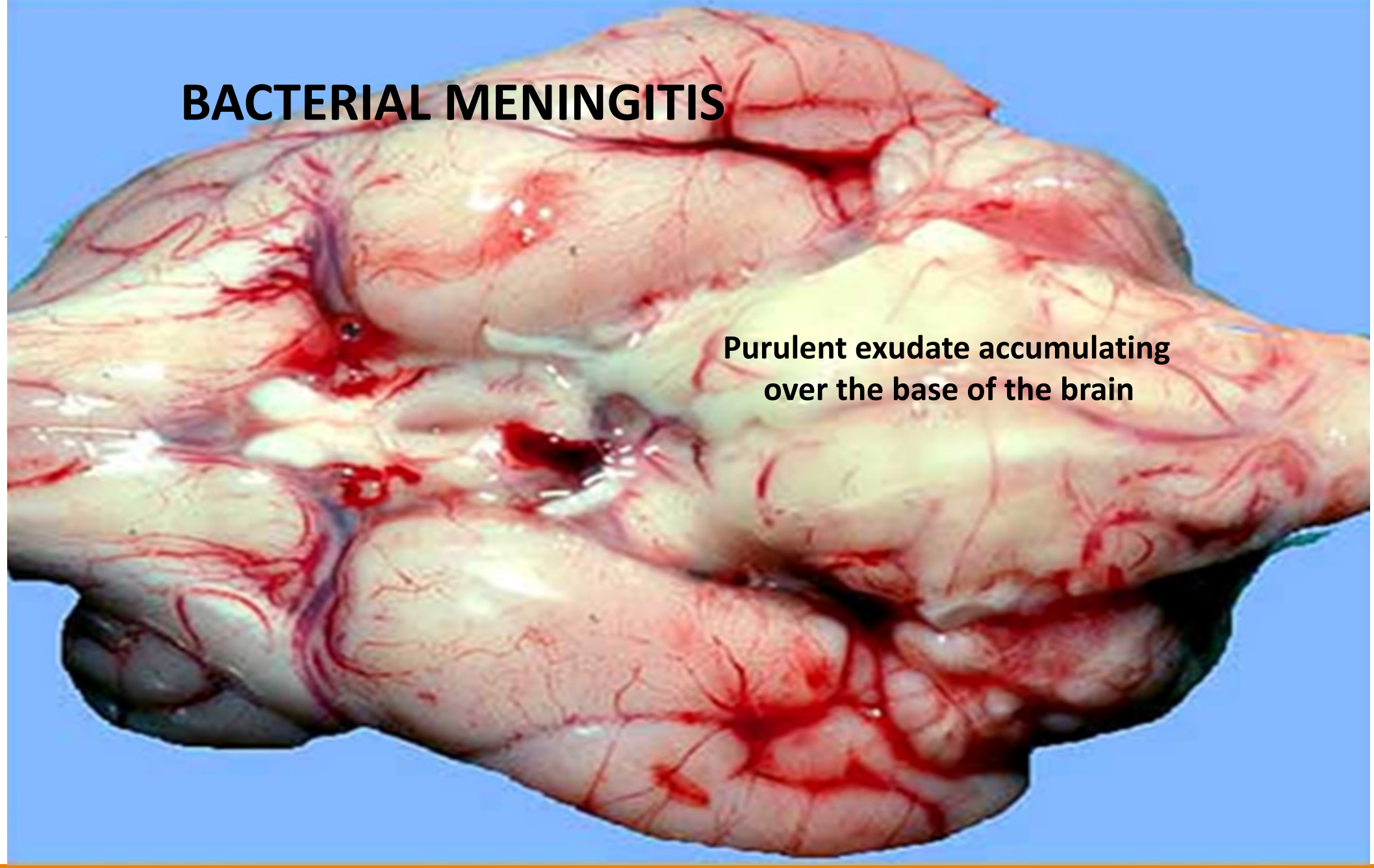
Attendant cerebral oedema often severe and may cause herniation (cerebellar coning)

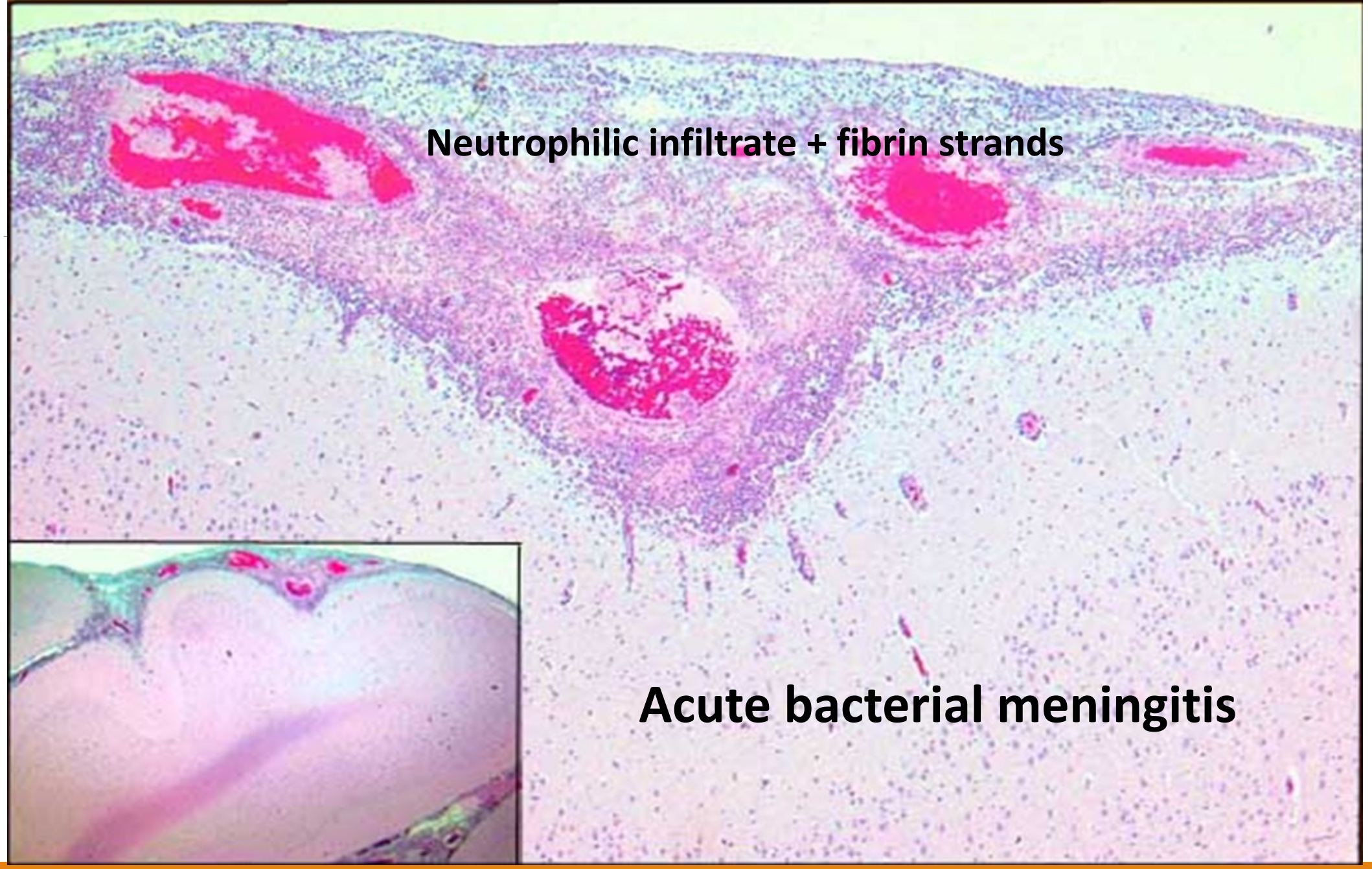
ACUTE SUPPURATIVE MENINGITIS

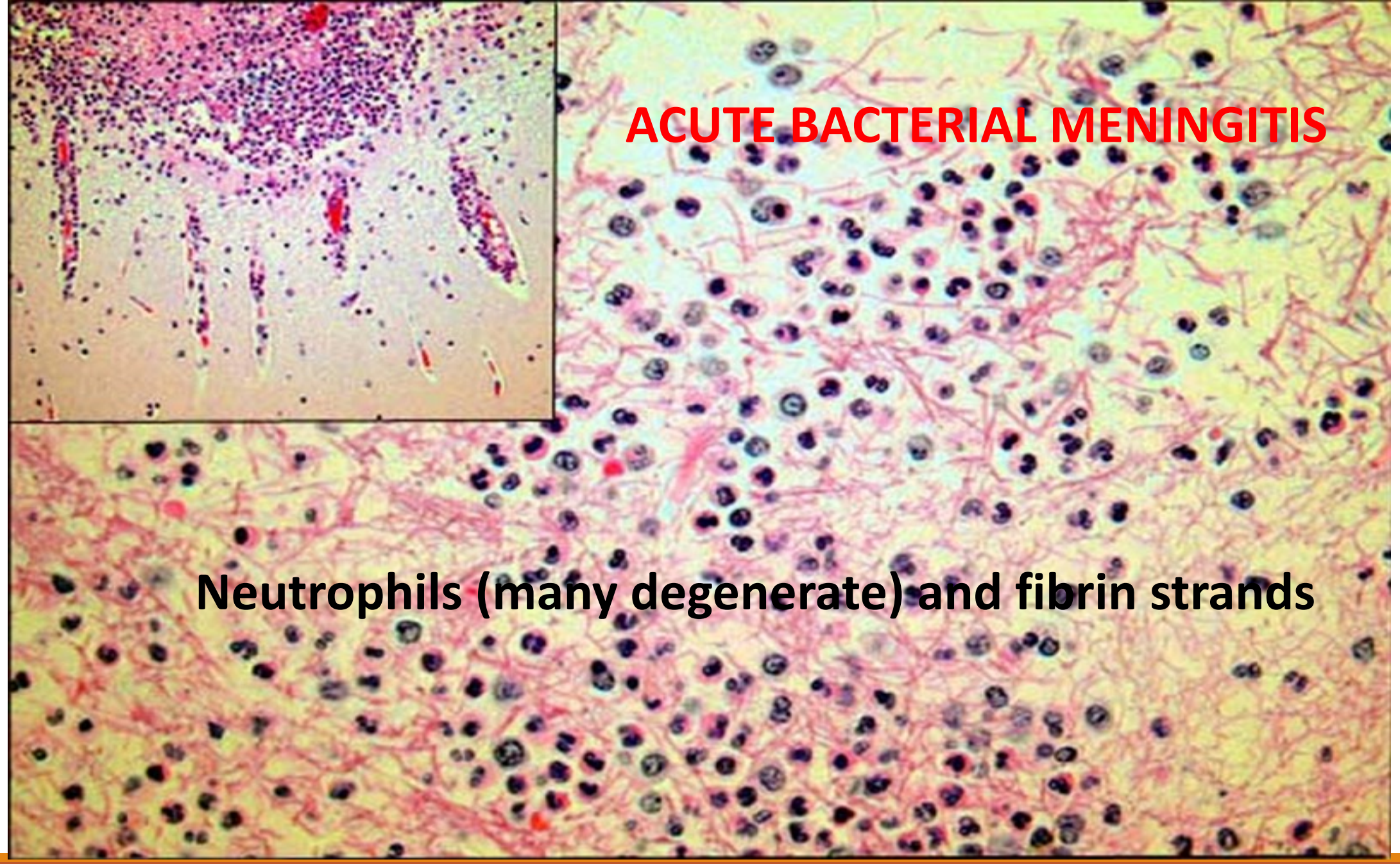


(arrows show purulent exudate)

BACTERIAL MENINGITIS




Neutrophilic infiltrate + fibrin strands
Acute bacterial meningitis


ACUTE BACTERIAL MENINGITIS
Neutrophils (many degenerate) and fibrin strands

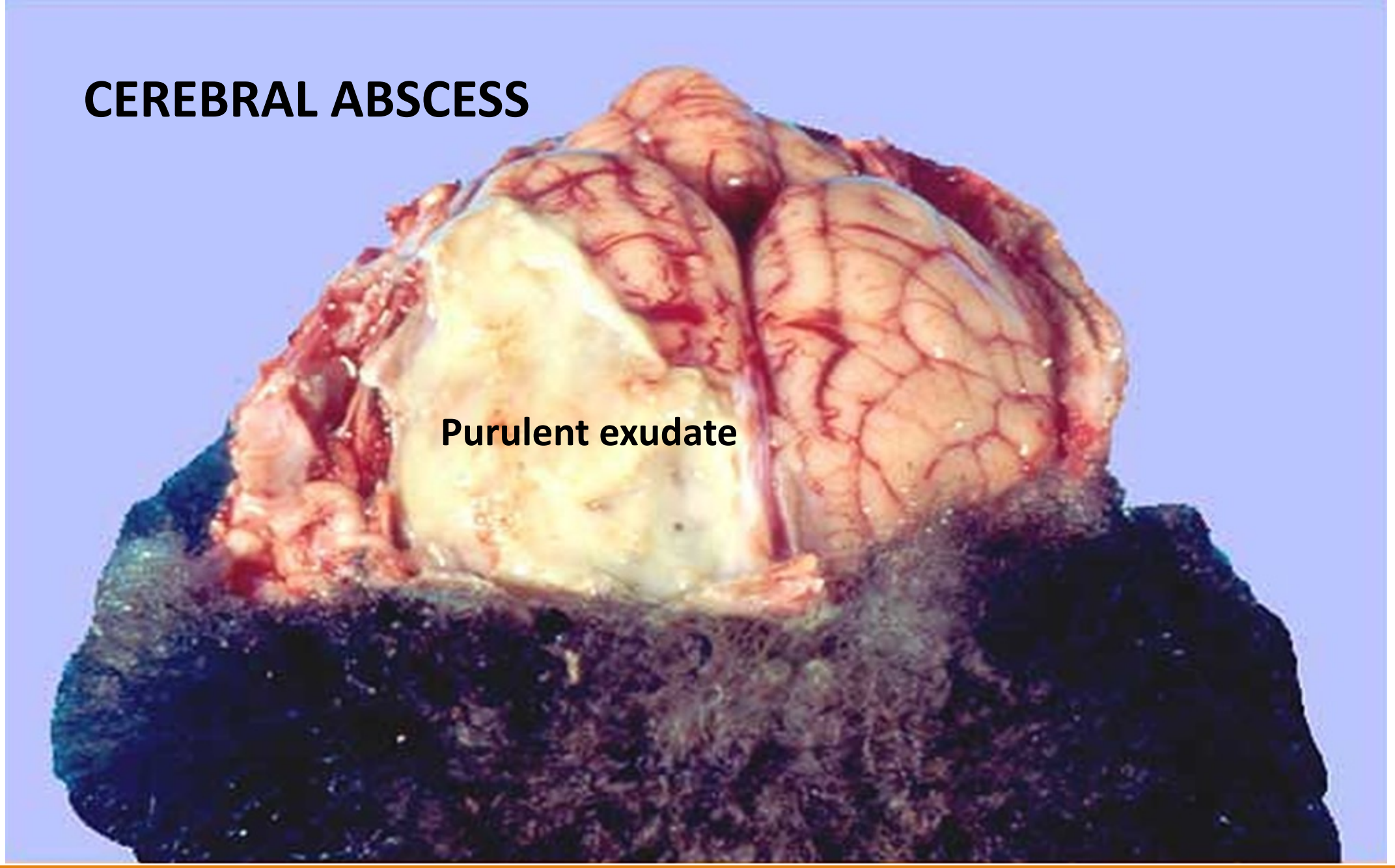
Cerebral abscessation

Intracranial abscesses are uncommon but serious and life-threatening

Arise from infections in contiguous structures (middle ear, teeth, sinuses), secondary to haematogenous spread from a distant site, after skull trauma or surgery or, less commonly, extension from meningitis

Microbial aetiology depends on age, site of primary infection, and immune status. Some are polymicrobic. Commonly *Strep* sp, but also *S. aureus*, *Enterobacteriaceae*, *Pseudomonas* and *Proteus* spp.

CEREBRAL ABSCESS



CEREBRAL ABSCESS