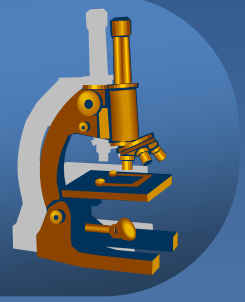
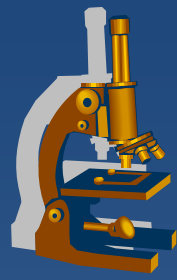
Systemic pathology



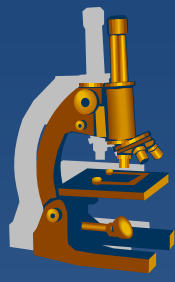
Nervous system

Inborn defects



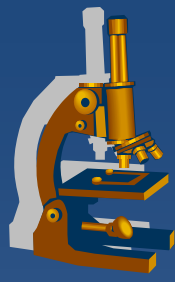
- approx. 3-4/ 100 000 live births
- Neural tube defects, incl. myelo- / encephalo- / meningocele
- Posterior fossa malformations
- Destructive lesions – commonly due to maternal infections (rubella, zika virus), hypoxia → microcephaly; focal lesions possible
- Chromosomal abnormalities (trisomy 21, …)
- …

Neural tube defects

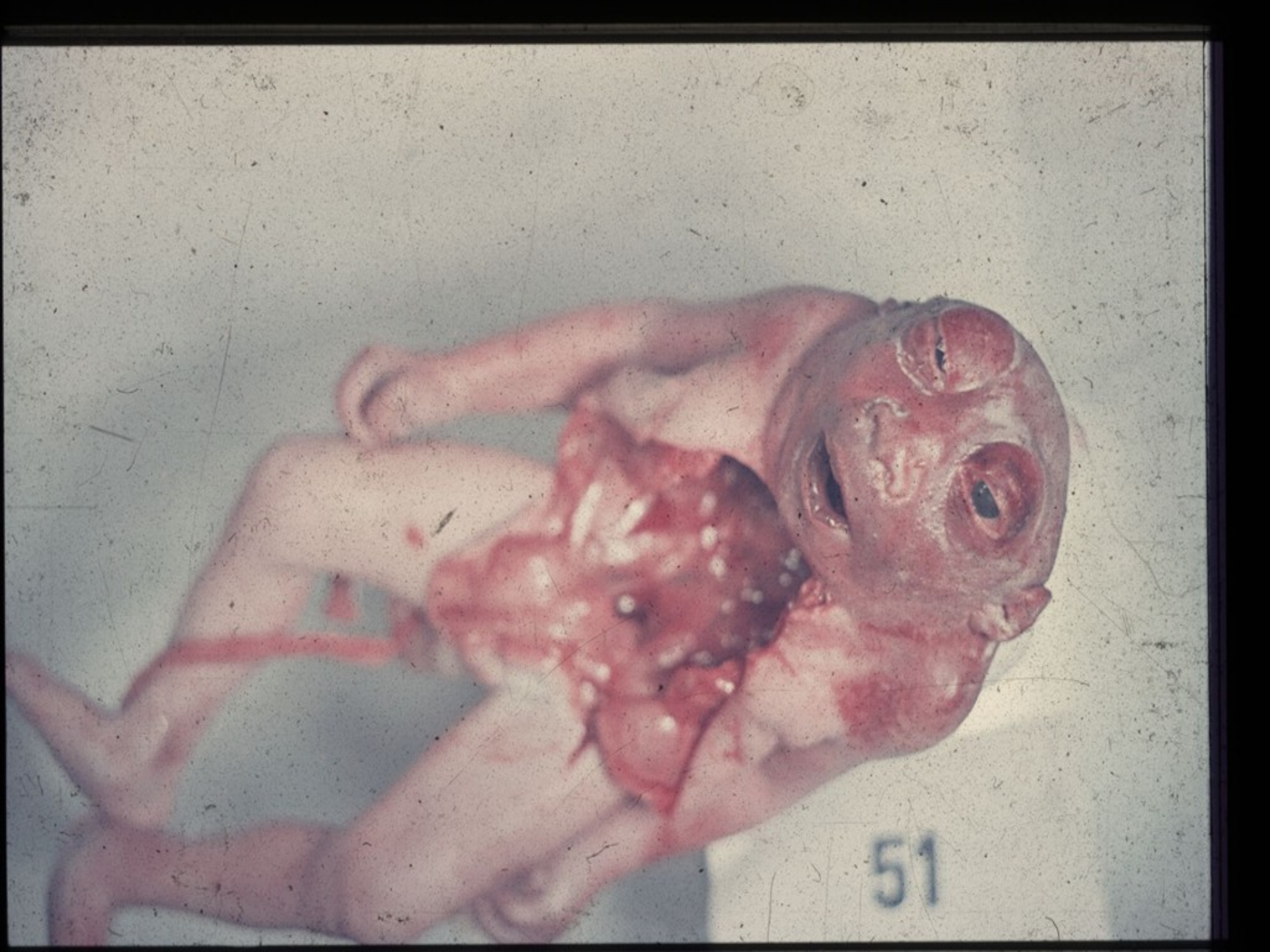


- most important and common inborn defect
- nonclosure or reopening of n.t.
- neural tissue, meninges, bone, soft tissue affected
- multifactorial (genetic, environmental)
- folate deficiency as risk factor (folate supplementation ↓ incidence)

Anencephaly



- absence of brain and calvaria
- brain development stopped at ~ 28 days
- incompatible with life, usually + other defects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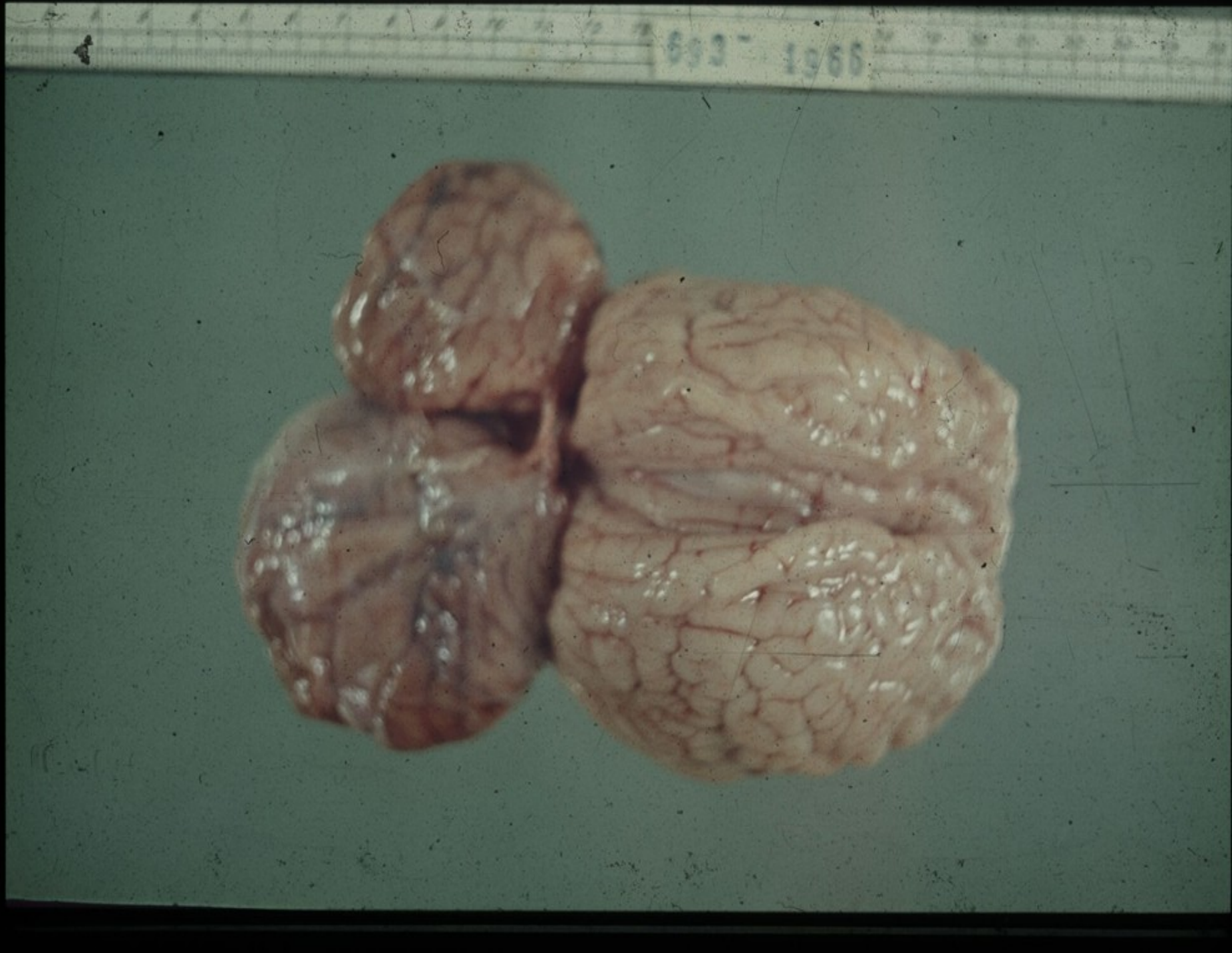
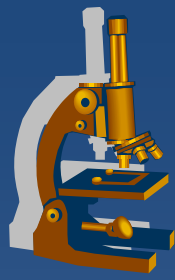
Encephalocele

- herniation of malformed brain through cranial defect
- usually occipital
- neurologic dysfunction, infection

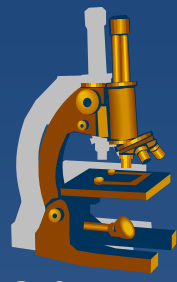
693 1966





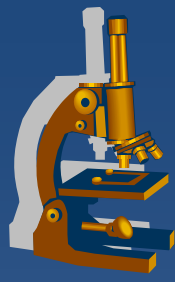
Brain swelling, ischemia

Brain swelling



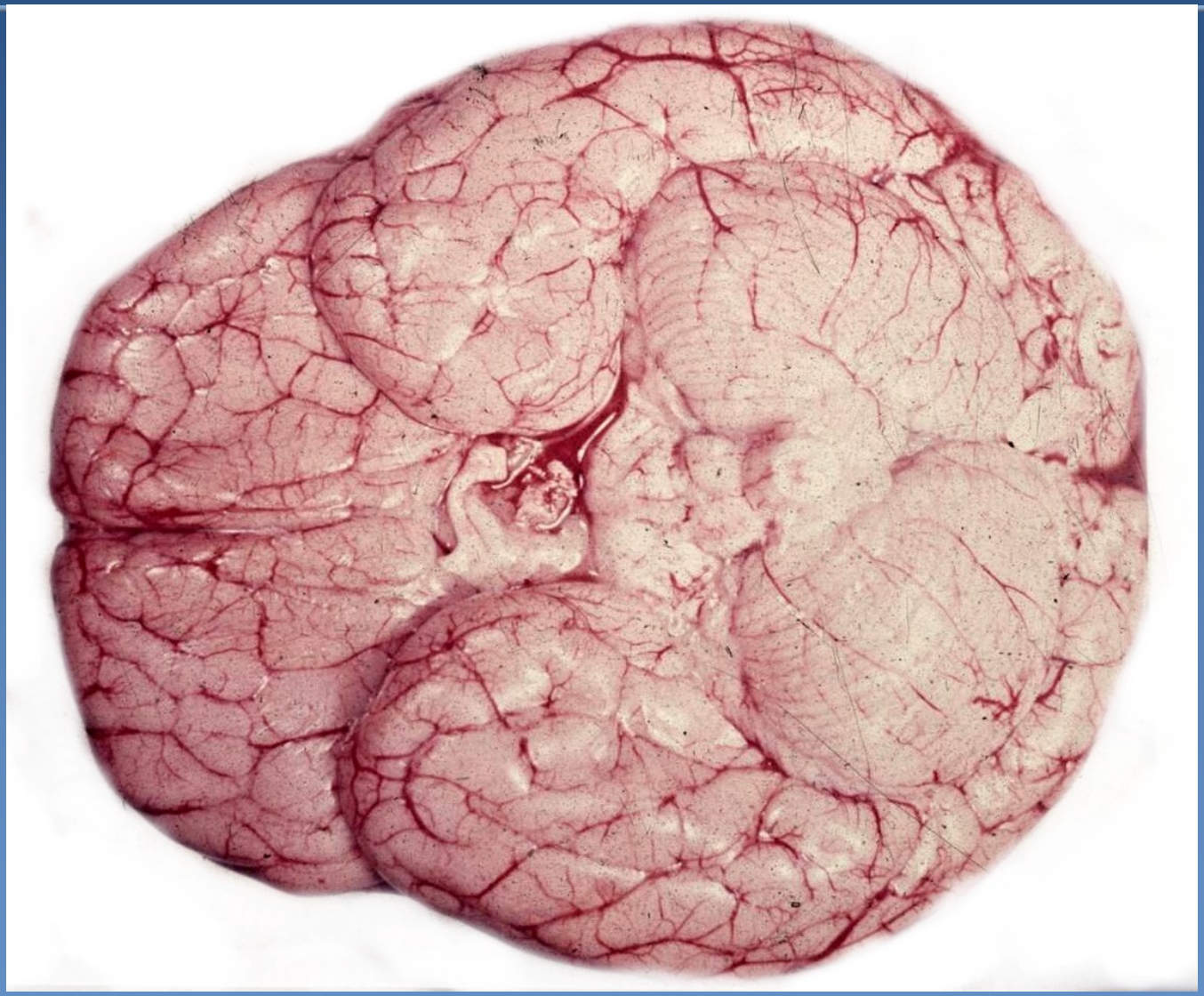
- **generalised increase in the volume of brain (blood, water, ions) → clinical signs related to raised intracranial pressure / intracranial shift / herniation**
- **diffuse** (vasodilatation, oedema – vasogenic, cytotoxic, interstitial)
- **focal** (space-occupying lesions – inflammation, tumor, trauma, vascular lesion)
- **herniations:**
  - ⇨ *supracallosal – interhemispheric undex falx cerebri*
  - ⇨ *transtentorial – temporal (3rd nerve, secondary braunstem haemorrhage)*
  - ⇨ *tonsillar – foramen magnum, vital centres compressed*

Brain swelling

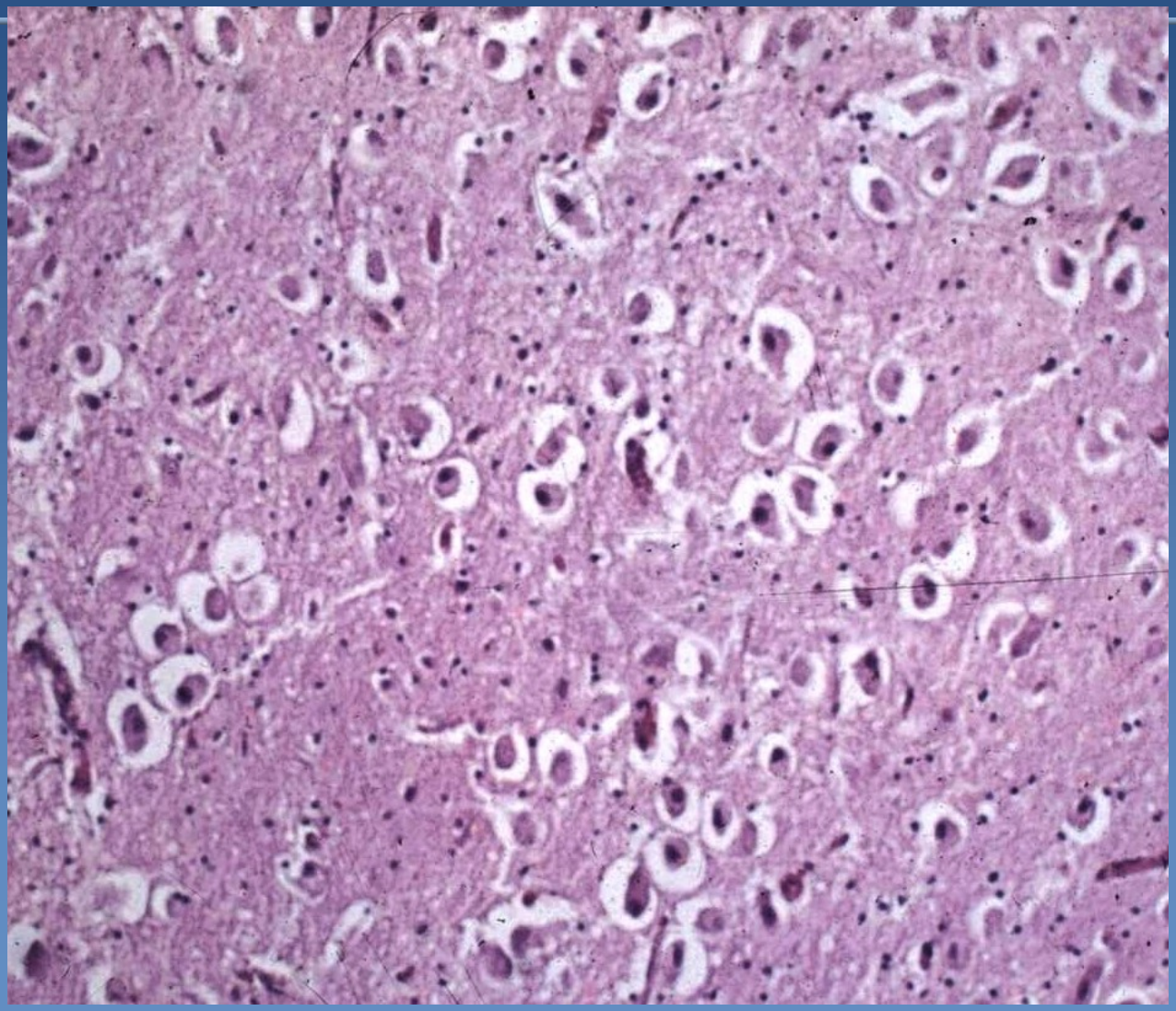


- **gross:**
  - *flattened gyri, narrow sulci, slit-like ventricles*
- **micro:**
  - *neuropil vacuolation*
  - *swelling of the cytoplasm and processes of astrocytes*
  - *perivascular optically empty spaces*
  - *myelin less vividly colored*
- **signs**
  - *headache, nausea, vomiting*
  - *optic nerve papilla with oedema*

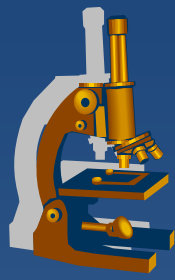
Diffuse brain swelling



Diffuse brain swelling

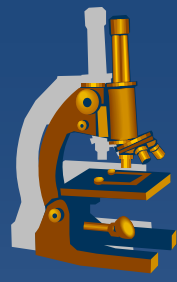


Brain swelling - pathogenesis



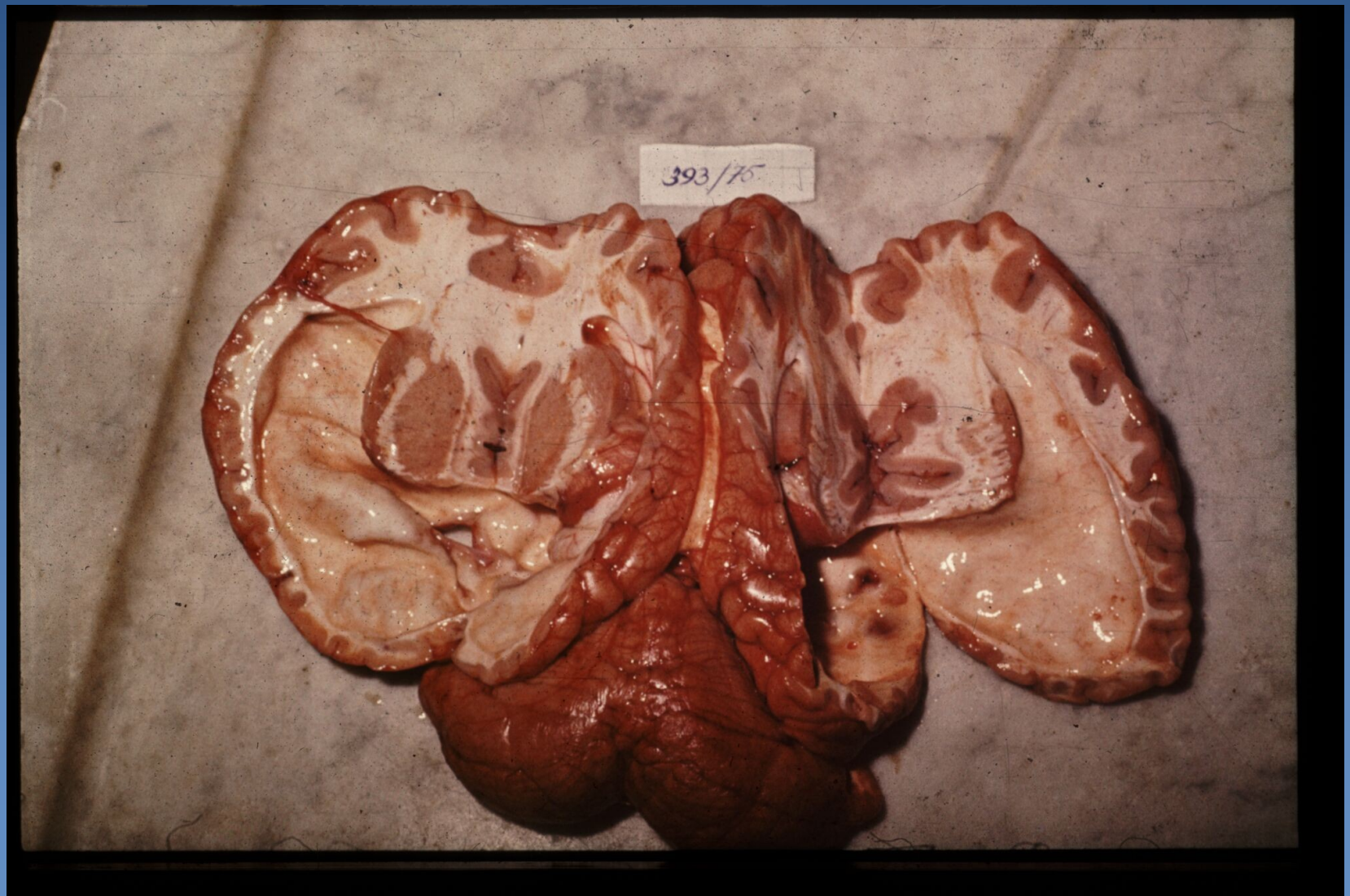
- **main types:**
  - ⇨ ***vasogenic***
    - due to increased cerebral vascular permeability (esp. by neoangiogenesis)
    - adjacent to tumors, abscesses, haemorrage, ischemia
  - ⇨ ***cytotoxic***
    - due to hypoxia / ischemia , toxic damage – cell membrane injury, ↑intracellular fluid
  - ⇨ ***interstitial***
    - due to damage of ventricular lining (hydrocephalus, CSF diffusion into the white matter)

Hydrocephalus

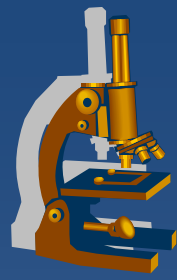


- **increased amonut of CSF, ↑ intracranial pressure**
- **infants x older children, adults**
- **caused by:**
  - ⇨ ***increased CSF production***
    - chorioid plexus papilloma, rare
  - ⇨ ***decreased CSF resorption***
    - **meningitis, subarachnoid haematoma**
  - ⇨ ***obstruction to CSF flow***
    - **congenital x aquired – trauma, tumors, infection, blood coaguli, cyst**
  - ⇨ *hydrocephalus e vacuo (secondary/compensatory)*

Hydrocephalus

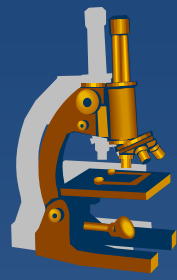


Cerebrovascular disorders



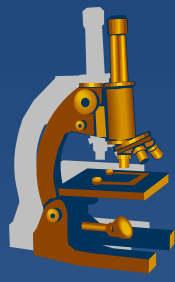
- Vascular malformations
  - ***commonly without signs***
  - ***possible intracranial haemorrhage***
  - ***arterio-venous malformations***
  - ***cavernous haemangioma***
- Stroke – acute neurologic status of vascular origin
  - ***ischemia – encephalomalatia***
  - ***intracranial haemorrhage***
  - ***acute head CT, widely different treatment***
- Brain disorders in systemic hypertension
  - ***acute hypertensive encephalopathy***
  - ***vascular dementia***

Global CNS ischemia



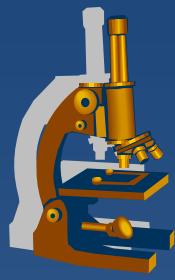
- Global hypoxic-ischemic encephalopathy
  - ***shock***
  - ***heart arrest***
  - ***severe hypotension***
- Sequels according to duration
  - ***complete repair***
  - ***brain death***

Encephalomalatia (cerebral infarction)



- **colliquative necrosis**
- **„white“ ischemic x haemorrhagic – blood reflux, venous**
- **clinically: stroke or transient ischaemic attack – TIA**
- **pathogenesis:**
  - *arterial thrombosis (AS, arteritis, arteriopathy)*
  - *thrombembolia*
  - *venous thrombosis*
  - *diffuse small vessel problems – spasm, vasculitis*
  - *external pressure (haematoma)*
  - *systemic hypoxia*
- **the size and distribution depends on:**
  - *diameter and localisation of affected artery*
  - *closure promptness*
  - *possibilities of collateral circulation*

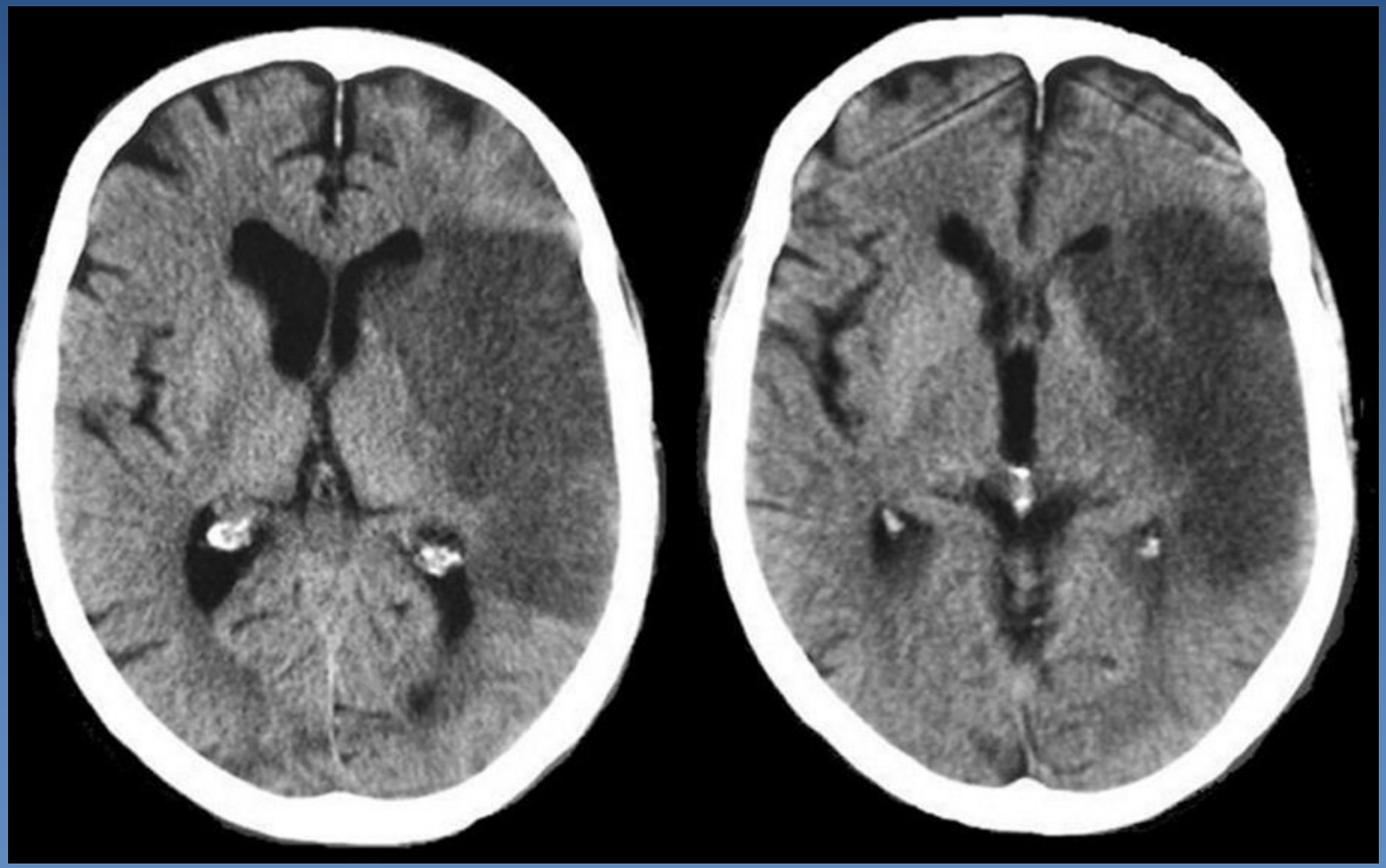
Encephalomalatia



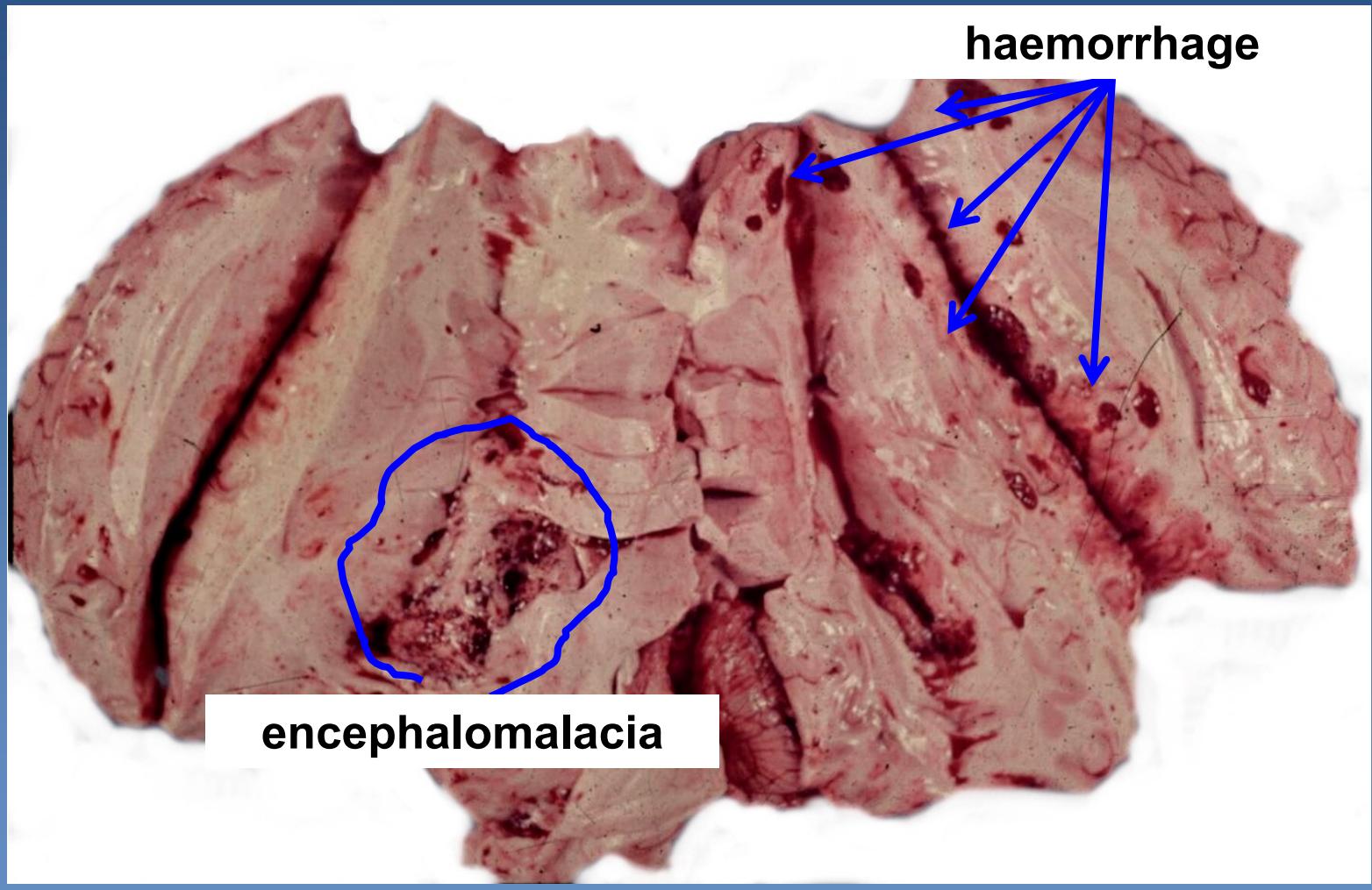
- **gross:**
  - *approx. 24hours – affected tissue softened and swollen, loss of border between grey and white matter*
  - *oedema*
  - *infarcted tissue undergoes colliquative necrosis*

- **micro:**
  - ***neuronal ischemia*** *(loss of cytoplasmic basophilia, nuclei), endothelial + glial oedema*
  - ***neutrophils, after 2 days infiltration with macrophages*** *(cytoplasm filled with the lipid products of myelin breakdown)*
  - ***reactive astrocytes and proliferating capillaries at the edge of the infarct***
  - ***Necrotic tissue phagocytosed → fluid-filled pseudocystic cavity lined by glial tissue***

Encephalomalatia

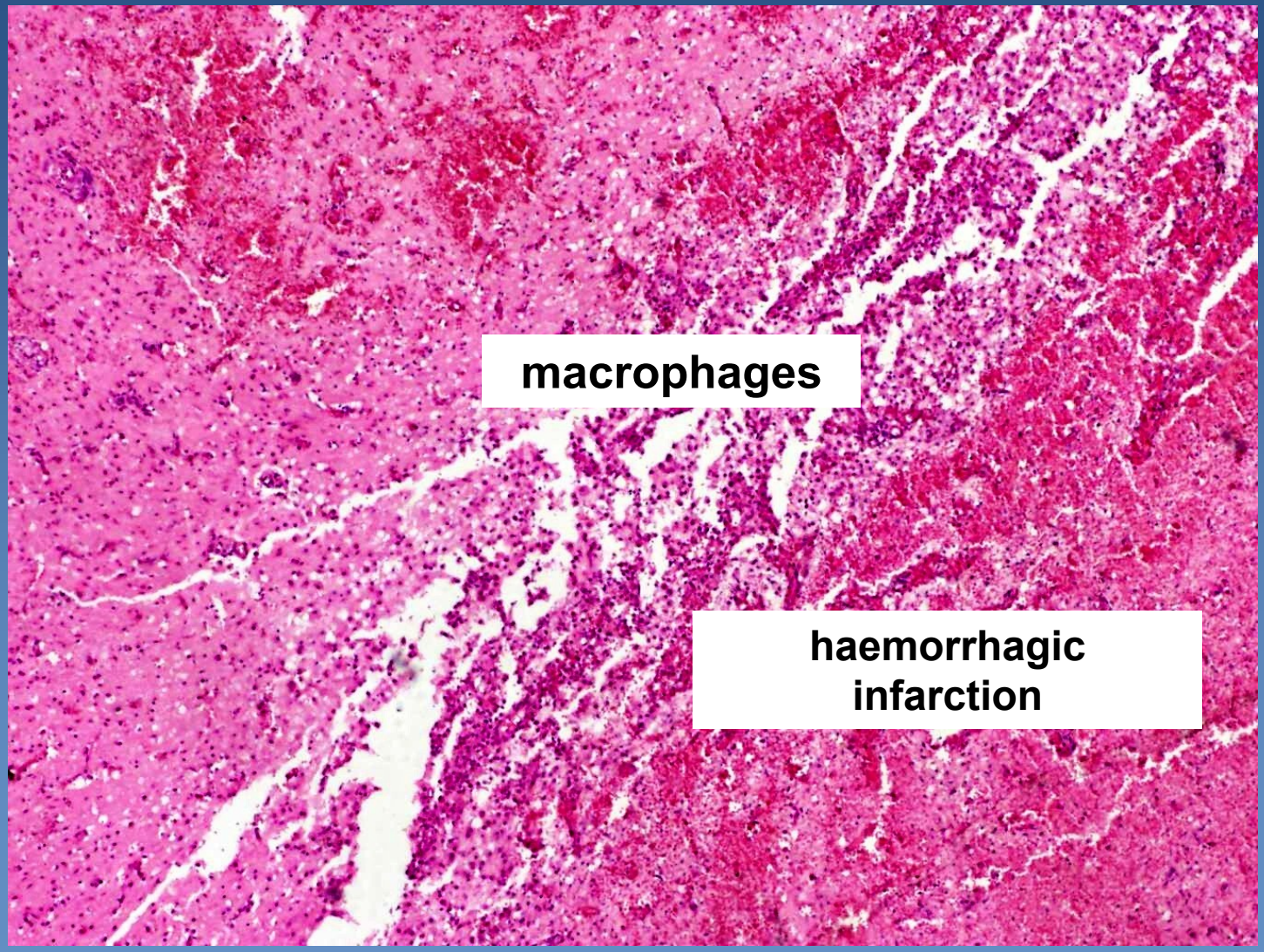


Encephalomalatia (cerebral infarction)

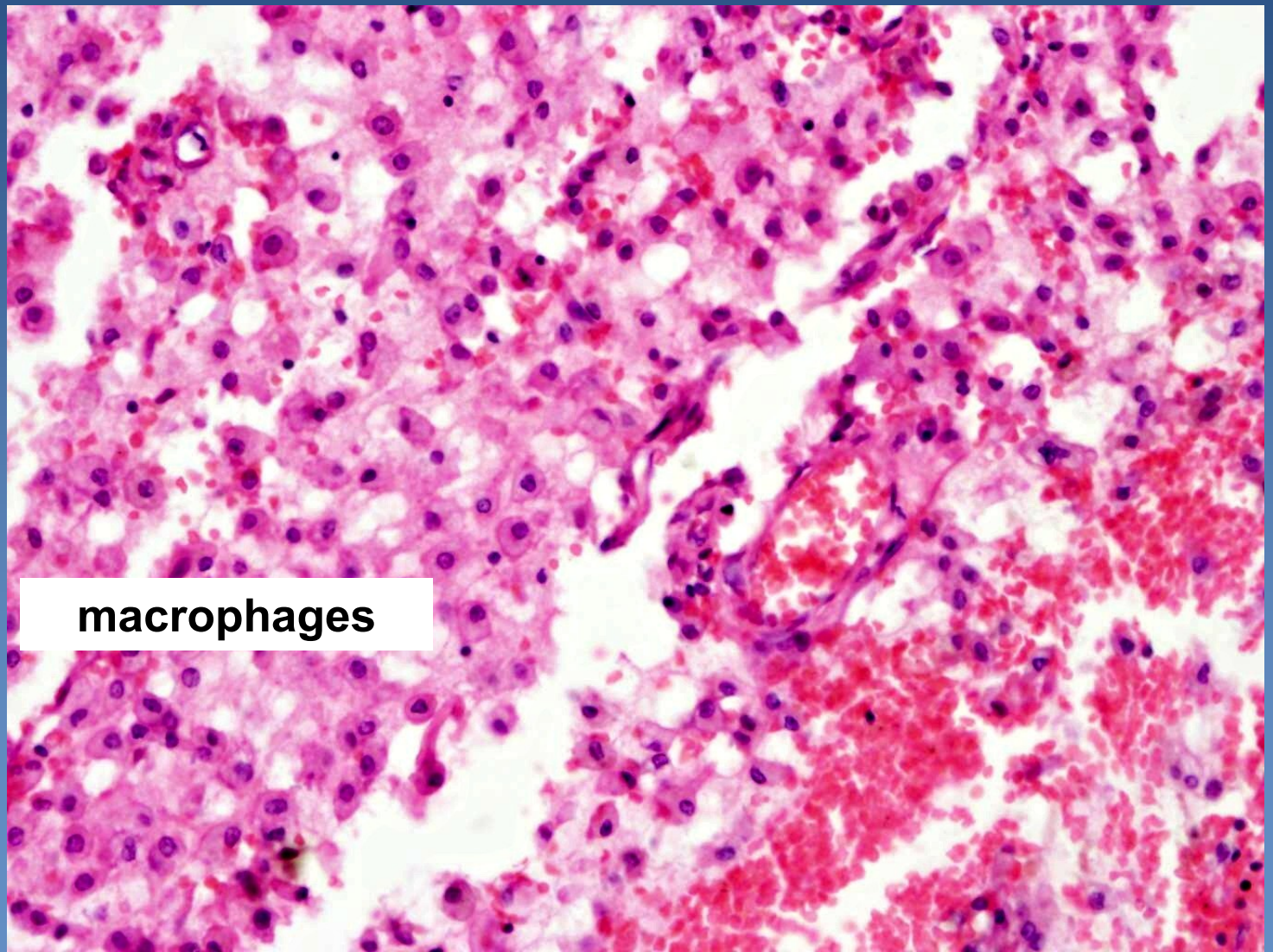


Encephalomalatia

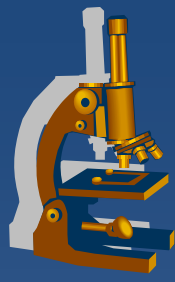
(+ reactive macrophages)



Encephalomalatia



Intracranial haemorrhage

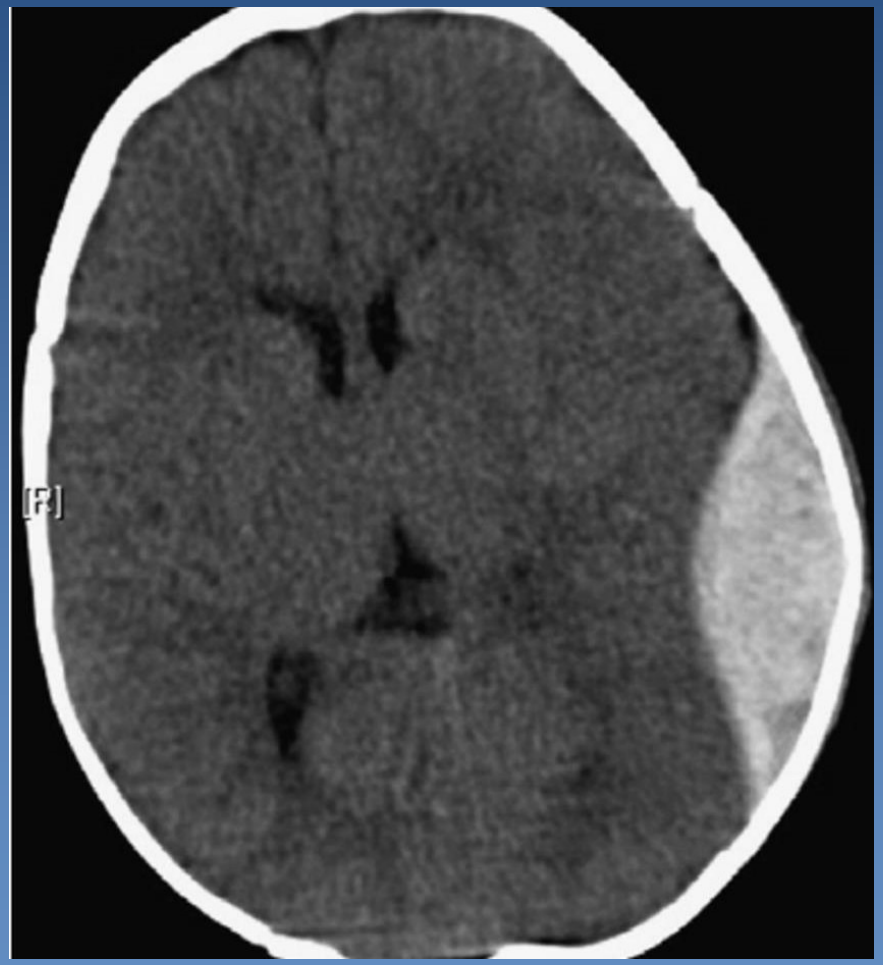


- **Extradural – epidural** (haemorrhage between skull and dura mater)
  - ⇨ *mostly due to skull fracture (rupture of a. meningea media)*
  - ⇨ *arterial, traumatic, acute, urgent neurosurgery necessary*
  - ⇨ *clinically: short lucid interval , increased intracranial pressure*

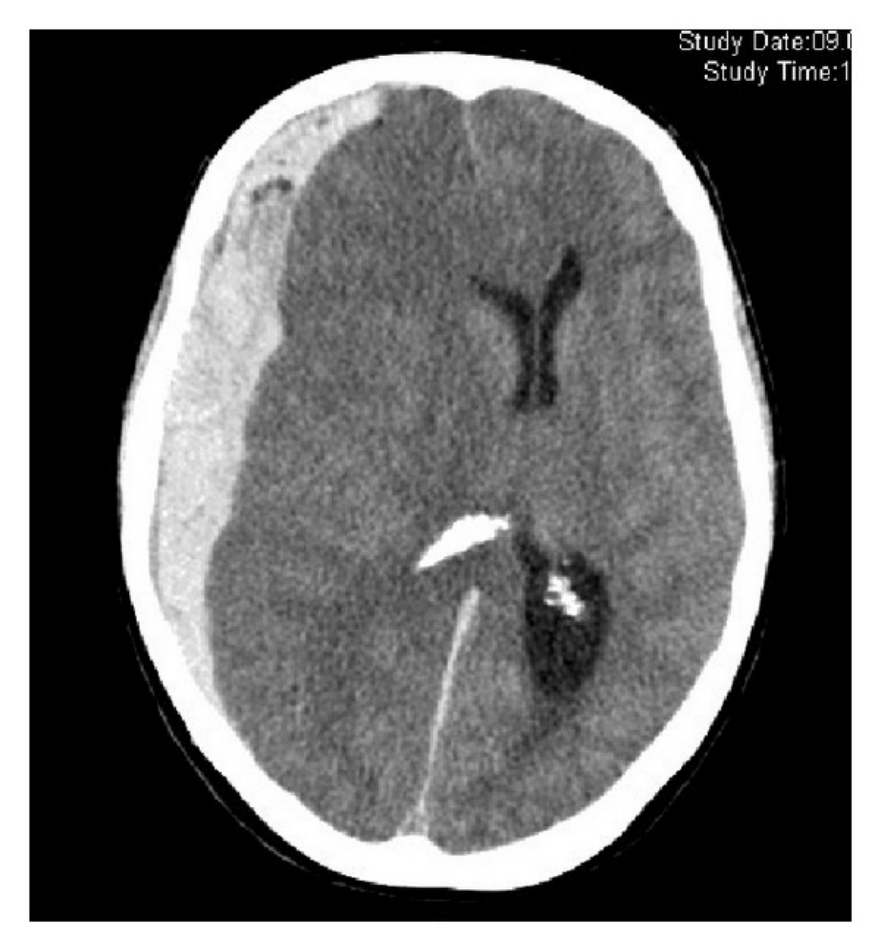
- **Subdural** (haemorrhage between dura and arachnoid matter)
  - ⇨ *rupture of venous sinuses or small bridging veins*
  - ⇨ *acute : later onset (2 days),seizures, headache, consciousness alteration*
  - ⇨ *x chronic (particularly in elderly - headache, memory loss and confusion, personality change)*

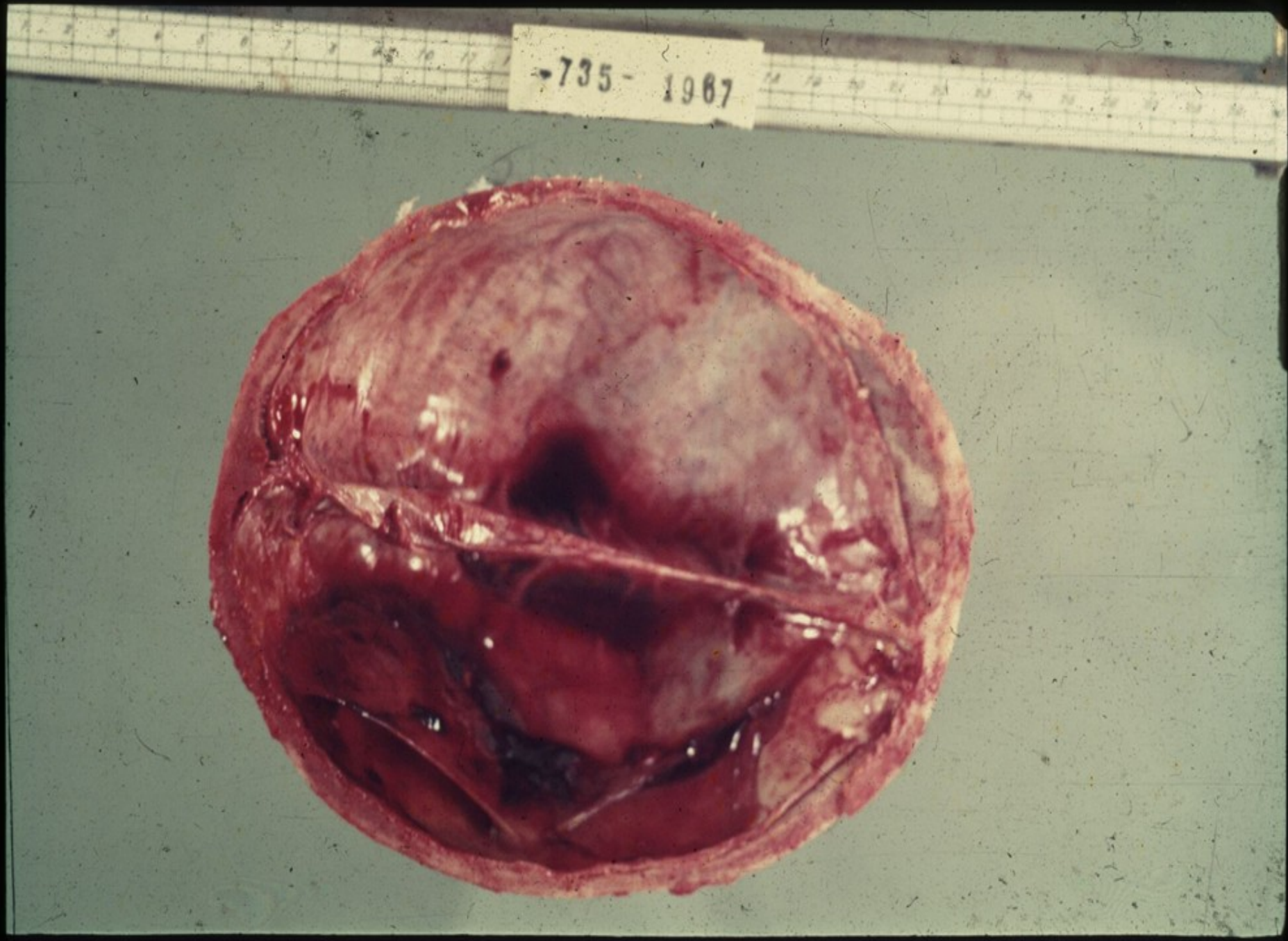
- **Subarachnoid** (haemorrhage between arachnoid matter and pia mater)
  - ⇨ *inborn defect: aneurysm (saccular „berry“ aneurysm on the circle of Willisi)*
  - ⇨ *AS, hypertension, tumor, coagulative disorders*
  - ⇨ *sudden severe headache, rapid loss of consciousness*

Epidural haemorrhage



Subdural haemorrhage

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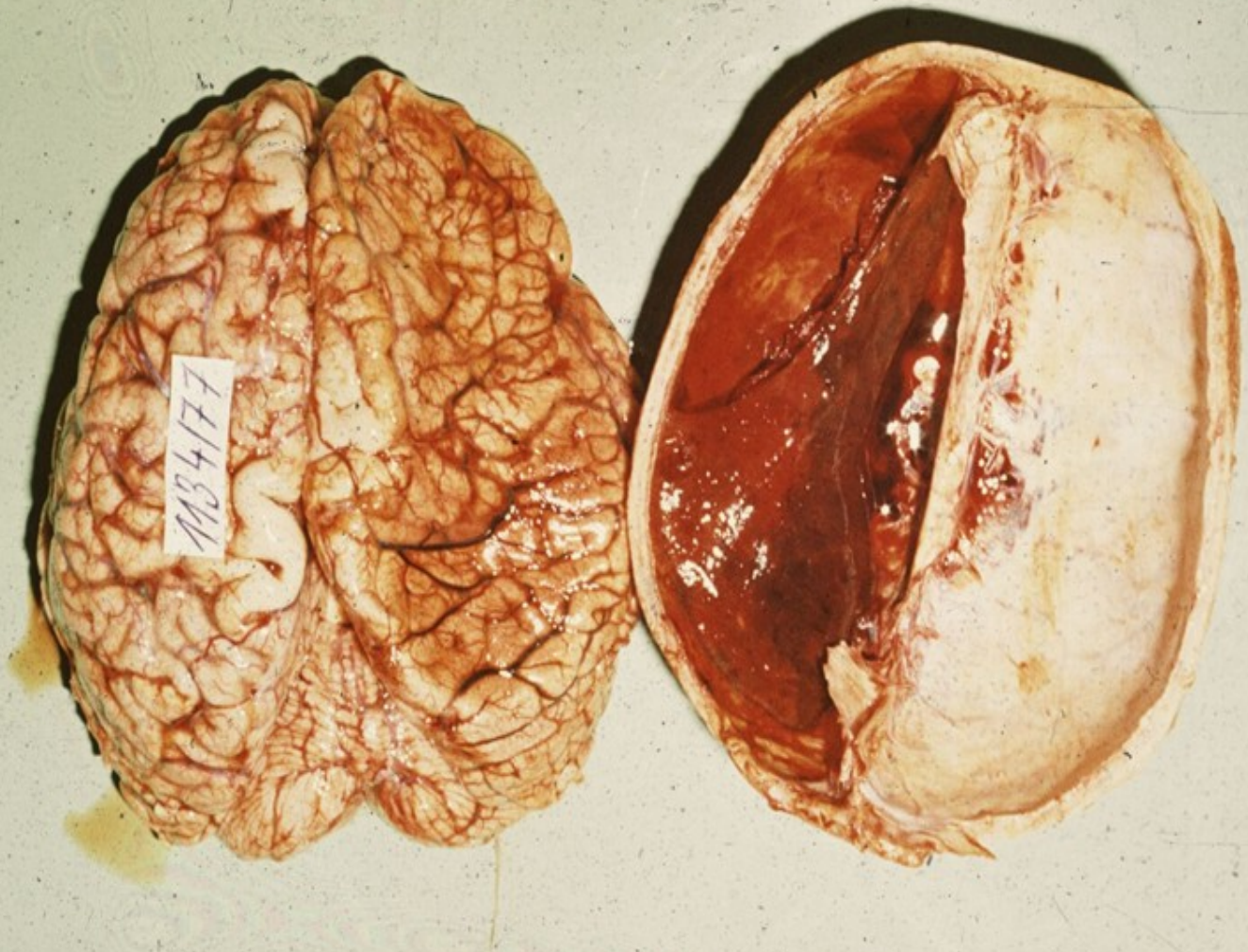
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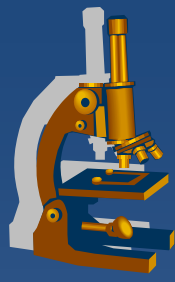
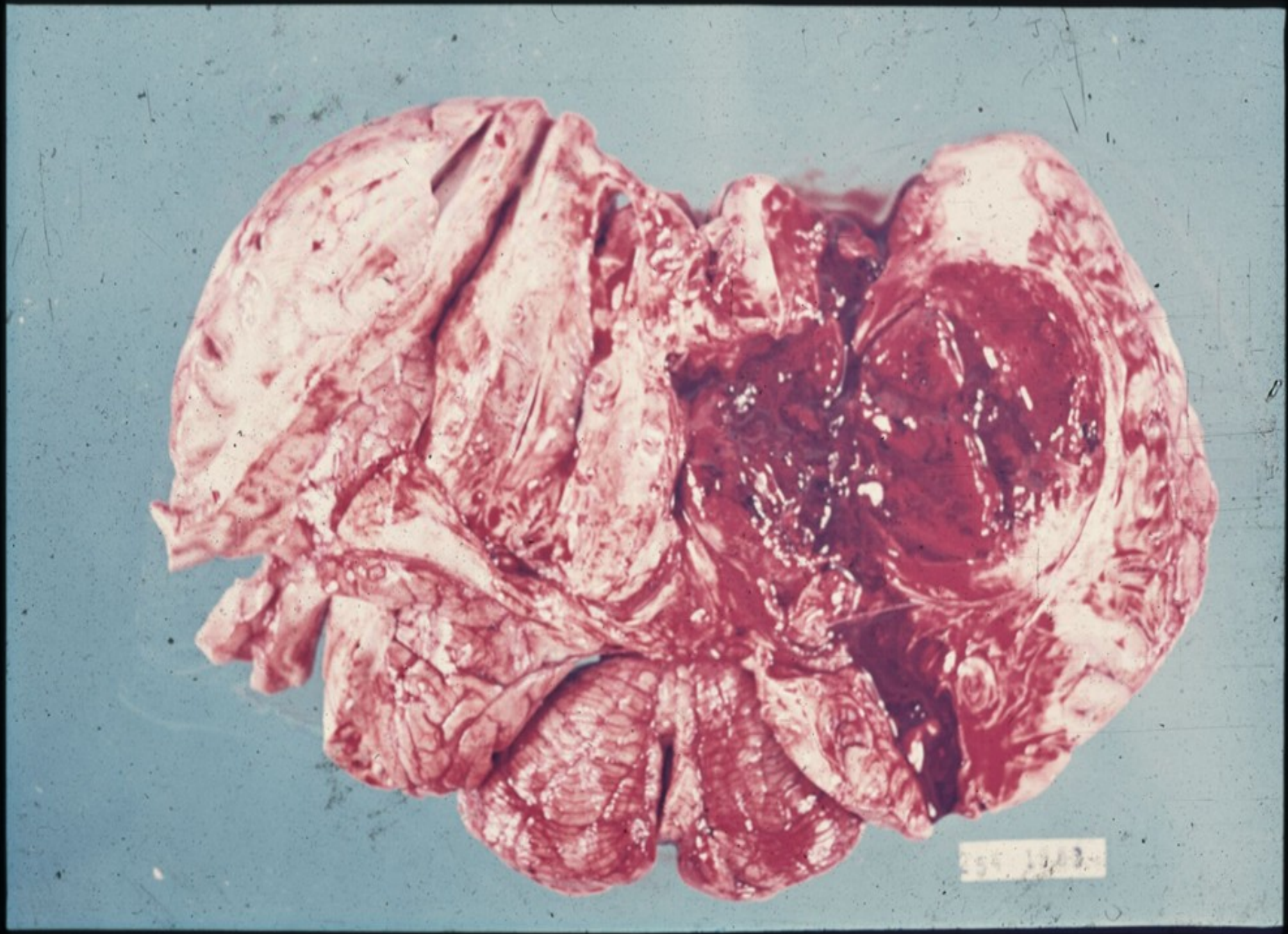
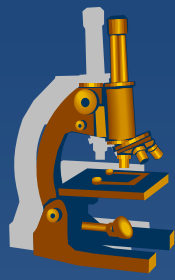
Intracranial haemorrhage



- **Intracerebral**
  - ⇨ ***nontraumatic arterial***
    - hypertension + regressive vessel wall changes → rupture of blood vessel
    - AS
    - vasculitis, amyloid angiopathy, tumors
    - secondary bleeding into a brain infarction
  - ⇨ ***traumatic***
  - ⇨ *premature newborn*
    - extension into ventricular system, subarachnoid space - possible hydrocephalus
- **Intraventricular (haemocephalus)**
  - ⇨ secondary after haemorrhage extension into ventricular system



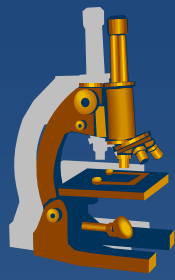
CNS infections



- **etiology**
  - ***bacterial*** *incl. tb, rickettsia*
  - ***viral***
  - *fungal, parasitic (protozoan, etc.)…*

  - ***haematogenous spread***
  - ***local extension – direct spread (adjacent inflammations)***
  - ***trauma – direct implantation***
  - ***along the peripheral nerves***
  - ***iatrogenic infection***

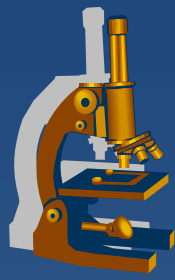
Leptomeningititis



- ⇨ *chemical (irritation)*
- ⇨ *acute pyogenic (bacterial)*
- ⇨ *acute aseptic – lymphocytic (viral)*
- ⇨ *chronic (granulomatous tuberculous; fungal)*

direct spread x blood-borne

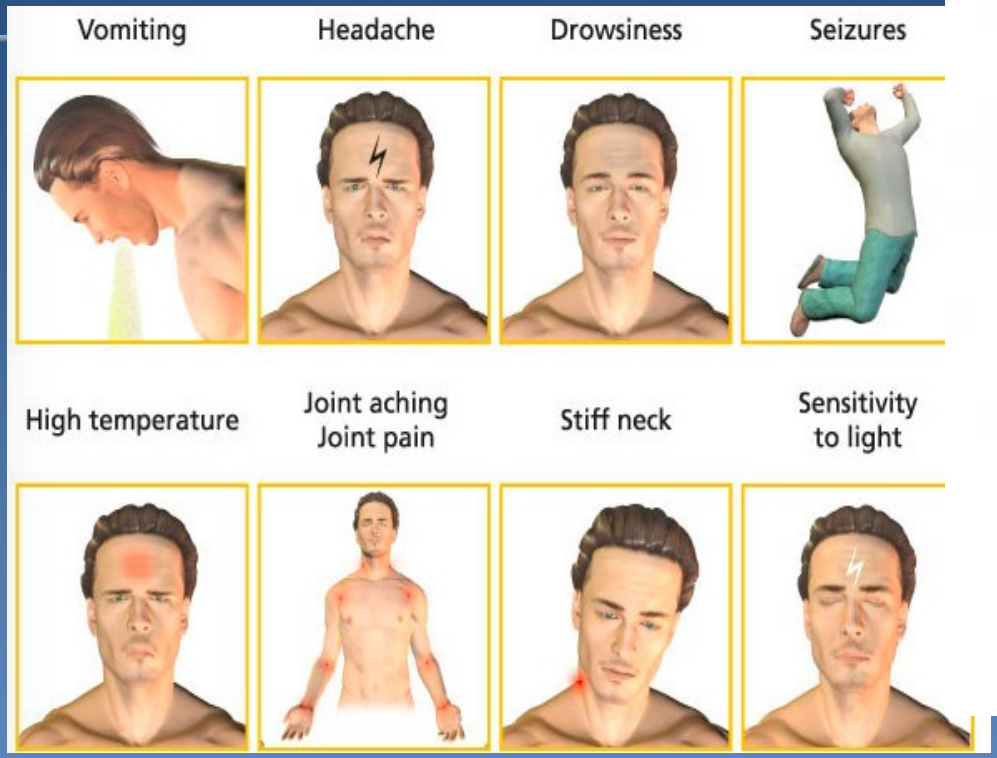
Bacterial leptomeningitis



- **symptoms:**
  - *headache, joint + muscle pain*
  - *sleepiness, fever, vomiting, loss of consciousness, convulsion*
  - *petechial rash*
  - *photophobia*
  - *signs of meningeal irritation*
  - *sepsis*

  - *!! acute onset, rapid diagnosis + ATB therapy necessary*

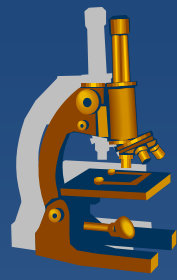
Purulent leptomeningitis



One of the physically demonstrable symptoms of meningitis is Brudzinski's sign. Severe neck stiffness causes a patient's hips and knees to flex when the neck is flexed.

Another of the physically demonstrable symptoms of meningitis is Kernig's sign. Severe stiffness of the hamstrings causes an inability to straighten the leg when the hip is flexed to 90 degrees.

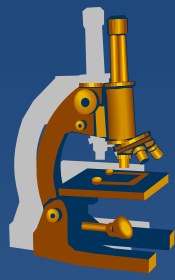
Bacterial leptomeningitis



- **etiology:**
  - ***In neonates:*** *E. coli, Str. agalactiae, Listeria*
  - ***2-5 years.:*** *Str. pneumoniae* ***(****Haemophilus now rare)*
  - ***5-30 years:*** *Neisseria meningitidis (type B)*
  - ***over 30 years:*** *Str. pneumoniae, staph., etc.*
- **Gross:**
  - ***pia mater hyperemic, pus deposits***
  - ***opaque CSF***
  - ***brain swelling, sometimes cortical necrosis***

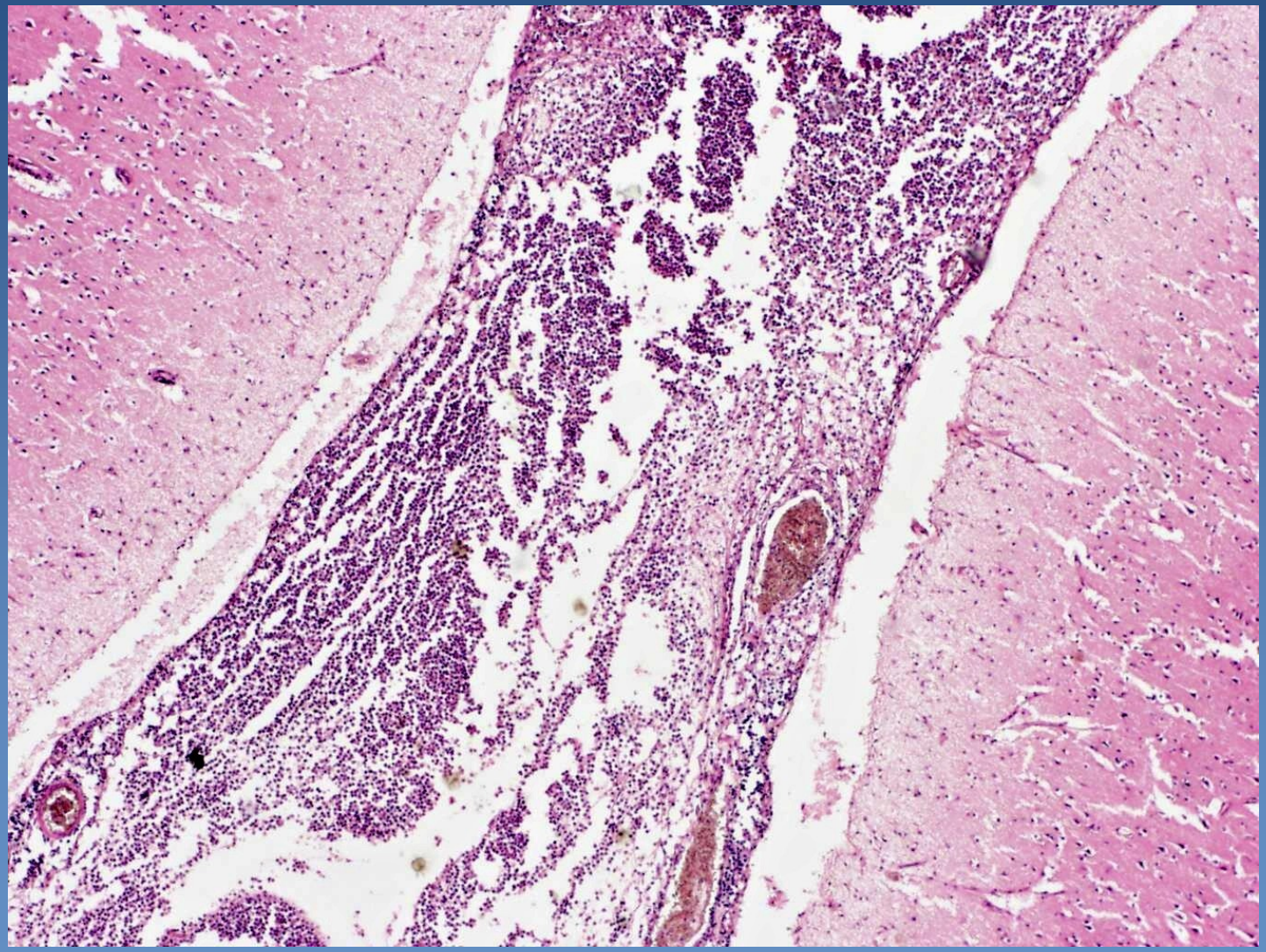
Bacterial leptomeningitis

Bacterial leptomeningitis

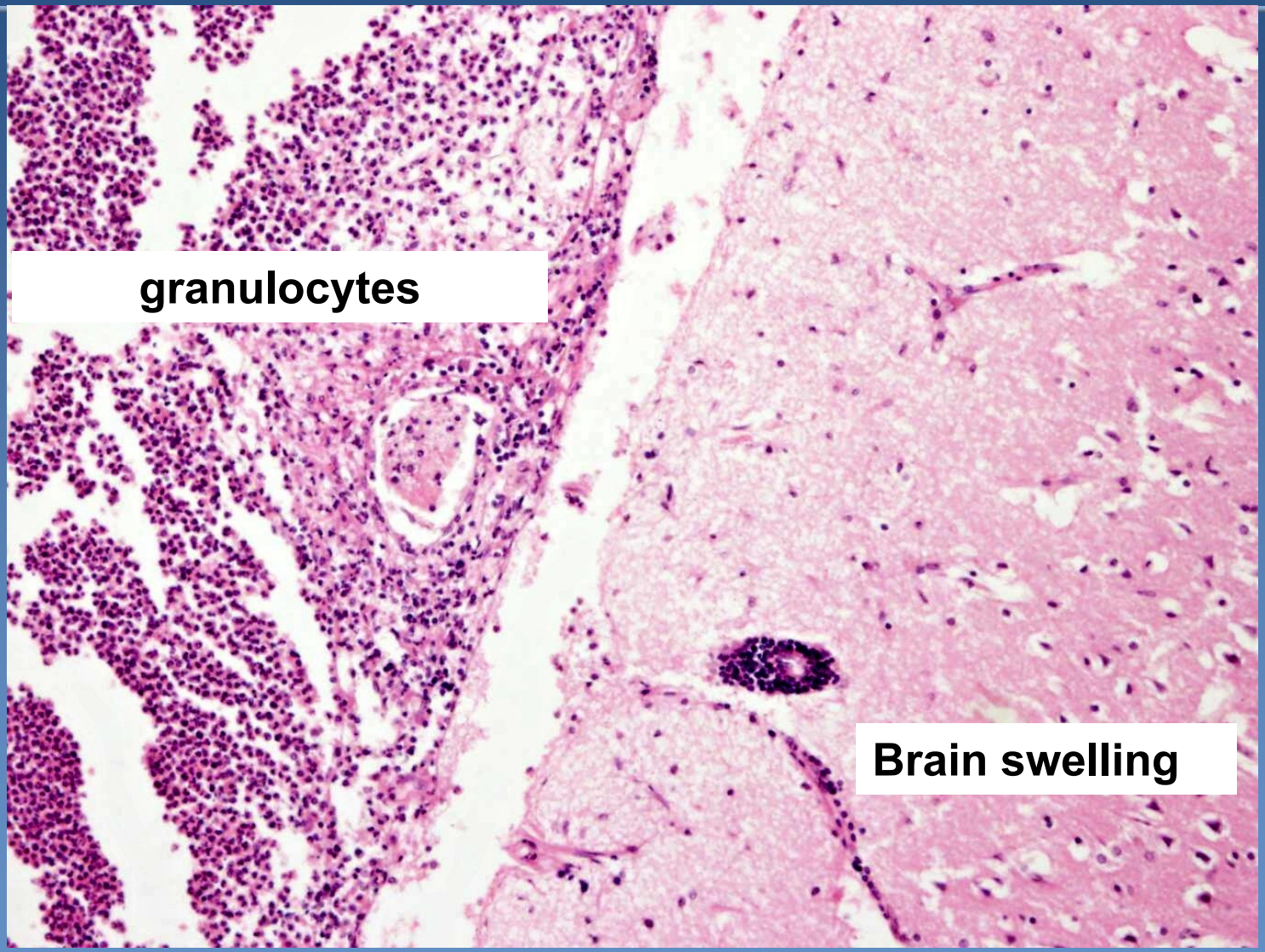


- **micro:**
  - ⇨ *hyperemia, neutrophilic + macrophagic infiltrate, secondary phlebitis + thrombosis*
- **complications:**
  - ⇨ *cerebral abscess*
  - ⇨ *subdural empyema, pyogenic sinus thrombophlebitis*
  - ⇨ *cerebral infarction*
  - ⇨ *DIC, adrenal haemorrhage*
  - ⇨ *epilepsy*
  - ⇨ *permanent psychomotoric disorders*
  - ⇨ *leptomeningeal fibrosis, subarachnoid cysts, obstructive hydrocephalus*

Bacterial leptomeningitis

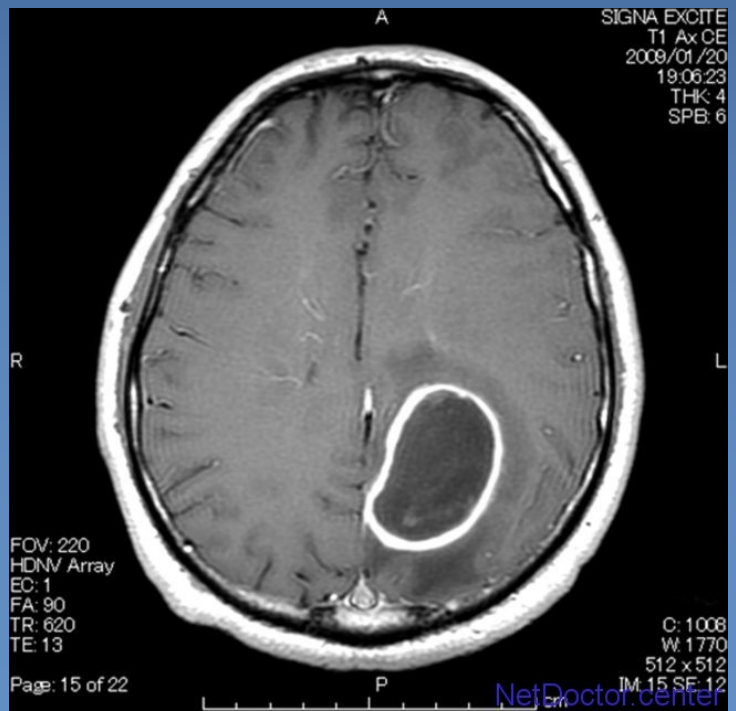


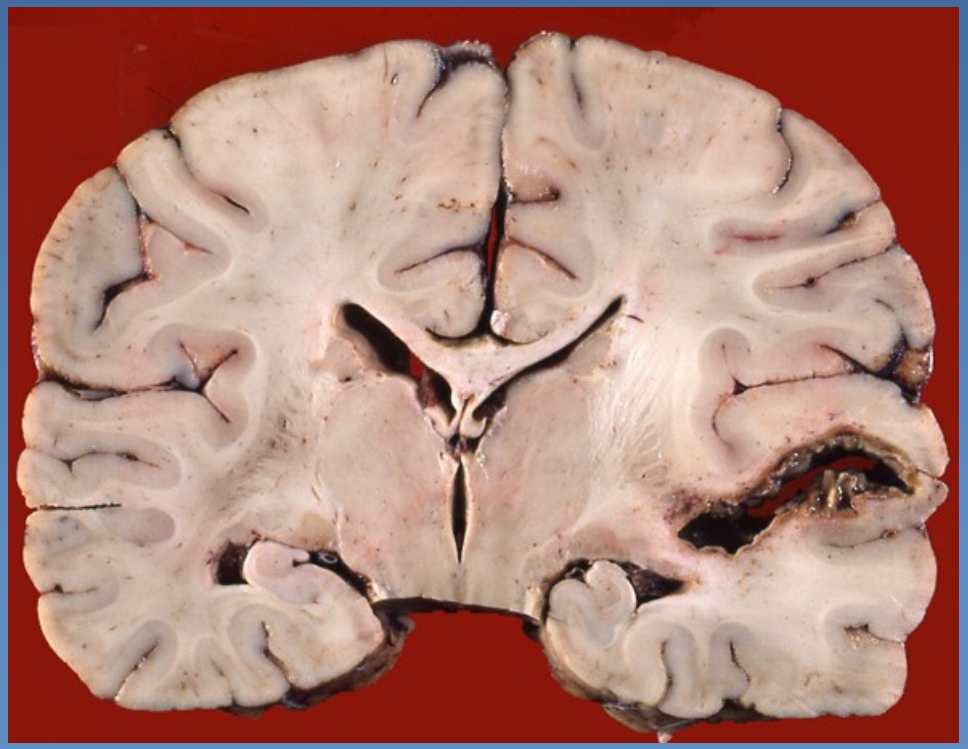
Bacterial leptomeningitis



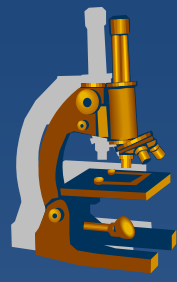
Brain abscess

- direct spread from meningitis
- hematogenous
  - ⇨ ***most common due to acute infectious endocarditis***
  - ⇨ ***multiple foci***



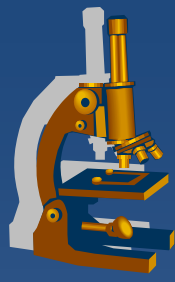


Acute aseptic meningitis



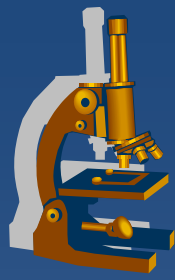
- infectious
  - ⇨ *viral (mumps, coxackie, echoviruses, EBV, HSV)*
  - ⇨ *usually self-limited*
  - ⇨ *gross: hyperemic pia mater, slight edema*
  - ⇨ *micro: lymphocytic infiltration*
- chemical or other irritant

Chronic meningitis



- granulomatous
  - ⇨ ***Mycobacterium tbc., granulomas, obliterative endarteritis***
  - ⇨ ***meningovascular neurosyphilis***
  - ⇨ ***fungi: Cryptococcus neoformans, Aspergillus, etc.***
- chronic
  - ⇨ ***Lyme disease – aseptic meningitis***
- immune deficiency
  - ⇨ ***AIDS, immunosuppression, cachexia***

Tuberculous meningitis

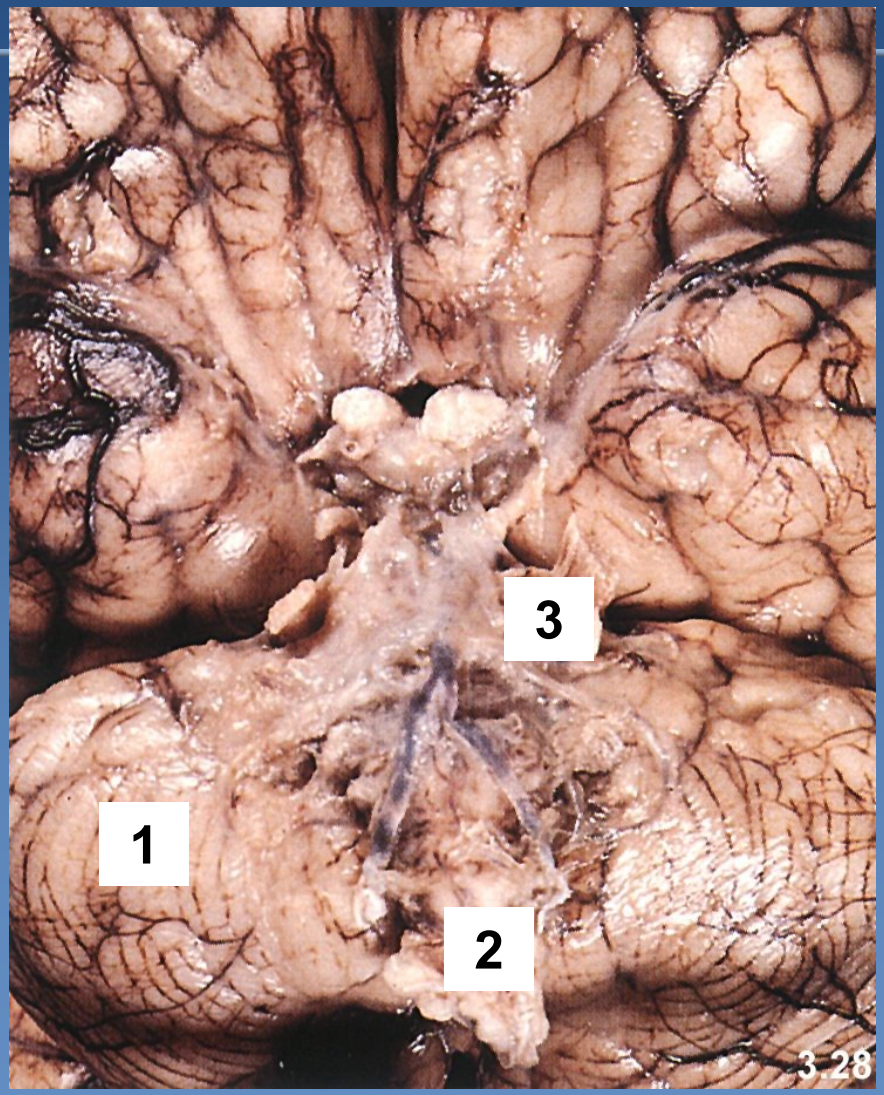


- **etiology:** ***mycobacterium tuberculosis***
- **spread:** ***usually hematogenous in primary pulmonary tuberculosis***
- AIDS (M. avium-intracellulare complex)
- **gross: exudative -** ***thick gelatinous exudate, most marked at the base of the brain;***

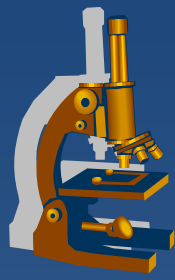
  proliferative: ***small white granulomas***

tuberculous meningitis

1 cerebellum
2 oblongata
3 gelatinous inflammatory infiltrate

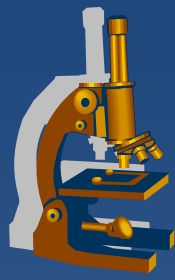


Encephalitis



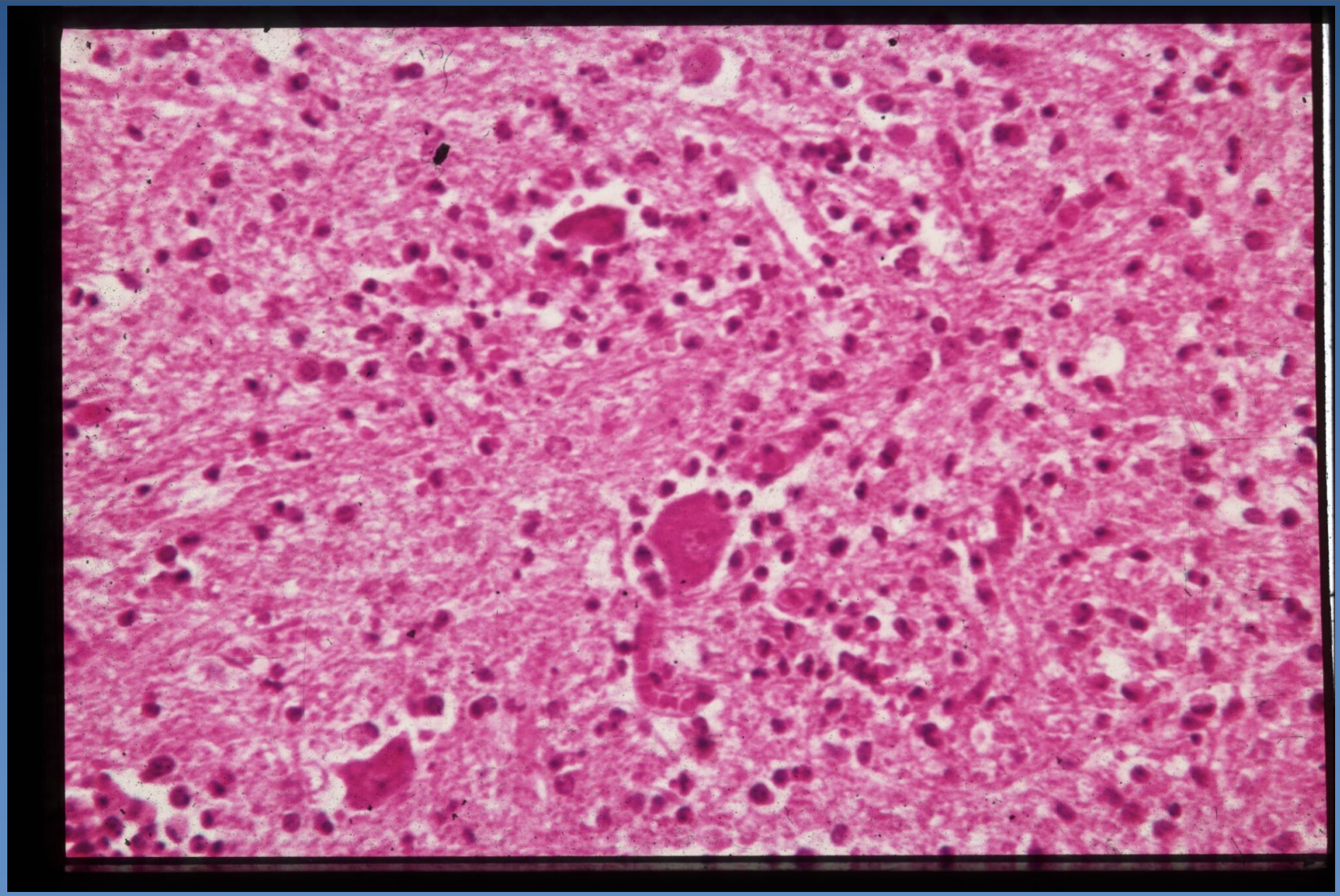
- **primary**
  - ⇨ *neurotropic viruses*
  - ⇨ *anthropozoonozes - from animals transmitted to humans*
- **secondary**
  - ⇨ *other underlying disease*
    - **viruses (HSV, enterovirus, mumps), rickettsia, parasites (toxoplasmosis…), spirochets (lues), fungi.**
- **micro (viral encephalitis):**
  - ⇨ *neuronal damage, reactive glial changes*
  - ⇨ *perivascular „cuff“ infiltrate of lymphocytes, plasma cell*

Viral encephalitis - myelitis

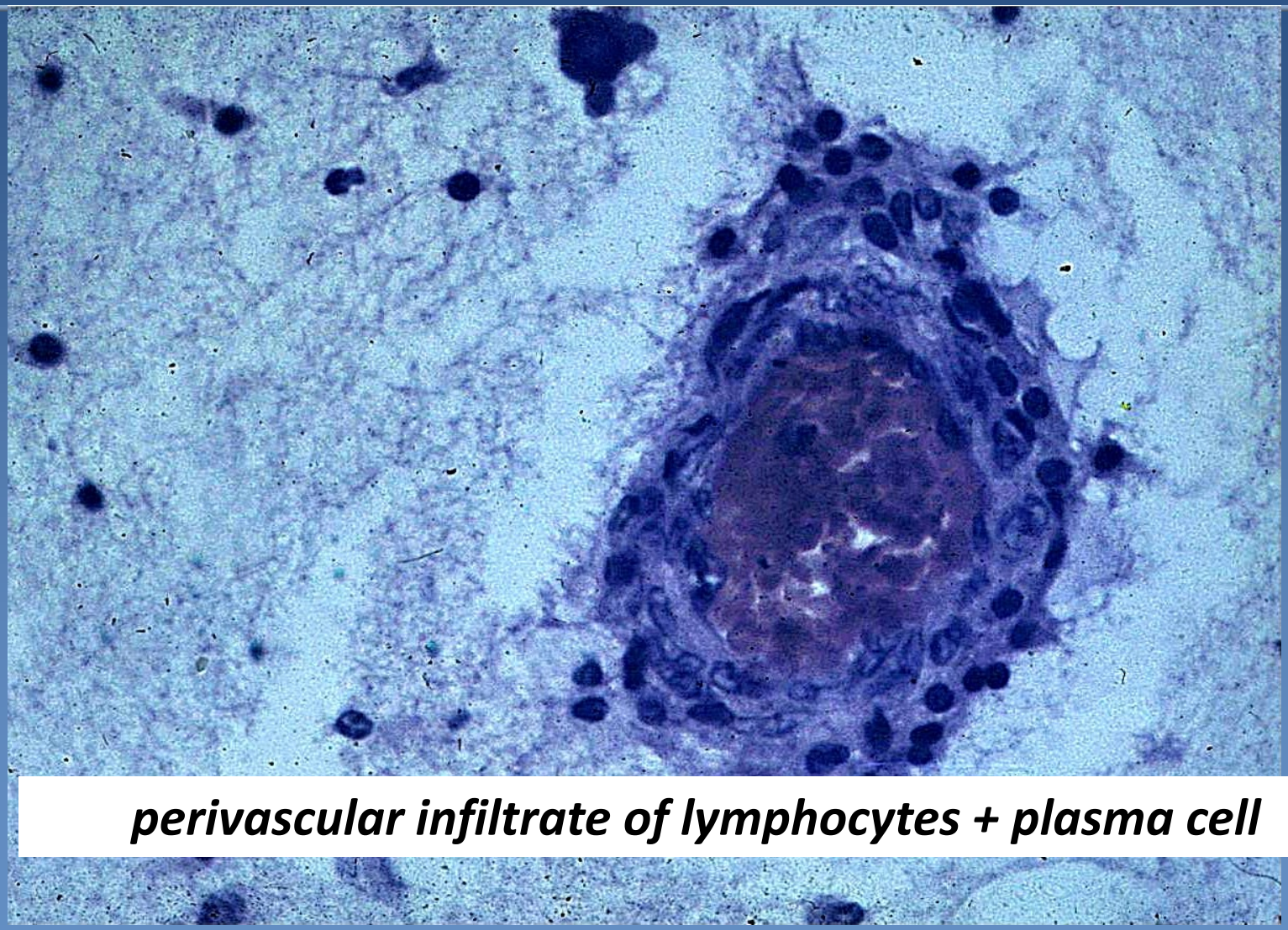


- **usually + meningitis**
- **spread:** ***haematogenous x neural (retrograde)***
- **tropism** - specific cell type or area involved
- **etiology:**
  - ⇨***arthropod-borne (tick-borne), mumps, enteroviruses (poliomyelitis), HSV, CMV, EBV, HIV, rabies***
- **gross:**
  - ⇨***hyperemic meninges, brain edema***
- **micro:**
  - ⇨ ***perivascular, parenchymal mononuclear cell infiltrate, glial cell reaction, oedema, neuronophagia, viral inclusions***
- ***possibility of latency, immune-mediated disease, late sequelae***

Viral encephalitis - myelitis

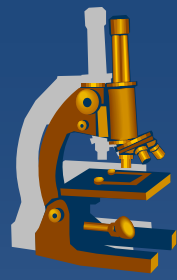


Viral encephalitis



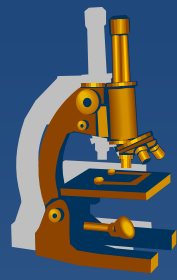
perivascular infiltrate of lymphocytes + plasma cell

Viral encephalitis



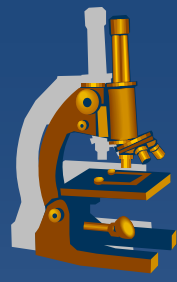
- **with the formation of inclusion bodies**
  - ⇨ *Rabies*
  - ⇨ *HSV1, HSV2*
  - ⇨ *Poliomyelitis*
- **Without inclusion bodies**
  - ⇨ *tick-borne viral encephalitis*
  - ⇨ *HIV-associated encephalitis*

Encephalitis



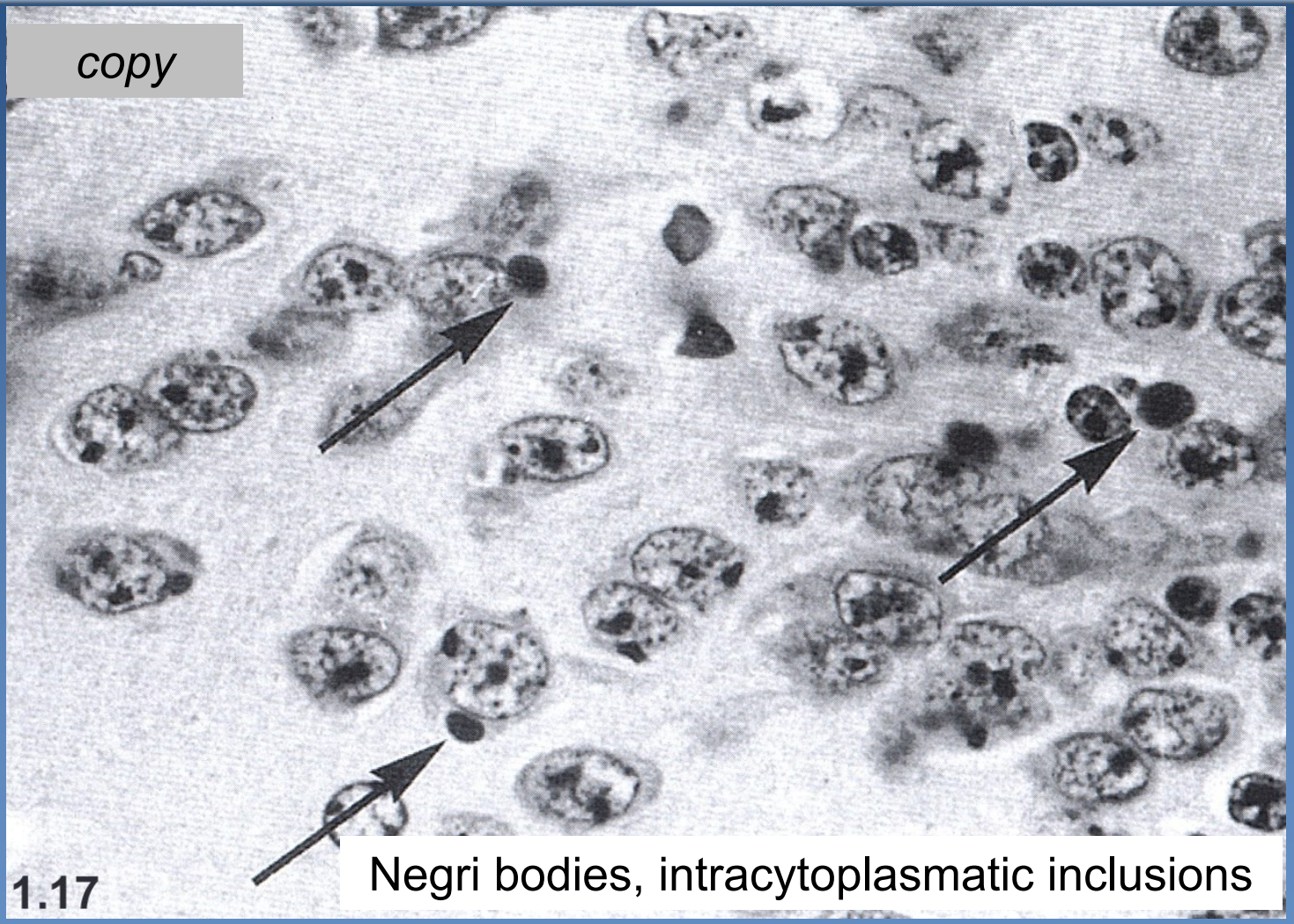
- Others
  - ⇨ ***Acute disseminated encephalomyelitis – immune-associated demyelinisation***
  - ⇨ ***Subacute sclerosing panencephalitis (measles virus)***
  - ⇨ ***Typhoid fever - rickettsiae***
  - ⇨ ***Neurosyphilis***

Viral encefalitis
with inclusion bodies



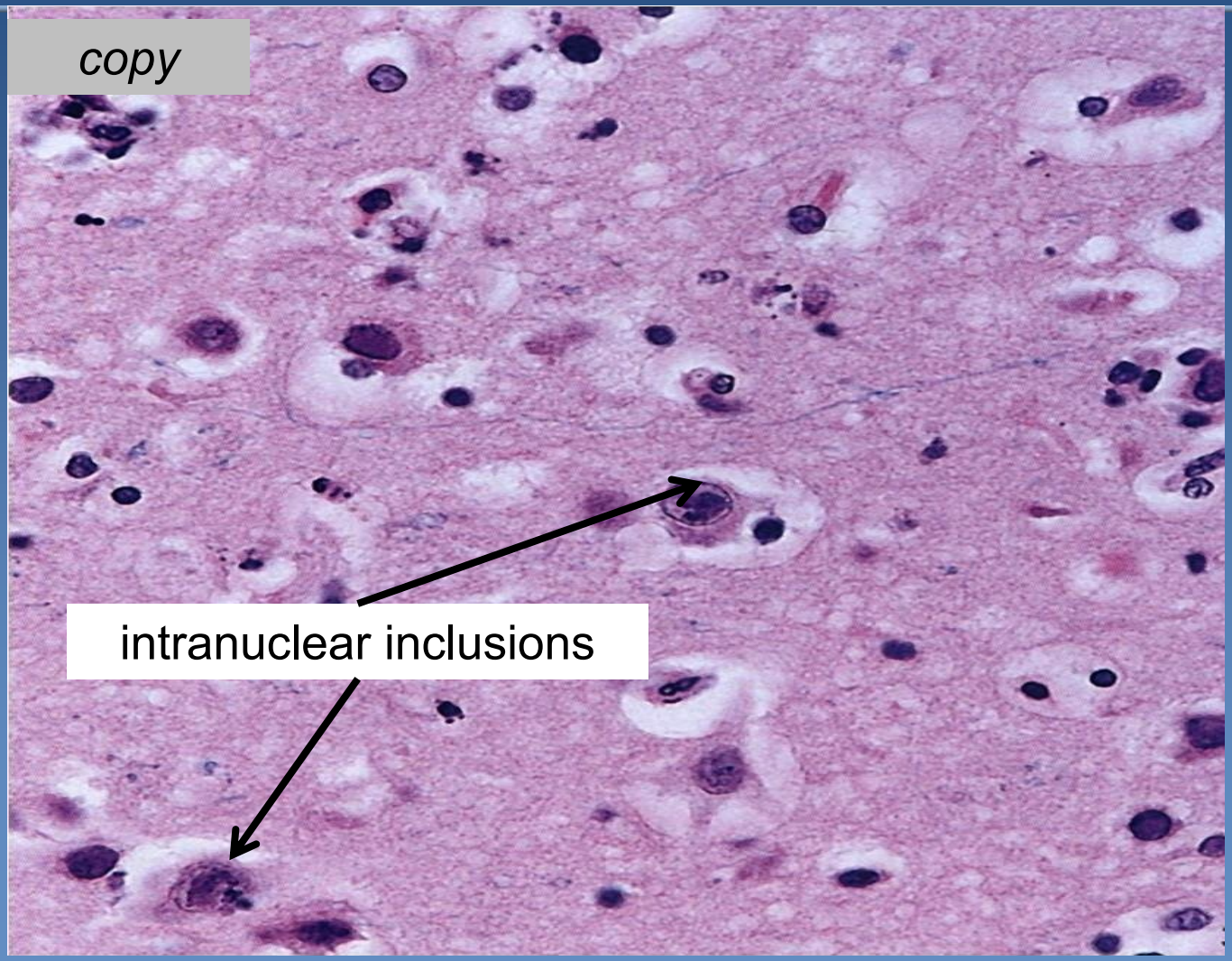
- **rabies, lyssa**
  - ⇨ *incubation 2-12 weeks → with axonal retrograde flow to the brainstem, spinal cord, dorsal root ganglia, cerebral cortex, cerebellum, hippocampus*
  - ⇨ *micro **Negri bodies** (eosinophilic inclusions of the size of red blood cells in the cytoplasm of neurons)*
  - ⇨ *postexposure prophylaxis - vaccination*
- **herpetic encephalitis (HSV1, HSV2)**
  - ⇨ ***frontal cortex,** other parts of the gray matter*
  - ⇨ *hemorrhagic necrosis, intranuclear inclusions*
  - ⇨ *severe (sometimes fatal) course*
  - ⇨ *HSV2 infection possible in newborns*

Rabies

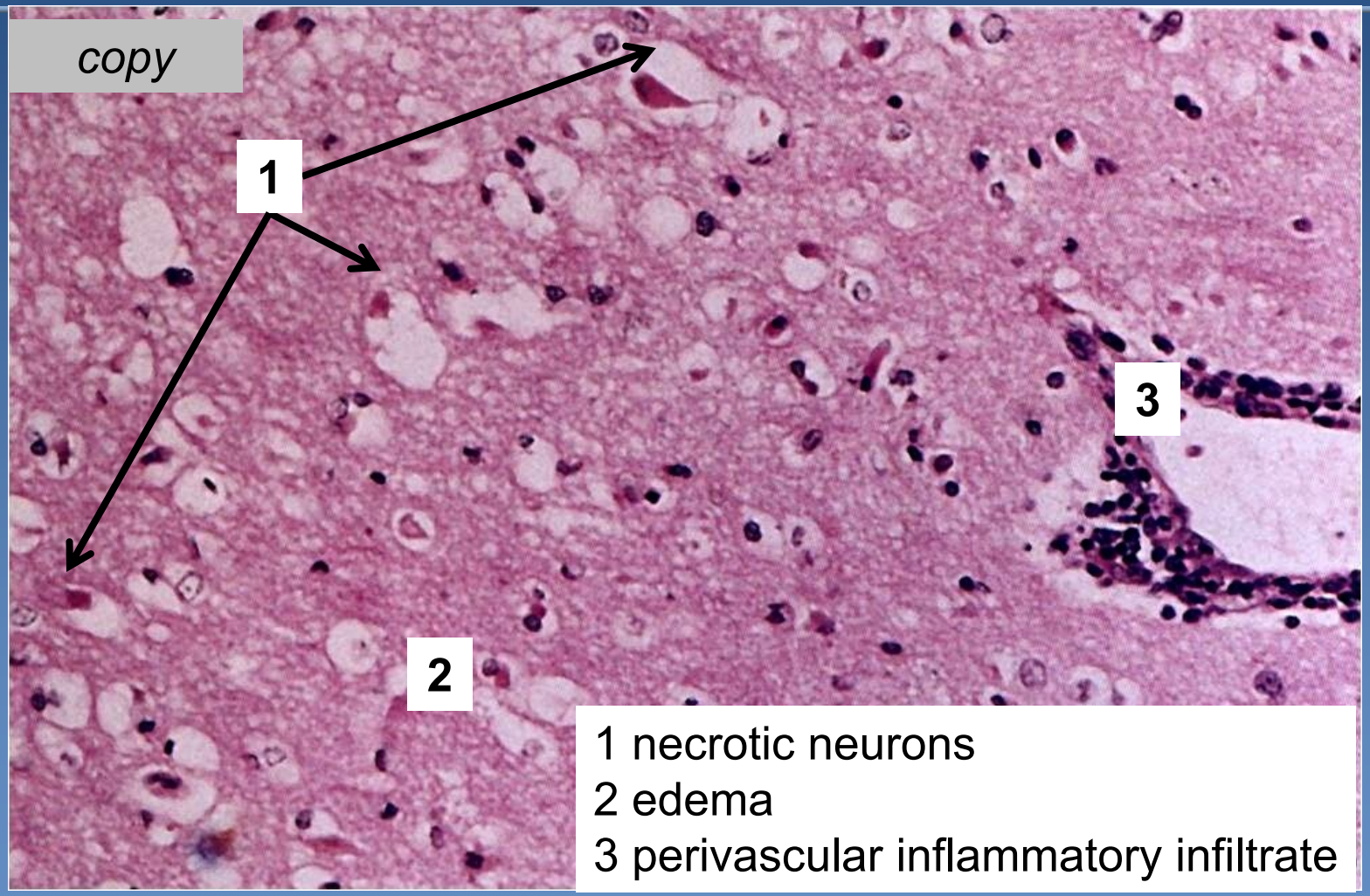


Negri bodies, intracytoplasmatic inclusions

Herpetic encephalitis

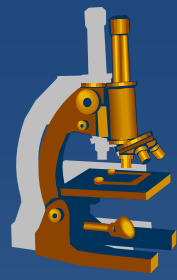


Herpetic encephalitis



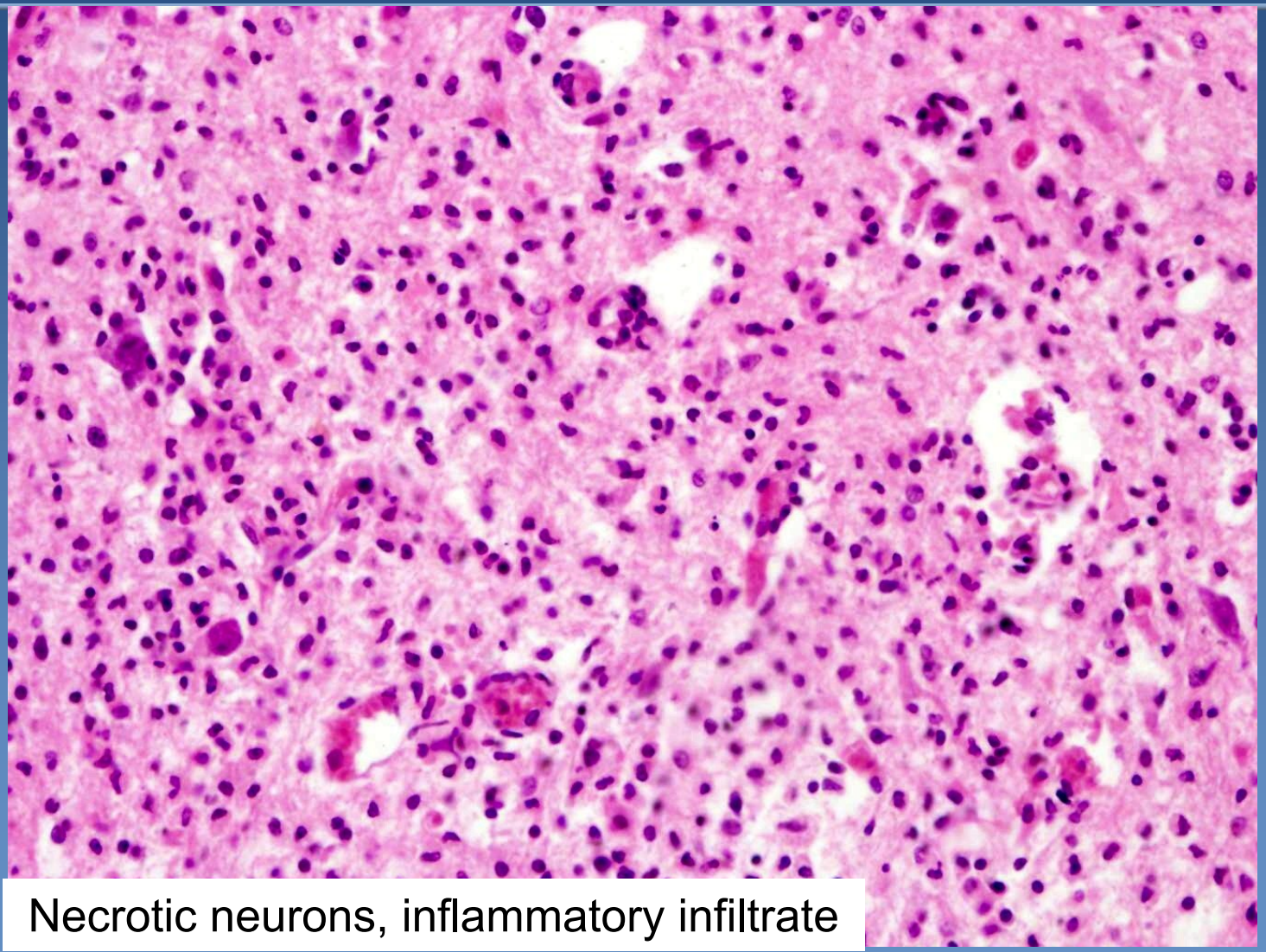
1 necrotic neurons
2 edema
3 perivascular inflammatory infiltrate

Viral encefalitis
with inclusion bodies



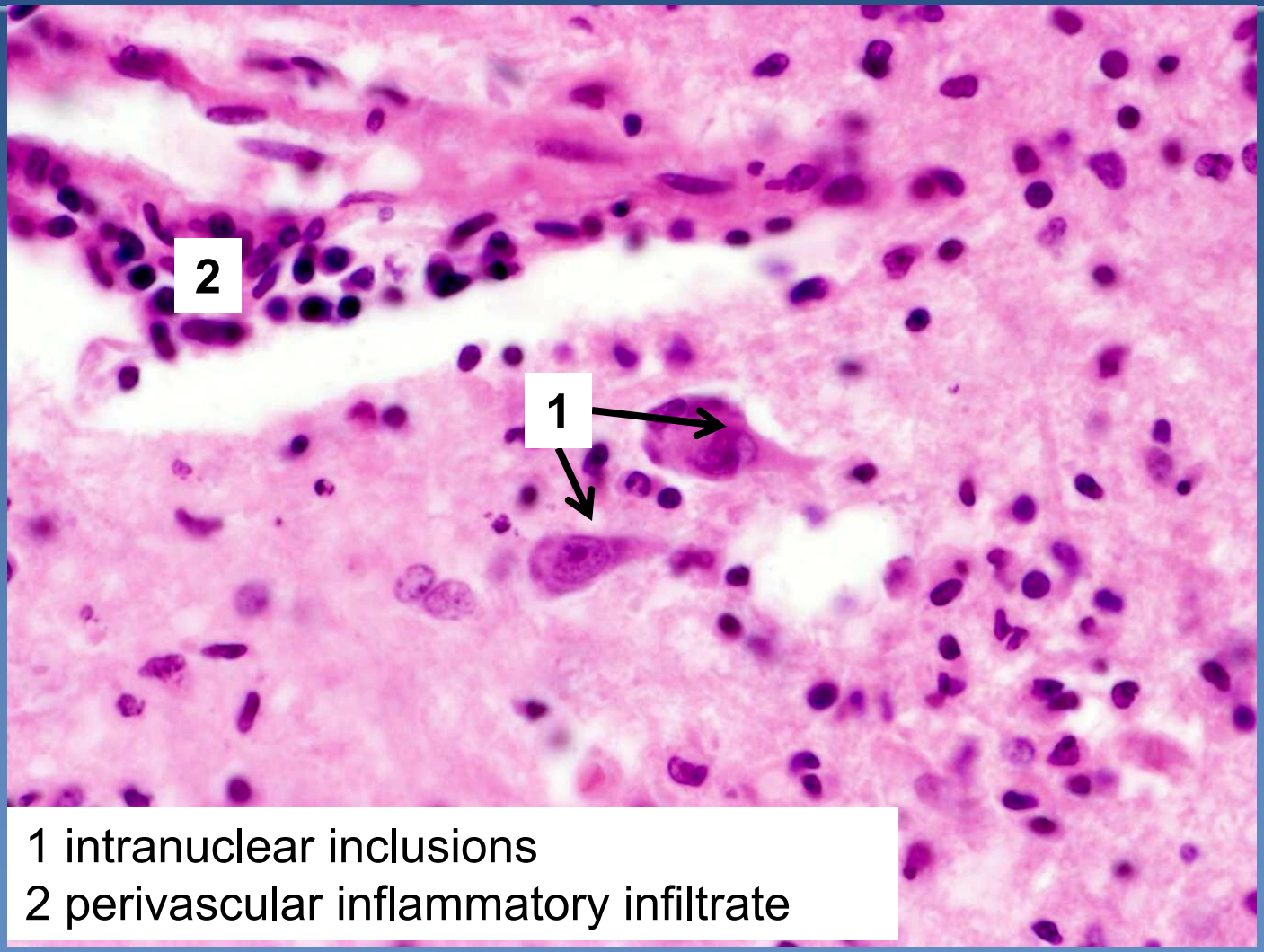
- **Poliomyelitis**
  - ⇨ *enteroviruses, coxsackie, ECHO*
  - ⇨ *pharyngitis, enteritis, myocarditis, myositis…*
  - ⇨ *approx. in 10% affinity to the motoric neurons → anterior horns of the spinal cord, (gyrus precentralis) → symptoms of paralysis in 1 %*
  - ⇨ *anterior horns of the spinal cord markedly swollen, hyperemic*
  - ⇨ *small intranuclear inclusions → neuronal necrosis → inflammatory reaction + neuronophagia → gliosis*
- **CMV encephalitis**
  - ⇨ *fetal, posttransplantation infection*
  - ⇨ *necrotizing encephalitis mostly in periventricular regions*

Poliomyelitis



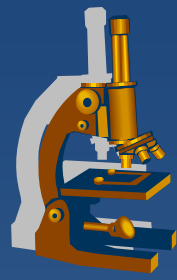
Necrotic neurons, inflammatory infiltrate

Poliomyelitis



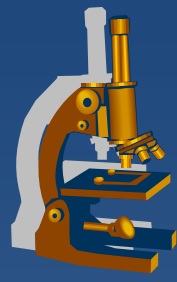
1 intranuclear inclusions
2 perivascular inflammatory infiltrate

Viral encephalitis
without inclusion bodies



- **Tick-borne encephalitis (Middle Europe)**
  - ⇨ ***mostly asymptomatic***
  - ⇨ ***symptoms rarely***
    - convulsions, confusion, delirium, coma, often with focal neurological deficits such as reflex asymmetry
  - ⇨ ***meningeal form, meningoencephalitic or encephalomyelitic form***
    - *both gray and white matter affected (panencefalitis)*
    - *permanent sequels less common*
    - *prevention – vaccination*
    - *no specific treatment available yet*

Viral encephalitis without inclusion bodies



- **HIV encephalitis**
- **HIV-associated dementia**

⇨ *acute aseptic meningitis in 10% of HIV + patients*

⇨ *subacute/chronic HIV encephalitis*

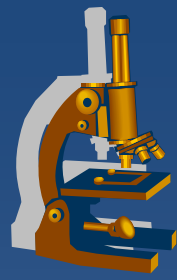
- brain atrophy, glial scars, microglial nodules
- cognitive deficiency - dementia

⇨ *vacuolar myelopathy*

⇨ ***opportunistic encephalitis (herpetic, CMV, toxoplasmosis)***

⇨ ***EBV-associated primary DLBCL***

Neurosyphilis



⇨ ***different CNS changes in the 2nd, 3rd stage***

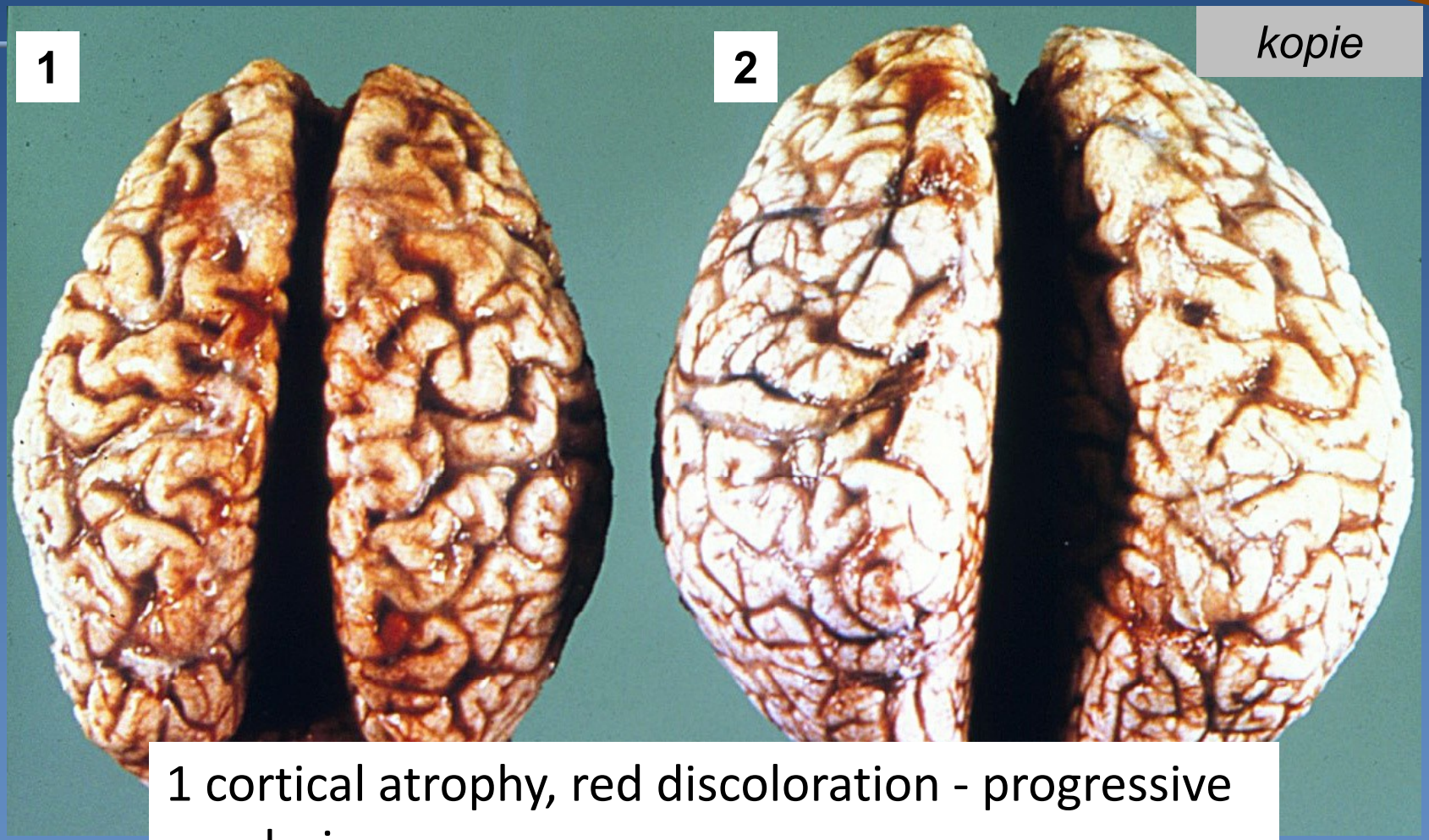
⇨ ***meningovascular form***

- chronic meningitis
  - miliary gummata, mostly on the base
- obliterative (Heubner) endarteritis
  - focal medial destruction, lymphocytic infiltration

⇨ ***parenchymatous form***

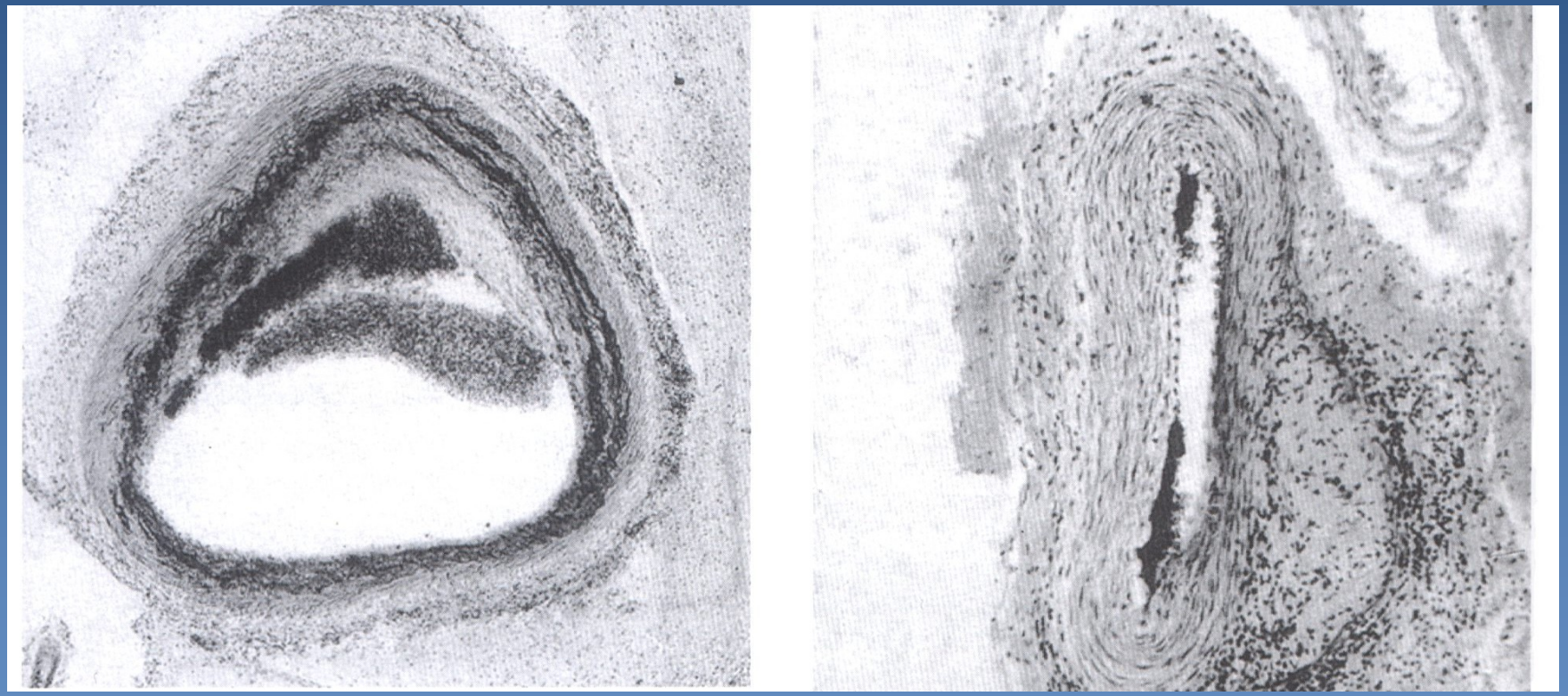
- atrophic cortex + hemosiderin; gummata
- progressive mental deficit ⟶ dementia, progressive paralysis
- tabes dorsalis – sensory nerves of the dorsal roots

Neurosyphilis



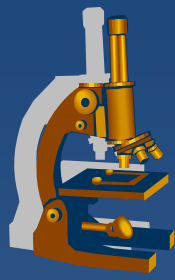
1 cortical atrophy, red discoloration - progressive paralysis
2 initial stage

Neurosyphilis
Heubner arteritis



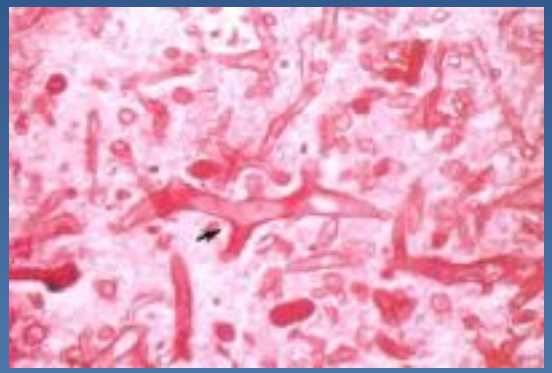
Focal thinning + destruction of media, lymphocytes in adventitia

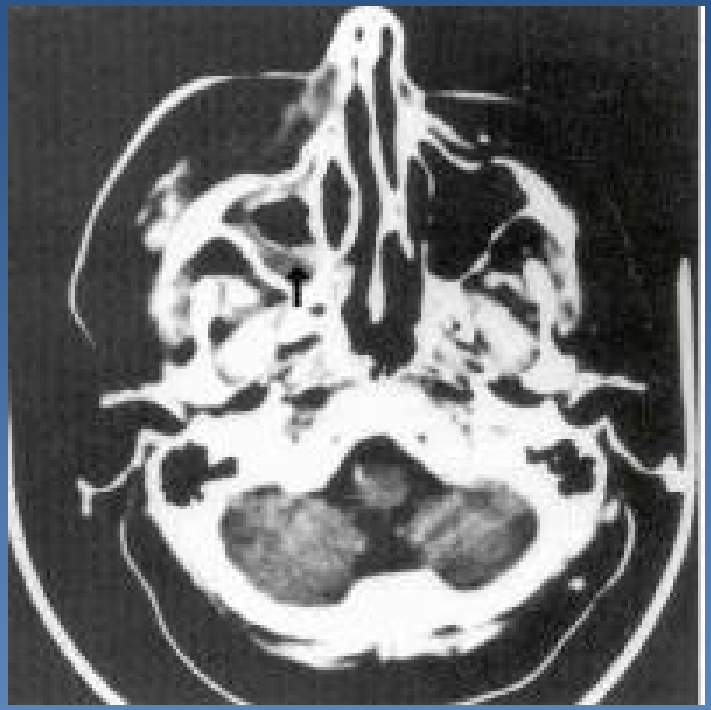
Mycotic CNS infections

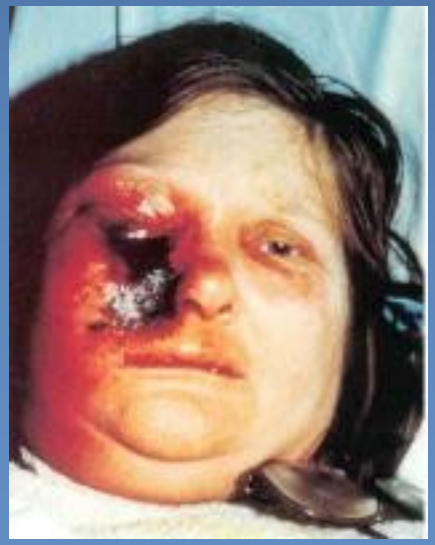


- opportunistic
- abscess or granulomatous inflammation
- entry
  - ⇨ ***hematogenous – candida, aspergillus***
  - ⇨ ***mucormycosis sinusitis - direct spread from nasal/paranasal cavity, destructive ocular, brain lesions, opportunistic in the debilitated, immunocompromised, or acidotic patient.***
- Cryptococcus
  - ⇨ ***in bird‘s droppings***
  - ⇨ ***inhalation into lungs***
  - ⇨ ***by blood into meninges***

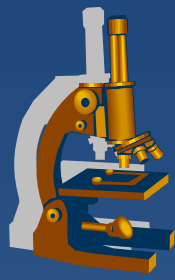
Invasive brain mucormycosis





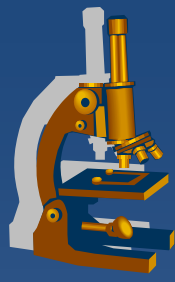


Parasitic CNS infections



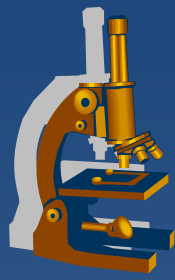
- Toxoplasmosis
  - ***transplacental infection – necrotising periventricular inflammation + calcifications***
  - ***hydrocephalus, periventricular calcifications, chorioretinitis***
  - ***in immunosuppressed adults – multifocal necrotising inflammation***
- Neurocysticercosis
  - ***Taenia solium larvae during hematogenous spread may form progressive brain cystic lesion***
  - ***secondary epilepsy***

prion encephalopathy



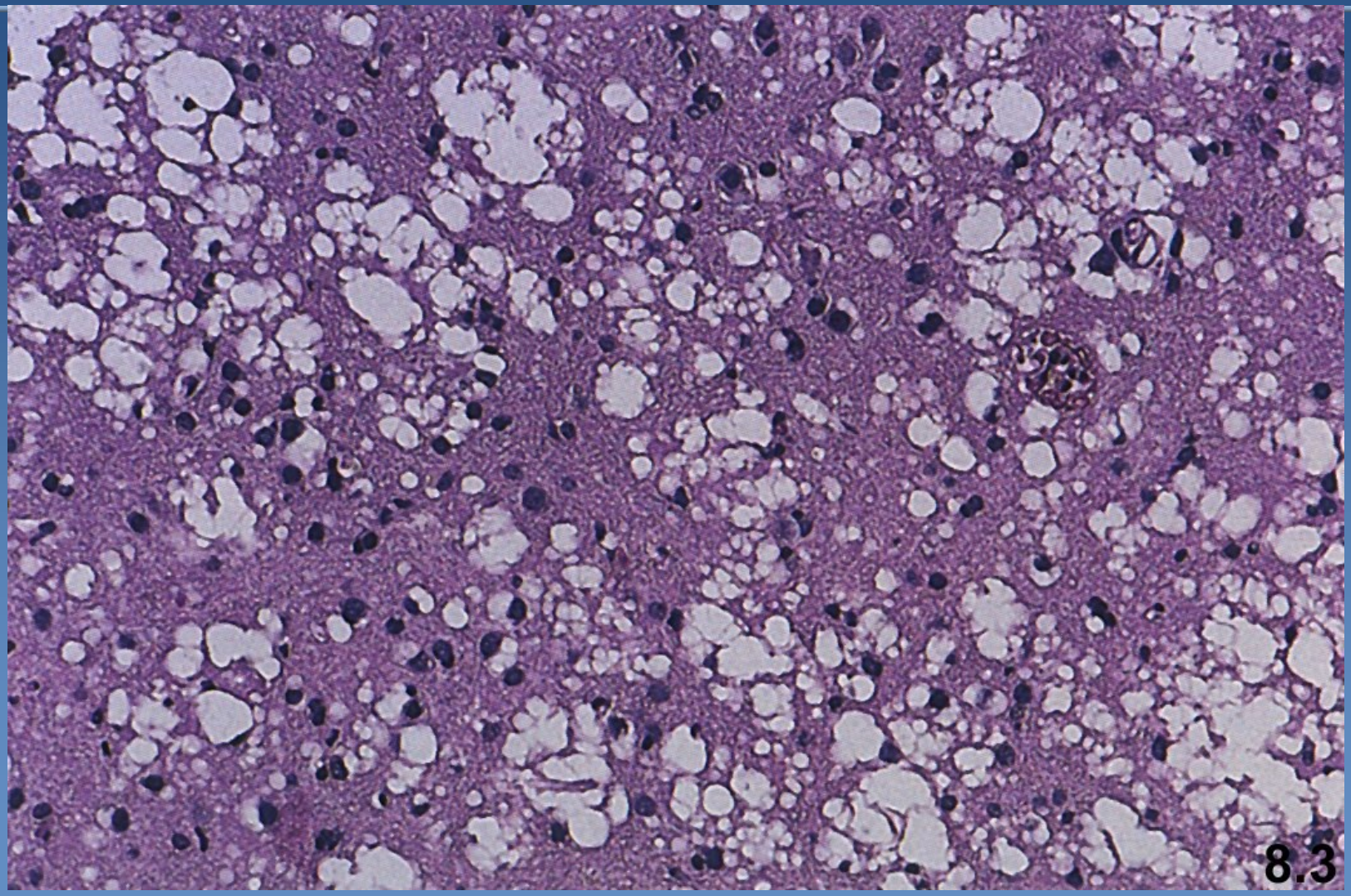
- **Prions** *(proteinaceous infectious particles)*
  - ⇨ ***protein particles capable of inducing conformational change of tissue PrPc to pathogenic PrPSc***
  - ⇨ ***micro:***
    - **spongiform encephalopathy – microscopic vacuolisation**
    - *numerical atrophy of neurons*
    - *reactive gliosis*
    - **missing inflammatory response!!**
  - ⇨ ***long incubation period, rapid progression (dementia)*** → ☹

prion encephalopathy



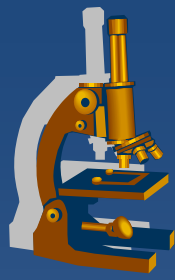
- Creutzfeldt-Jacob disease
  - ⇨ ***rapidly progressive dementia***
  - ⇨ ***around 7th life decade***
  - ⇨ ***sporadic***
  - ⇨ ***familial – genetic mutation in PrP gene***
  - ⇨ ***iatrogenic***
  - ⇨ ***new variant***
    - BSE-associated, alimentary spread, young patients

Creutzfeldt-Jacob disease



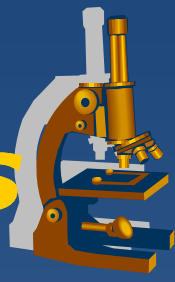
Metabolic and toxic encephalopathies

- inborn
  - ***Wilson disease***
    - AR, disturbance of copper ions into bile, Cu organ accumulation + oxygen radicals damage, brain damage – parkinsonism + cognitive deficiency, Kayser-Fleischer corneal ring
- acquired
  - ***vitamin B1***
    - alcoholism, chronic malnutrition
    - acute confusion, ataxia
    - chronic memory loss
  - ***B12 deficiency***
    - pernicious anaemia
    - spinal cord degeneration



Neurodegenerative diseases

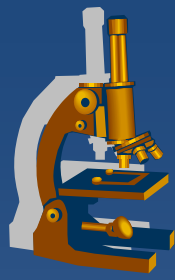
Neurodegenerative diseases



- loss of specific groups of neurons → typical clinical signs (with overlap)
  - ⇨ ***apoptosis + oxygen radicals – neuronal damage***
  - ⇨ ***pathological protein aggregates***
    - disease-specific – classification
  - ⇨ ***genetic risk***

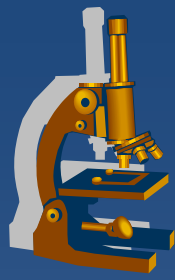
! Signs of dementia commonly due to another problem (drugs/toxins, infection, tumor, metabolic, vitamin deficiency, …), work-up necessary

Neurodegenerative diseases



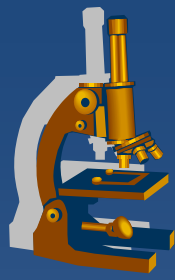
- cortex – dementia
  - ⇨ ***cognitive functions – memory, orientation, learning, speach, ...***
  - ⇨ ***i. e. Alzheimer‘s***
- subcortical basal ganglia
  - ⇨ ***extrapyramid syndromes***
  - ⇨ ***Parkinson‘s d. – tremor, dyskinesia, rigidity***
- motor neurone loss
  - ⇨ ***amyotrophic lateral sclerosis***
- spinocerebellar degeneration

Alzheimer´s disease



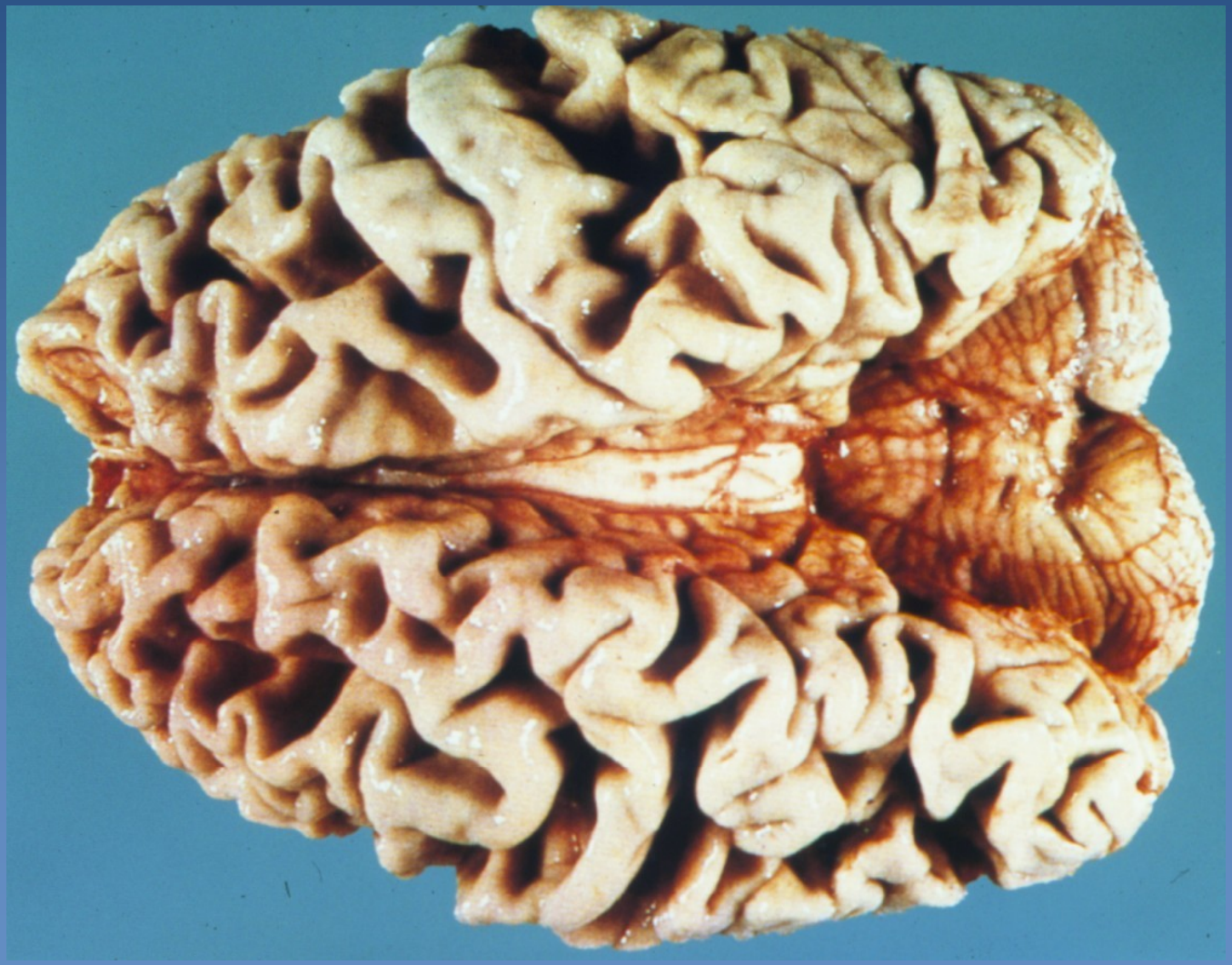
- **the most common neurodegenerative condition (>70%), mixed cause possible (+ vascular)**
- **(pre-) senile dementia**
  - ⇨ *possible start at the age of 50 (or sooner), usually later (incidence ↑ with age) → slow progression (-> 8-10+ years) → death due to inanition, bronchopneumonia*
  - ⇨ *M:F 1:2*
  - ⇨ *sporadic x familial (about 5%)*
  - ⇨ *presymptomatic stage (β-amyloid accumulation present, possible changes in liquor, blood – early diagnosis in the future)*
  - ⇨ *mild cognitive deficiency*
  - ⇨ *clinical Alzheimer‘s*

Alzheimer´s disease

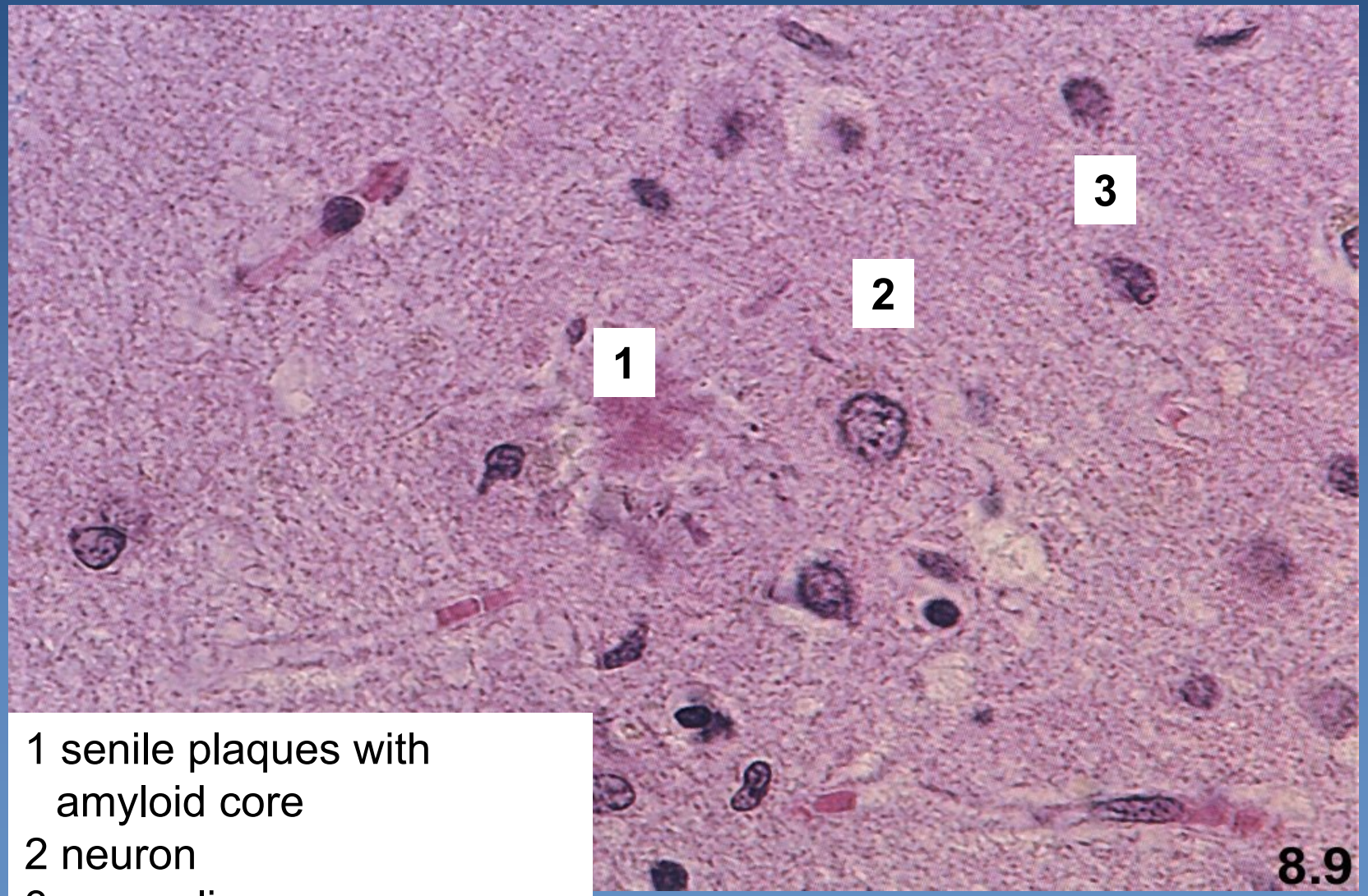


- **gross:**
  - *marked cortical atrophy (frontal, temporal)*
  - *loss of cortical grey and white matter, secondary hydrocephalus*
  - *limbic system affected - hippocampus*
- **micro:**
  - *neuronal loss*
  - *A-beta amyloid neuritic plaques*
  - *hyperphosphorylated tau protein - neurofibrillary tangles*
  - *amyloid angiopathy - deposits in the wall of capillaries and arterioles*
  - *non-specific changes, only more pronounced*

Alzheimer´s disease

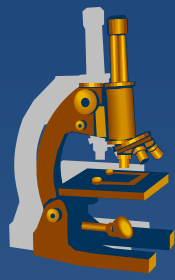


Alzheimer´s disease



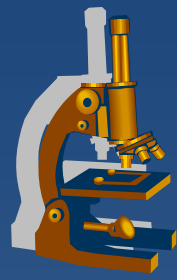
1 senile plaques with amyloid core
2 neuron
3 neuroglia

Frontotemporal lobar dementias



- heterogenous group
- atrophy of frontal and/or temporal lobes
- in younger age groups (<65), more rapid progression
- similar clinical picture – language + behaviour deterioration, personality changes
- may have specific protein aggregates -deposits (tau)
- sporadic or rare familial
- approx. 10% od dementias

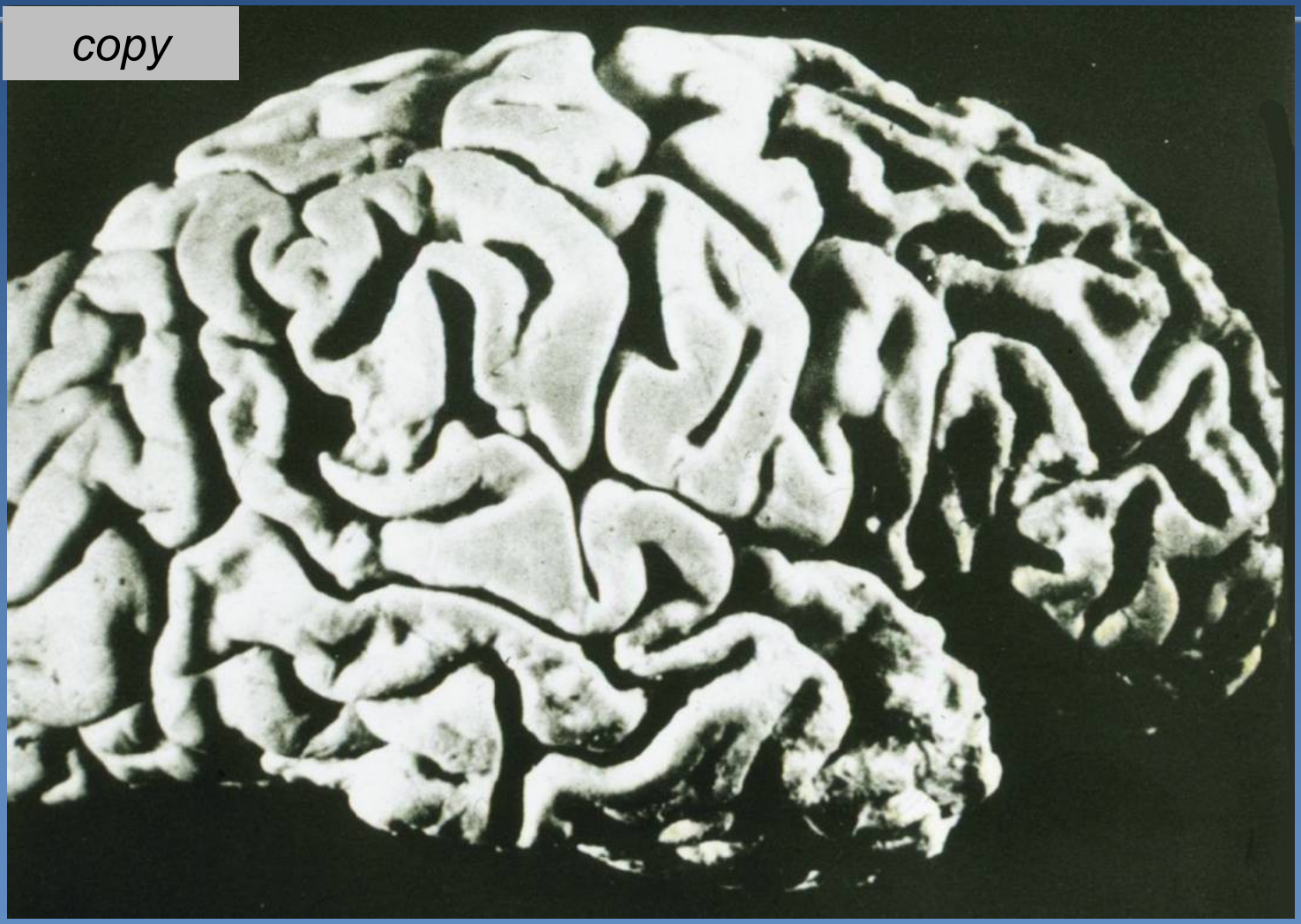
Pick's disease



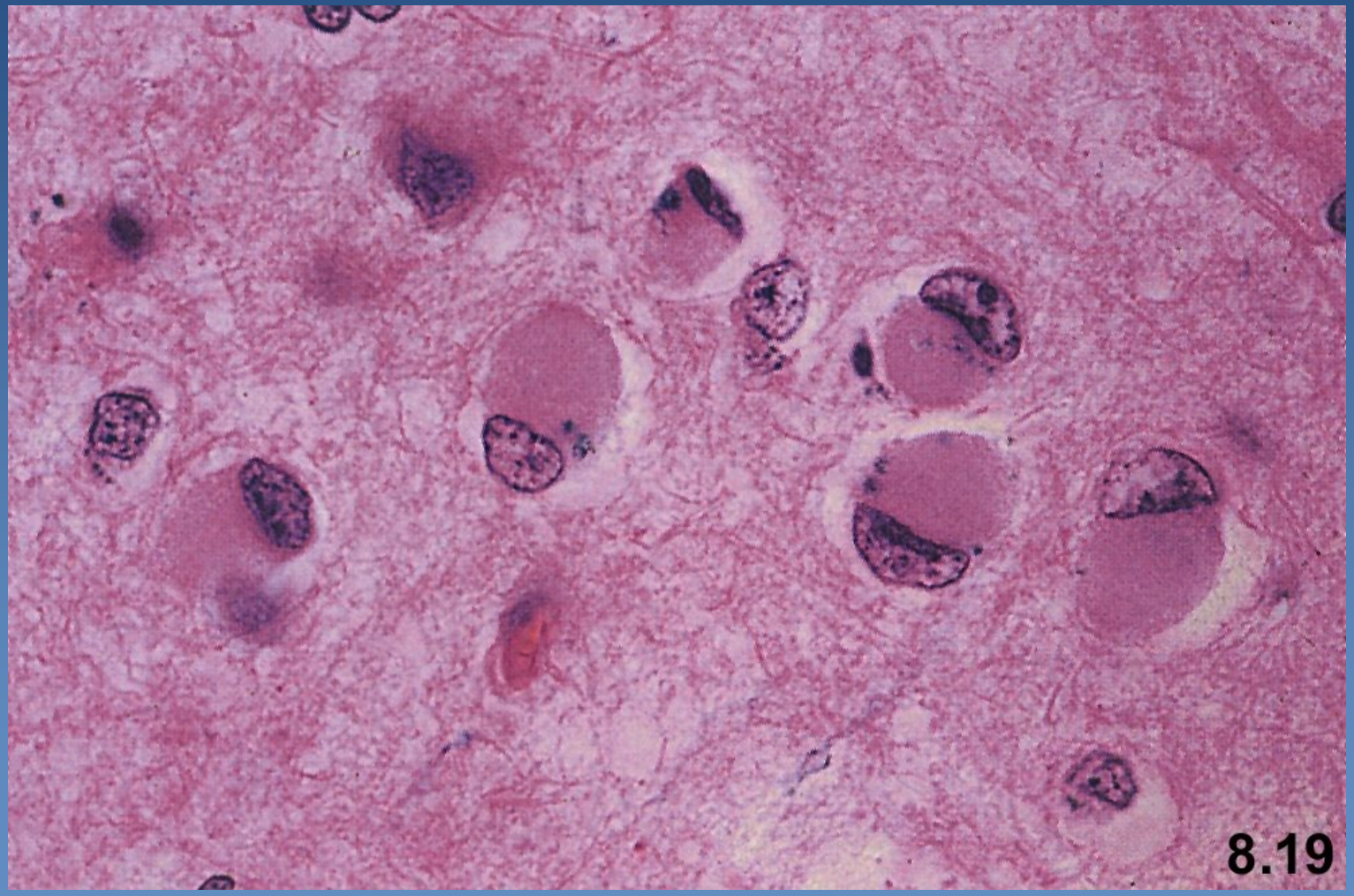
- 5% of dementias, frontotemporal lobar dementia M>F
- **gross**
  - ⇨ ***max. atrophy in the frontal and temporal lobe - lobar atrophy***
- **micro**
  - ⇨ ***loss of neurons in the I.-III. cortical layers***
  - ⇨ ***demyelination in the white matter***
  - ⇨ ***reactive gliosis***
  - ⇨ ***intracytoplasmic Pick bodies (filamentous abnormal protein inclusions)***

Pick's disease

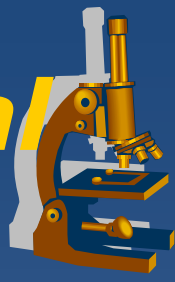
copy



Pick's disease

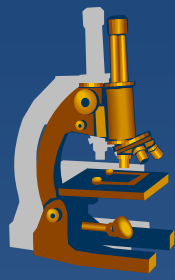


Degenerative diseases of basal ganglia and brainstem



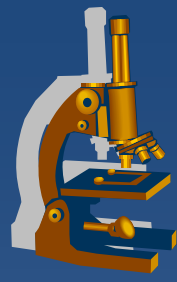
- extrapyramid syndromes
  - ***hypokinetic – parkinsonism, rigidity***
  - ***hyperkinetic – Huntington d., involuntary irregular movements – chorea***
- reduction of voluntary movements
- increase of involuntary movements

Parkinsonism



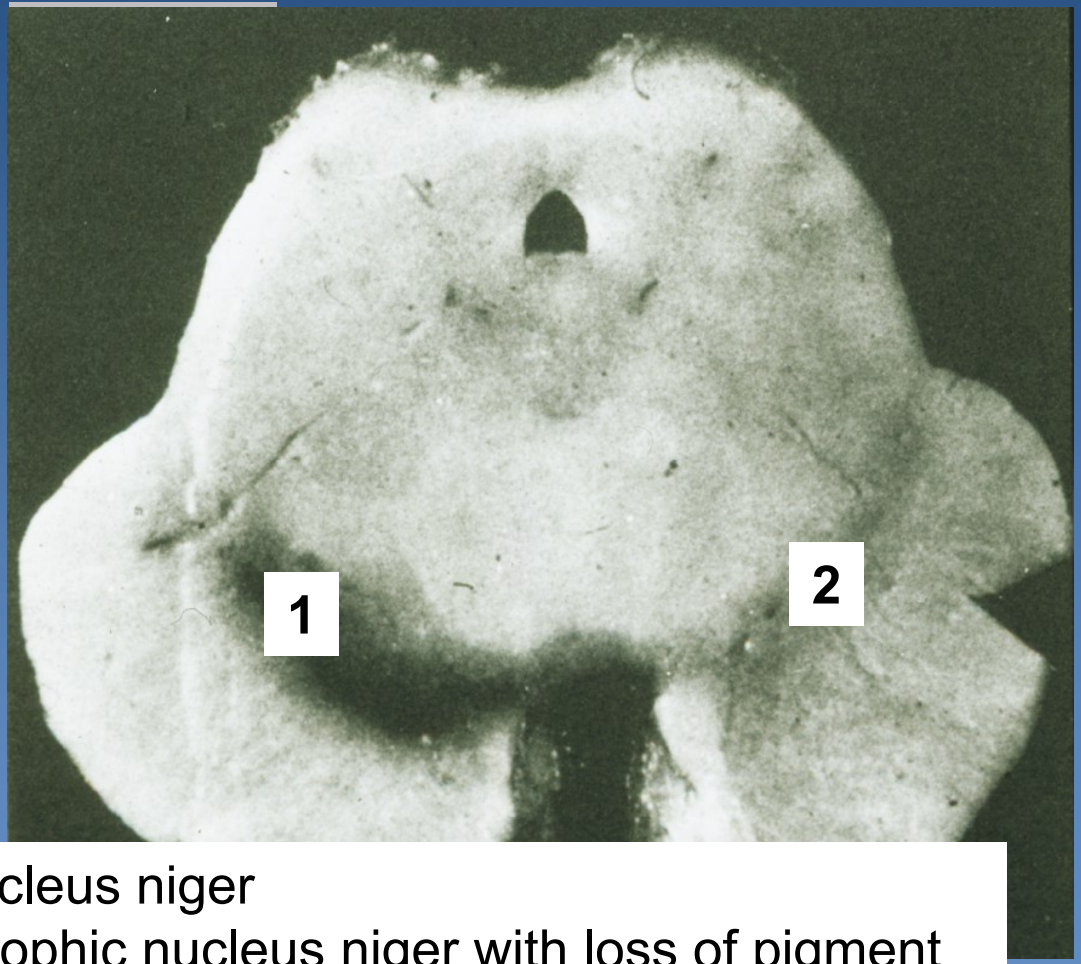
- **clinical condition due to the damaged nigro – striatal dopaminergic system**
- ↓ inhibitory neurotransmitter
- stiff facial expression, muscle rigidity, slowness of voluntary movements (bradykinesia), tremor, postural instability
- **forms:**
  - ⇨ ***Primary PS:***
    - **Parkinson's disease**
    - multiple system atrophy, i. e striatonigral degeneration
  - ⇨ ***Secondary PS:***
    - after encephalitis, in arteriosclerosis, after CO poisoning, other toxins, tumors, drugs, etc.

Parkinson's disease



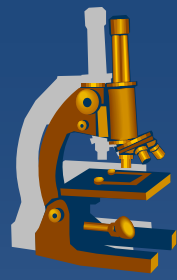
- **idiopathic**
  - ⇨ *mostly sporadic (exogenous incl. toxins, mitochondrial dysfunction?), minority familial (α-synuclein)*
  - ⇨ *usual age 40-70*
  - ⇨ *progressive course (10 years), may be + dementia*
- **gross**:
  - ⇨ *minor general changes, loss of dark color of substantia nigra*
- **micro:**
  - ⇨ *loss of neurons → astrogliosis*
  - ⇨ *numerous Lewy bodies (α-synuclein) in the cytoplasm of damaged neurons*

Parkinson's disease - brainstem



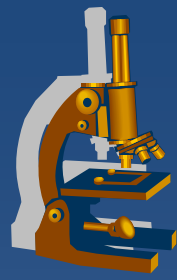
1 nucleus niger
2 atrophic nucleus niger with loss of pigment

Huntington's disease



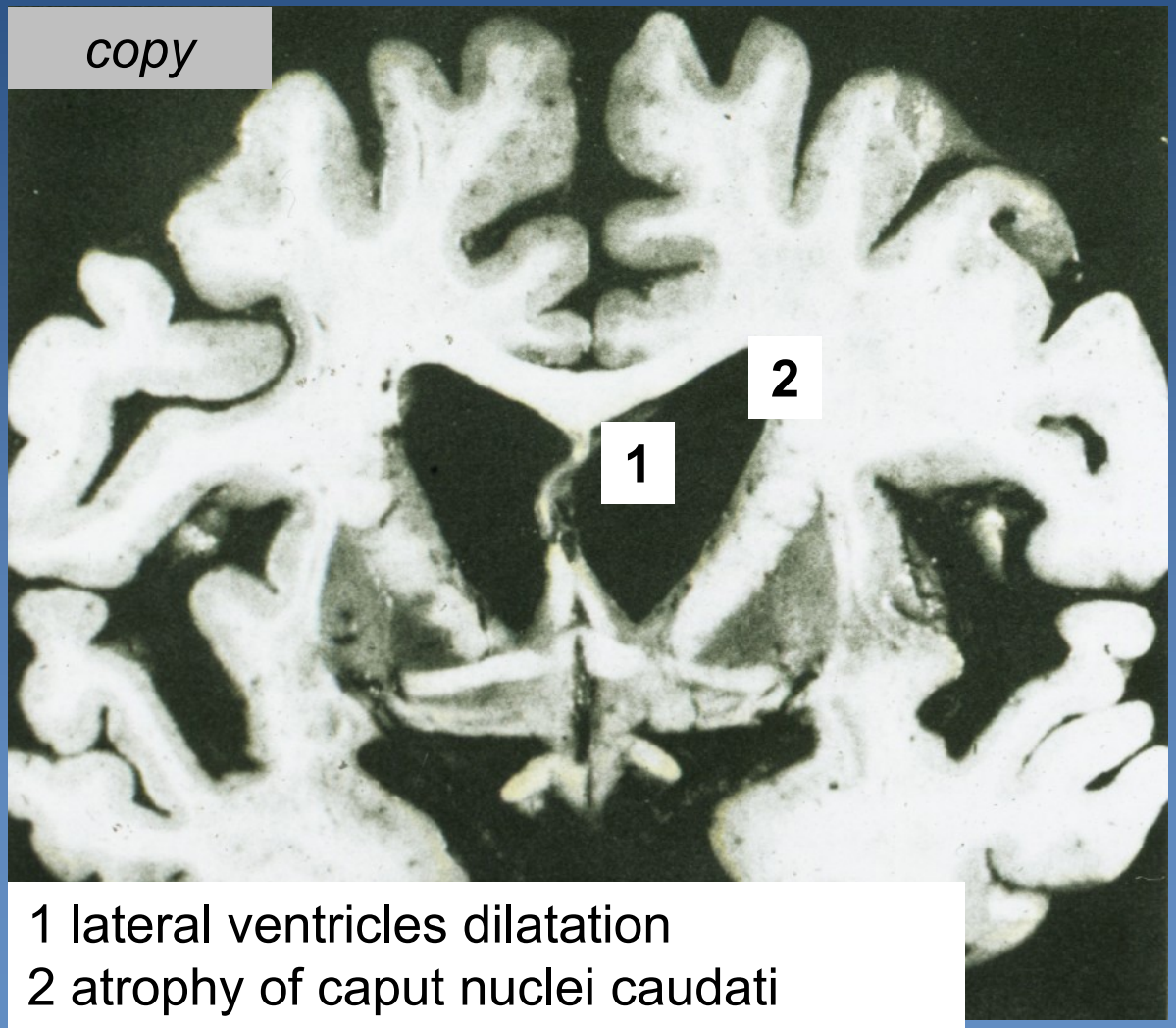
- **AD**
  - ⇨ ***gene on chromosome 4p – huntingtin protein***
    - CAG triplet repeats, if> 35 → disease
    - ↑ number of repeats ⟶ earlier onset, more rapid course
- **begins after age of 30 (4th, 5th decade)**
- progressive course (15-20 years)
- uncoordinated, jerky body movements, gradually dementia

Huntington's disease



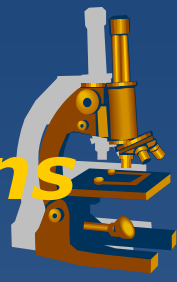
- **gross:**
  - *Atrophy of n. caudatus a putamen*
  - *dilated lateral + 3rd ventricle*
  - *cortical atrophy*
  - *brain weight reduction of up to 30%*
- **micro:**
  - *loss of neurons*
  - *fibrillary gliosis*

Huntington's disease



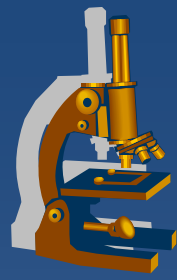
1 lateral ventricles dilatation
2 atrophy of caput nuclei caudati

Degenerative diseases of motoric neurons



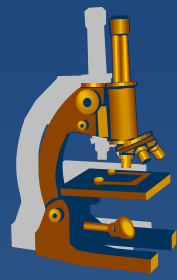
- **Amyotrophic lateral sclerosis**
  - ⇨ ***loss of brain + spinal cord motor neurons***
  - ⇨ ***adults, mostly male***
  - ⇨ ***5 % familial***
  - ⇨ ***micro***
    - loss of anterior spinal cord motoric neurons
    - leads to demyelinisation + atrophy of nerves
  - ⇨ ***skeletal muscles progressive loss of function, incl. diaphragm***
  - ⇨ ***fatal***
- **Spinocerebellar hereditary ataxia**
- **Spinal muscular atrophy**
  - ⇨ ***AR, children, muscle hypotonia***

Demyelinating diseases



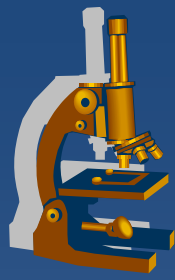
- **disintegration of myeline sheaths**
  - ⇨ ***axonal regression***
- primary x secondary (after axonal damage)
- **Immune-mediated disorders**
  - ⇨ ***multiple sclerosis***
  - ⇨ ***optic neuromyelitis***
    - bilateral optic nerve demyelinisation
  - ⇨ ***acute postviral/postvaccination encephalomyelitis***
- **Viral oligodendroglial infections**
  - ⇨ ***progressive multifocal leukoencephalopathy (JC virus)***
- **Inborn diseases**
  - ⇨ ***leucodystrophy – disorder of myeline formation and metabolism***

Multiple sclerosis



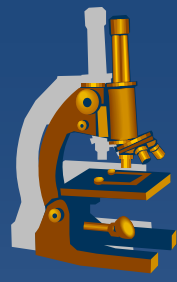
- more frequent in **women** between 20 and 40
- **unclear etiology**
  - ⇨ ***autoimmune myeline destruction triggered by exogenous factor (virus, chronic stress) in susceptible host (genetics – HLA DR2, vitamin D deficiency, smoking)***
- **progressive course,** episodic acute relapses with neurologic deficit, remisions
  - ⇨ ***variable presentation***
  - ⇨ ***sensoric, sensitive, motor dysfunction***
  - ⇨ ***ends in severe psychomotoric disturbance + cachexia***
  - ⇨ ***trophic ulcers, pressure sores, sepsis***

Multiple sclerosis



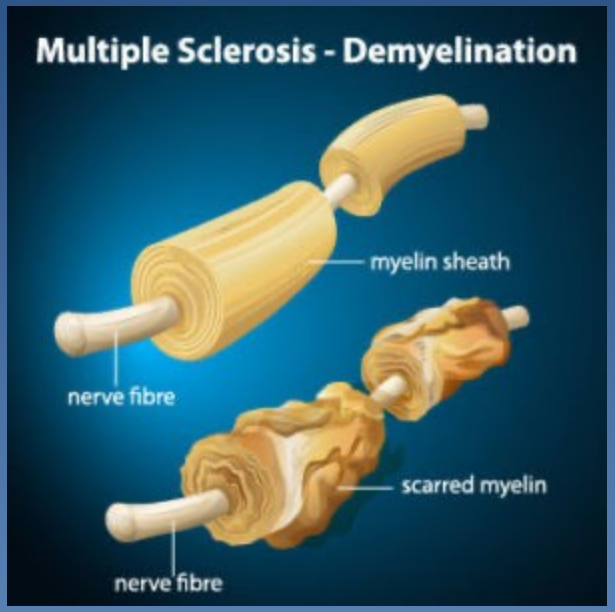
- **gross:**
  - ***white (less commonly gray) matter with multiple, well-demarcated, gray-tan solid lesions – plaques***
    - variable size mm-cm
  - ***Mostly periventricular**, but also in optic fasciculus….*
- **micro:**
  - ***Active plaques, early (pink, softer)***
    - myelin reduction, perivascular T- andB-cell infiltrate + activation of macrophages ⟶ axonal destruction
  - ***Inactive plaques:***
    - disappearance of oligodendrocytes and myelin, reactive gliosis, persistence of numerous nerve fibers without inflammation

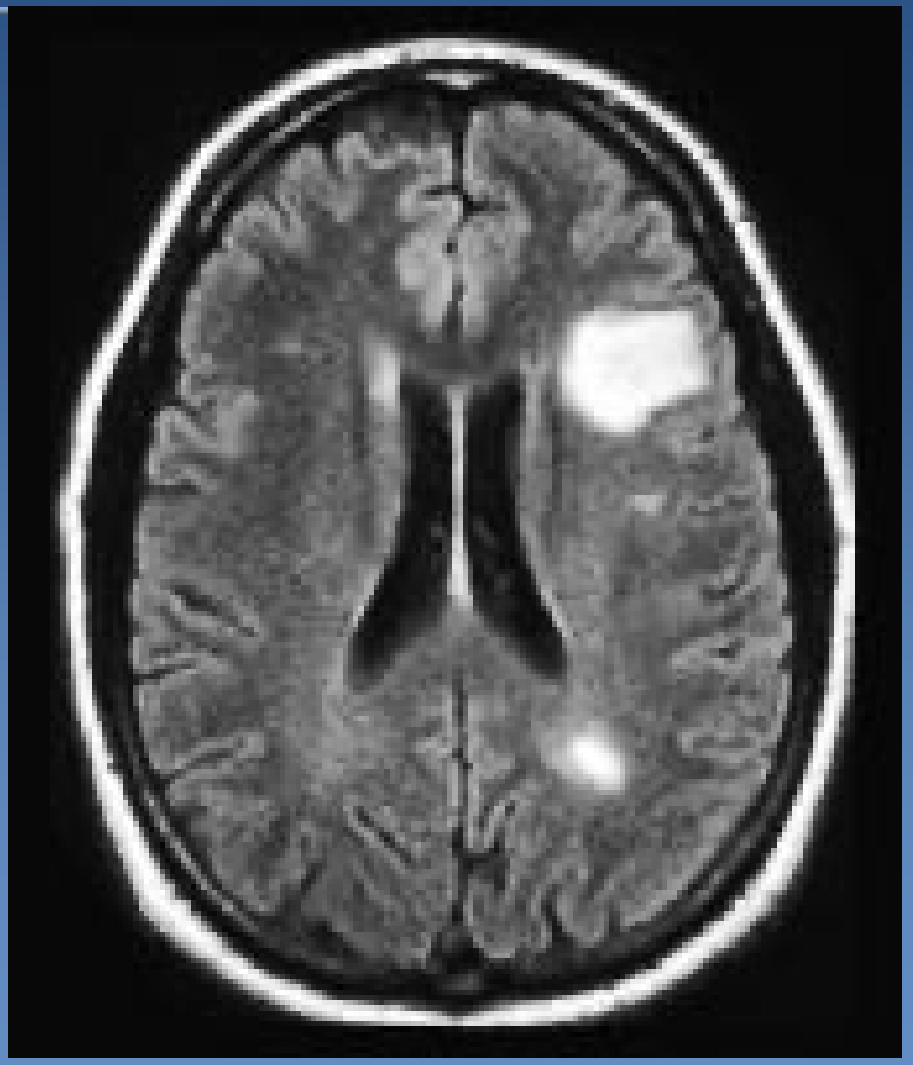
Multiple sclerosis



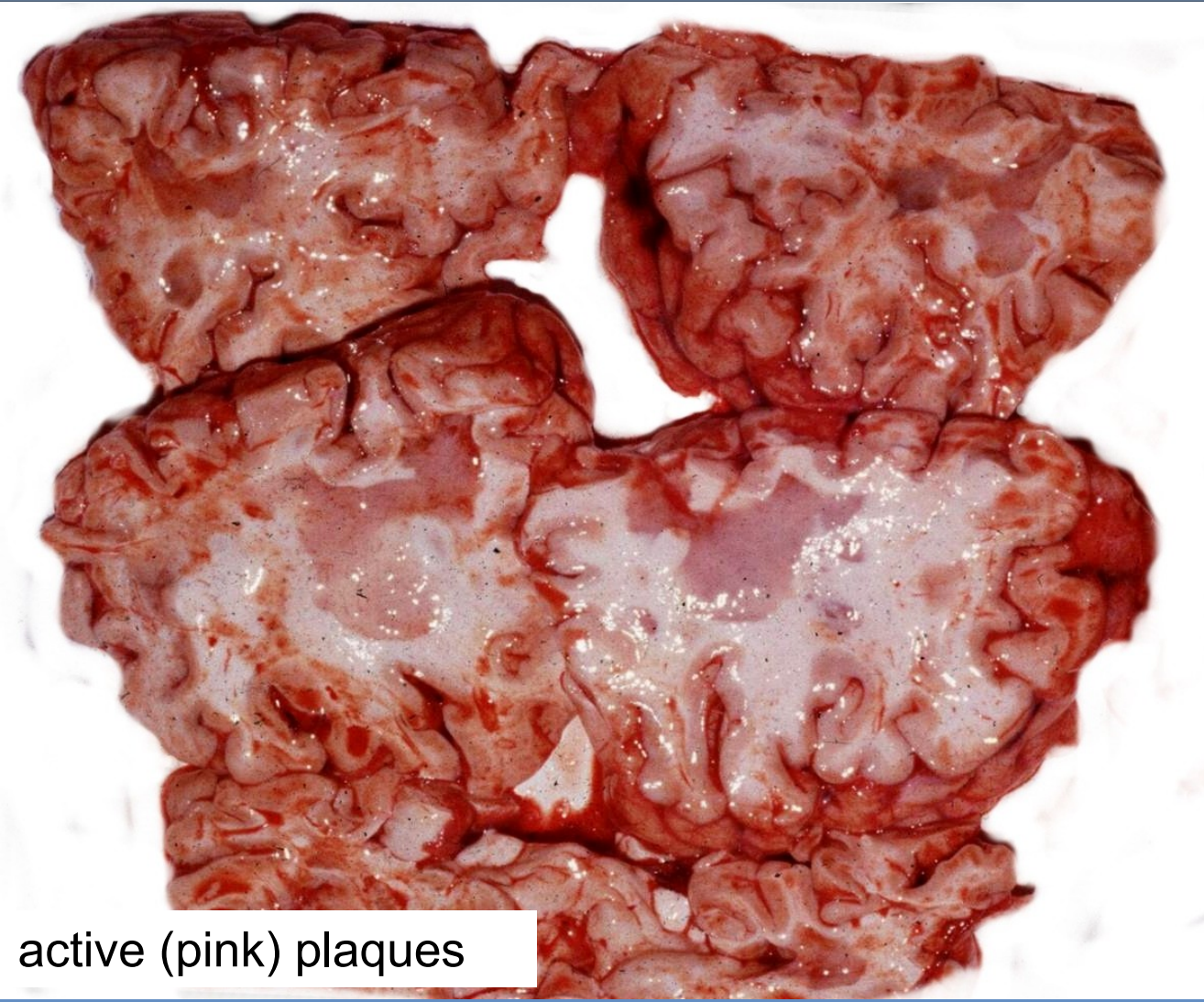
- **Acute form**
  - *fatal within a few weeks / months*
  - *may be in children*
  - *pink lesions (plaques) in white matter of the brainstem, spinal cord*
- **Primary progressive MS**
  - *permanent course without remissions*
- **Relapsing/remitting MS**
  - *most common, 10-15 years without treatment (immunosuppression + immunomodulation)*
- **Secondary progressive MS**
  - *late stage, decrease of inflammatory activity, dominant neurodegeneration,*
- **Neuromyelitis optica**
  - *fasciculus opticus → bilateral blindness*
  - *necrotic centre of plaques*

Multiple sclerosis

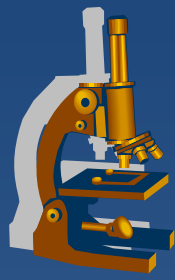




Multiple sclerosis

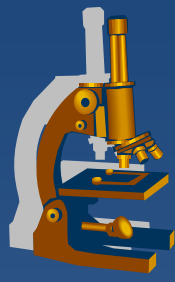


active (pink) plaques

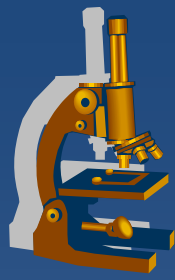


Tumors of the nervous system

neuroectodermal tumors

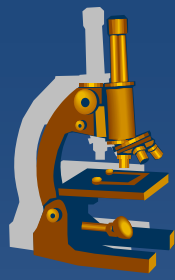


- tumors of the central nervous system
- peripheral neuroectodermal tumors
- tumors of the autonomic nervous system
- melanocytic tumors



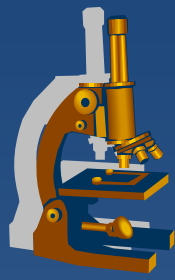
INTRACRANIAL TUMORS

Intracranial tumors



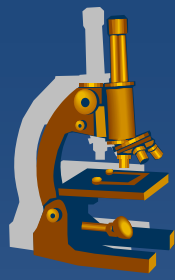
- primary extracerebral (meningioma, schwannoma, neurofibroma)
- primary intracerebral (gliomas – astrocytoma, oligodendroglioma, ependymoma, neuronal tumors, primitive neuroectodermal tumors PNET – medulloblastoma, endocrine t., vascular t., lymphomas
- secondary tumors – metastases leukemic infiltration

Intracranial tumors



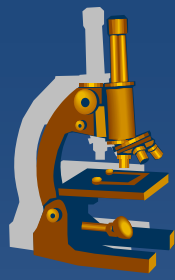
- focal signs according to the localisation (excitation, later loss of function incl. personality changes)
- general raised intracranial pressure (seizures, headache, visual defects, nausea etc.)
- bleeding
- histologically indolent brain tumors can kill the patient – growing in a position where they cannot be completely resected !

Biologic behaviour



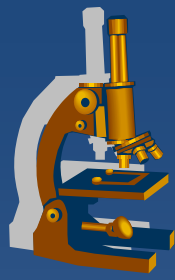
- WHO Grading – directly corresponds w. biologic behaviour
  - ⇨ ***Grade 1 – demarcated indolent neoplasia***
  - ⇨ ***Grade 2 – diffuse infiltrative slowly growing neoplasia***
  - ⇨ ***Grade 3 – diffuse infiltrative rapidly growing neoplasia***
  - ⇨ ***Grade 4 – aggressive neoplasia***

Biologic potential



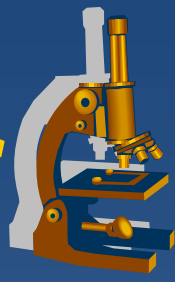
- possible infiltrating growth of histologically benign tumors
- localisation highly important (grave consequences even in benign tumors)
- rare metastases outside the CNS

Age factor



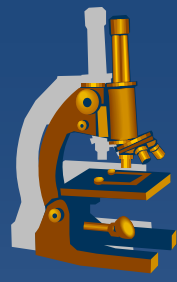
- in chidren - mostly primary intracerebral incl. PNET; infratentorially (posterior fossa)
- in adults – number of secondary t. rises with age; mostly supratentorially

Metastatic tumors of the CNS



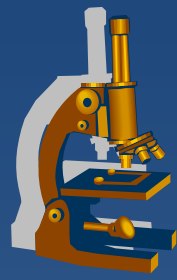
- CNS metastases in 25% of cancer deaths
- most common origin in adults
  - ***lung ca (small cell, adenocarcinoma)***
  - ***breast ca***
  - ***melanoma***
  - ***renal***
  - ***colorectal***
- most common origin in children
  - ***leukaemia, lymphoma***
  - ***osteosarcoma, rhabdomyosarcoma***

classification of intracranial tumors



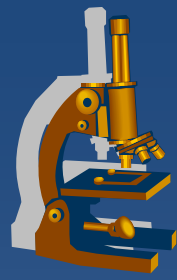
- **Astrocytic tumors**
- **Oligodendroglial tumors**
- **Ependymal tumors**
- Choroid plexus tumors
- Neuronal/glioneuronal tumors
- Pineal tumors
- **Embryonal tumors**

Glial tumors

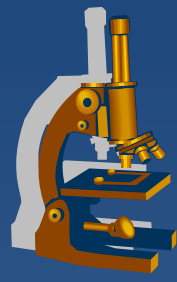


- **Diffuse astrocytic tumors**
  - *diffuse astrocytoma WHO G2*
  - *anaplastic astrocytoma WHO G3*
  - *glioblastoma WHO G4*
  - *diffuse middle-line glioma WHO G4*
    - brain stem, children + young adults, survival in months
- **Oligodendrogliomas**
  - *oligodendroglioma WHO G2*
  - *anaplastic oligodendroglioma WHO G3*
- **Demarcated astrocytic tumors**
  - *Pilocytic astrocytoma WHO G1*
  - *other rare tumors*

Glial tumors



- Ependymomas
  - ***ependymoma WHO G2***
  - ***anaplastic ependymoma WHO G3***
- Choroid plexus tumors
  - ***choroid plexus papilloma WHO G1***
  - ***atypical choroid plexus papilloma WHO G2***
  - ***choroid plexus carcinoma WHO G3***

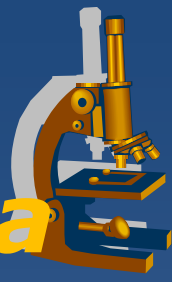


Diffuse astrocytoma

- **WHO G2**
- **2 different genetic variants according to the IDH gene mutation**
  - ⇨ ***diffuse astrocytoma, IDH-mutated, adults, good prognosis***
  - ⇨ ***diffuse astrocytoma, IDH-wildtype, bad prognosis in adults, good in children***
- **slow growth, high degree of differentiation**
- **!! intrinsic tendency for malignant progression to anaplastic astrocytoma → glioblastoma**

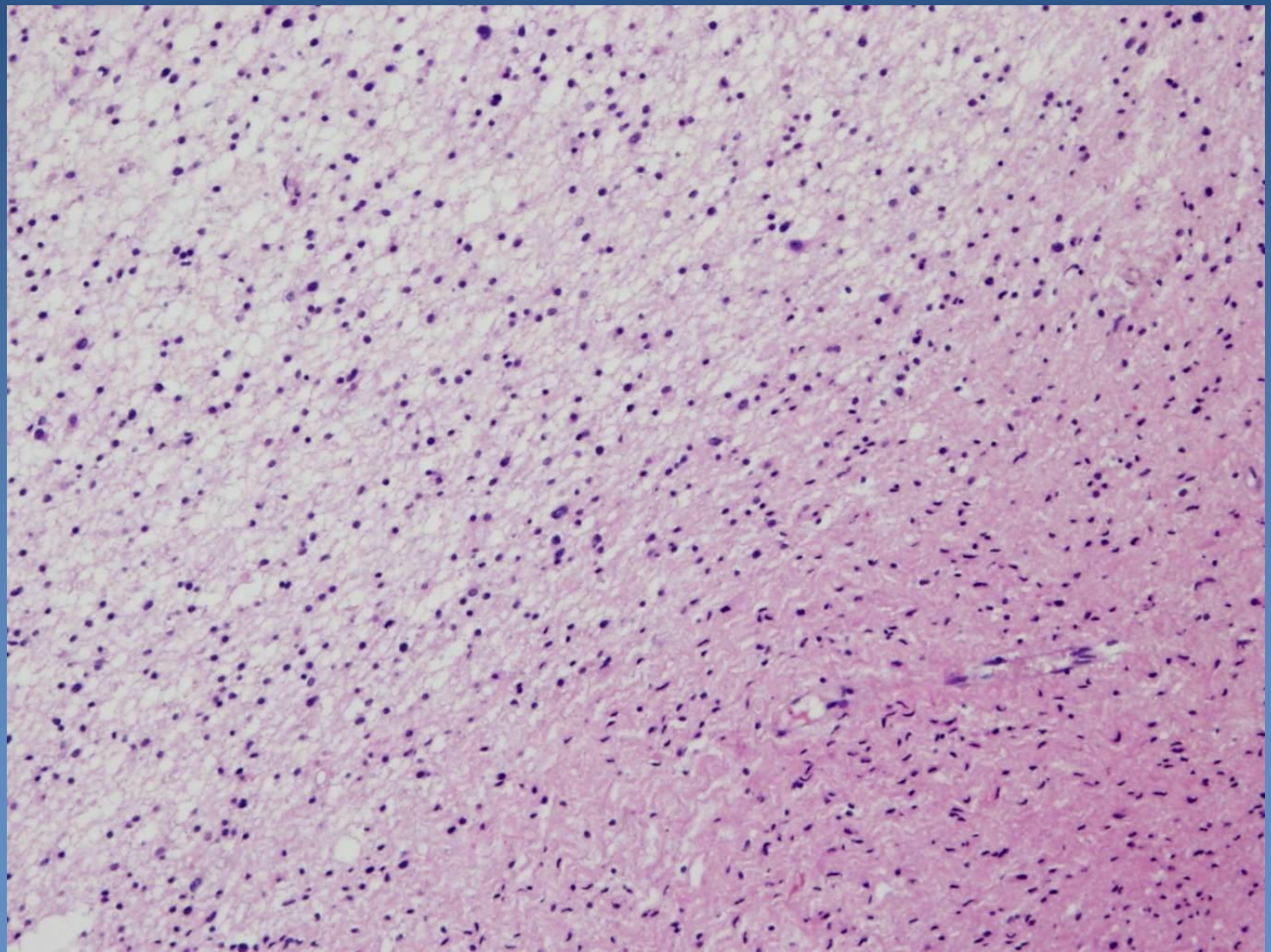
- **in all age groups**
  - ⇨ *mostly young adults, M>F*
- **Anywhere in the brain –**
  - ⇨ ***infiltrative tumor***

Astrocytic tumors
Diffuse (fibrillary) astrocytoma

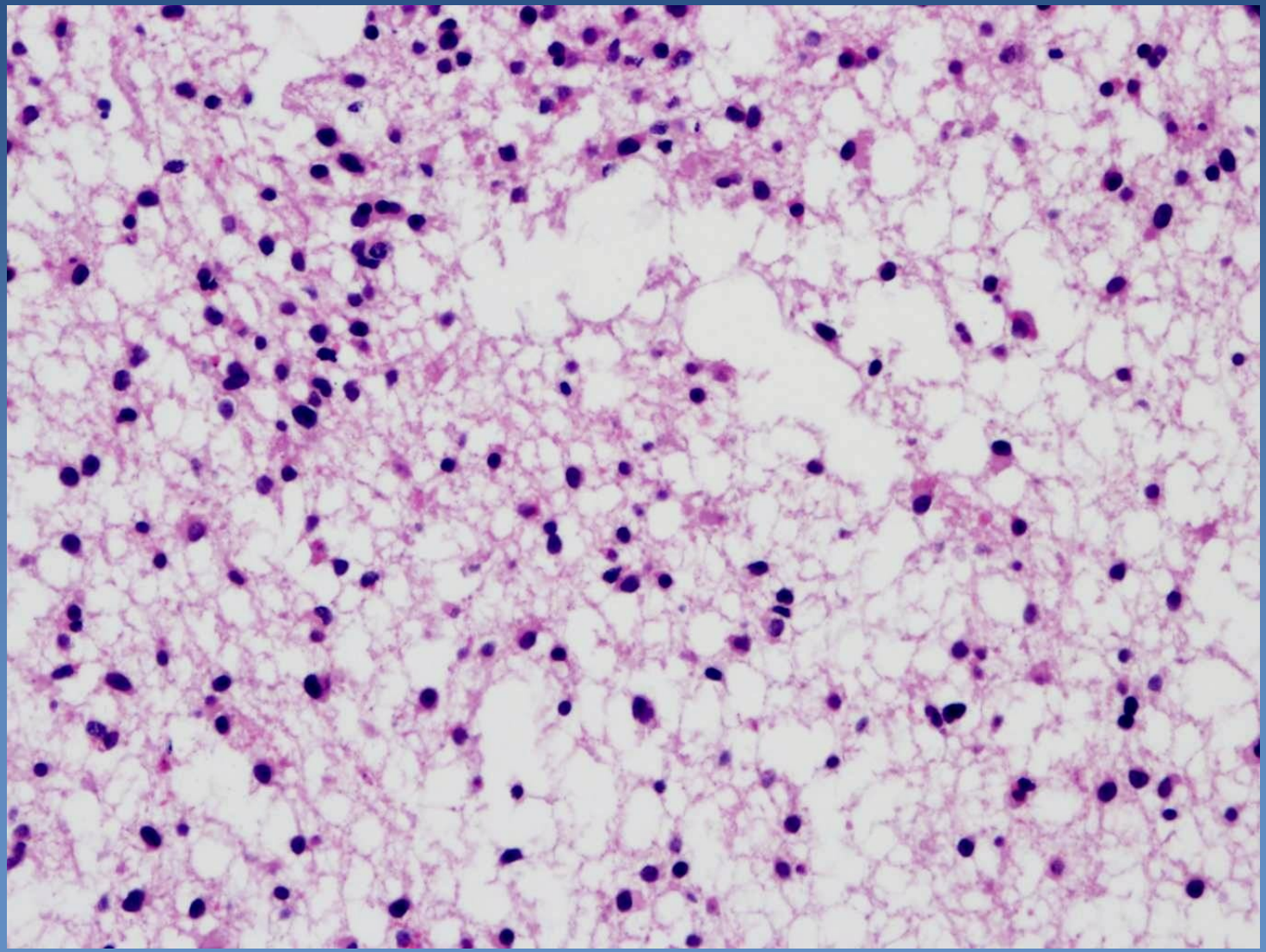


- **micro:**
  - ***well-differentiated fibrillary, germistocytic (mass of eosinophilic cytoplasm), rare protoplasmic astrocytes***
  - ***slightly increased cellularity in comparison with normal tissue***
  - ***stroma often microcystic***
  - ***usually no mitotic activity***
  - ***without necrosis or microvascular proliferation***

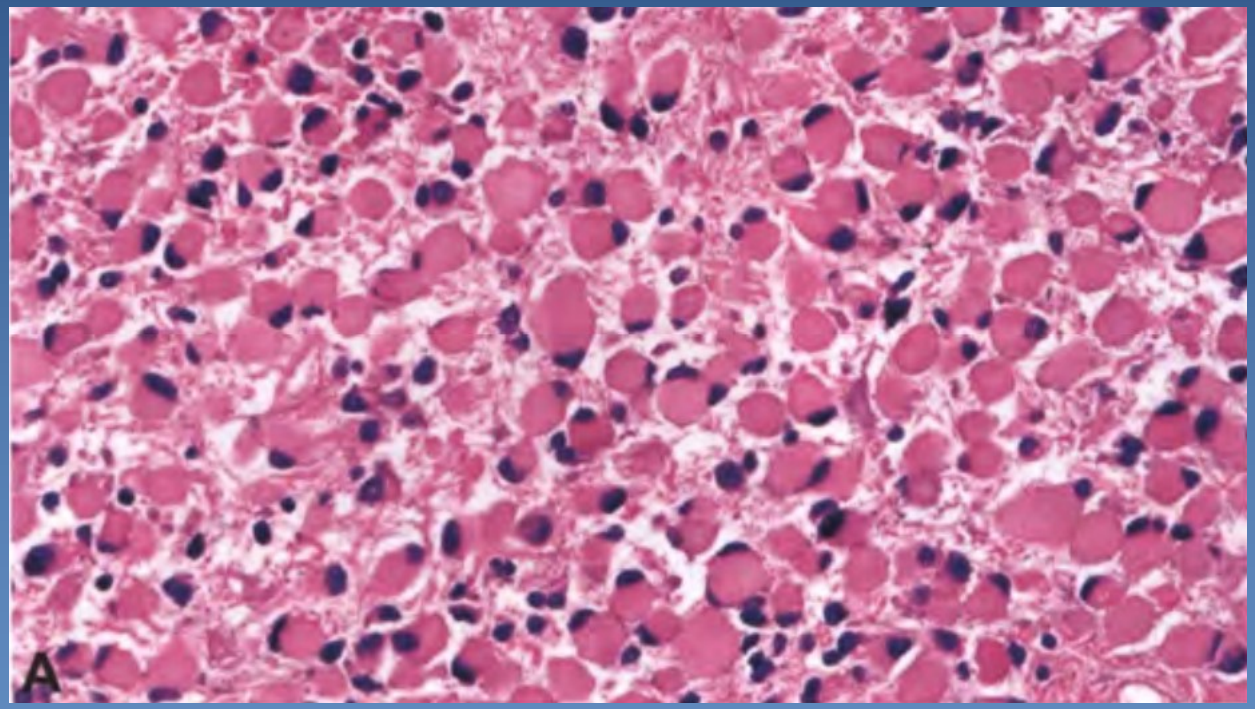
Diffuse (fibrillary) astrocytoma



Diffuse (fibrillary) astrocytoma

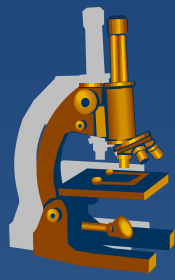


Diffuse astrocytoma, gemistocytic



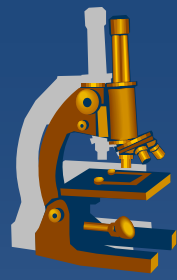
Astrocytic tumors

Glioblastoma WHO G4



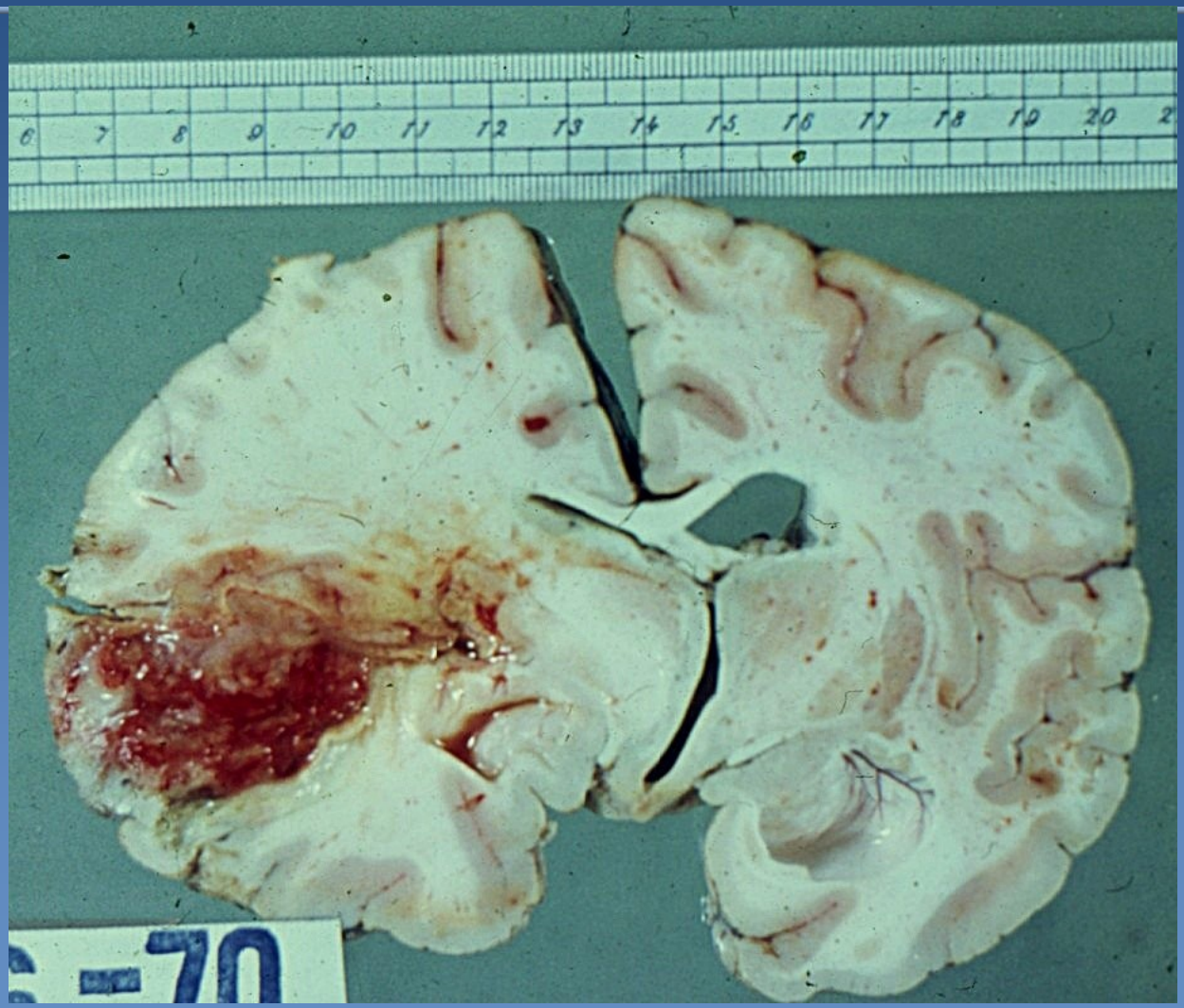
- most common primary in adults
- usually 45-75 years of age, may be in children
- 2 variants
  - ⇨ *glioblastoma WHO G4, IDH-mutated, better prognosis , younger patients*
  - ⇨ *glioblastoma WHO G4, IDH-wildtype, more common, worse prognosis, older patients*
- possible transformation from preexisting astrocytoma gr. II or III – secondary glioblastoma,
- aggressive, rapidly growth,
- gross:
  - ⇨ *variable appearance – white and firm regions, yellow and soft parts, foci of necrosis, cysts, hemorrhages*

Astrocytic tumors
Glioblastoma

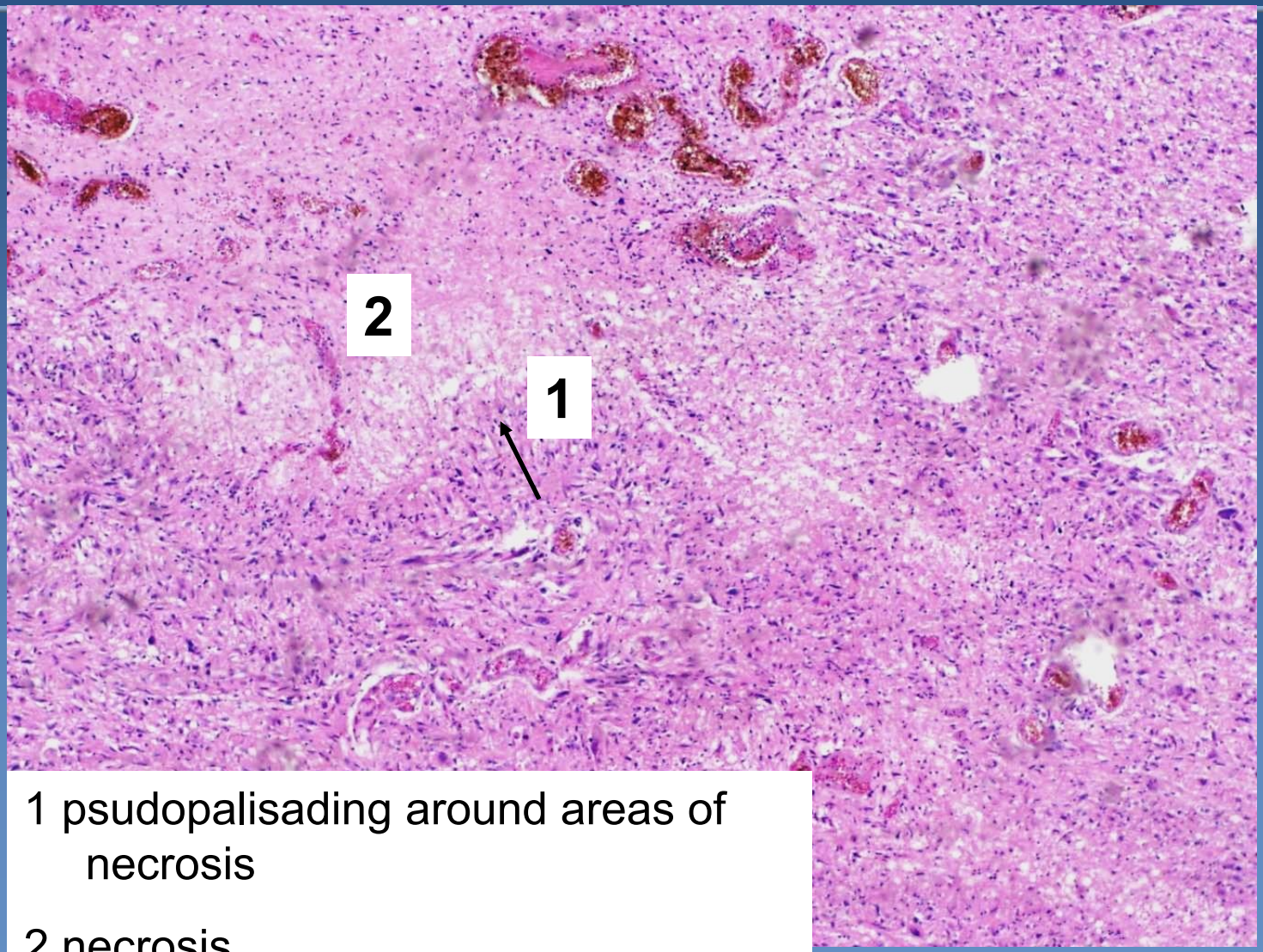


- **micro:**
  - ⇨ ***pleomorphic tumor cells - severe cellular and nuclear atypia***
  - ⇨ ***tumor is regionally heterogeneous***
    - alternatition of pleiomorphic and more regularly arranged areas
  - ⇨ ***high mitotic rate***
  - ⇨ ***conspicuous microvascular proliferation and / or necrosis***
  - ⇨ ***pseudopalisading of tumor cells around necrotic areas***

Glioblastoma



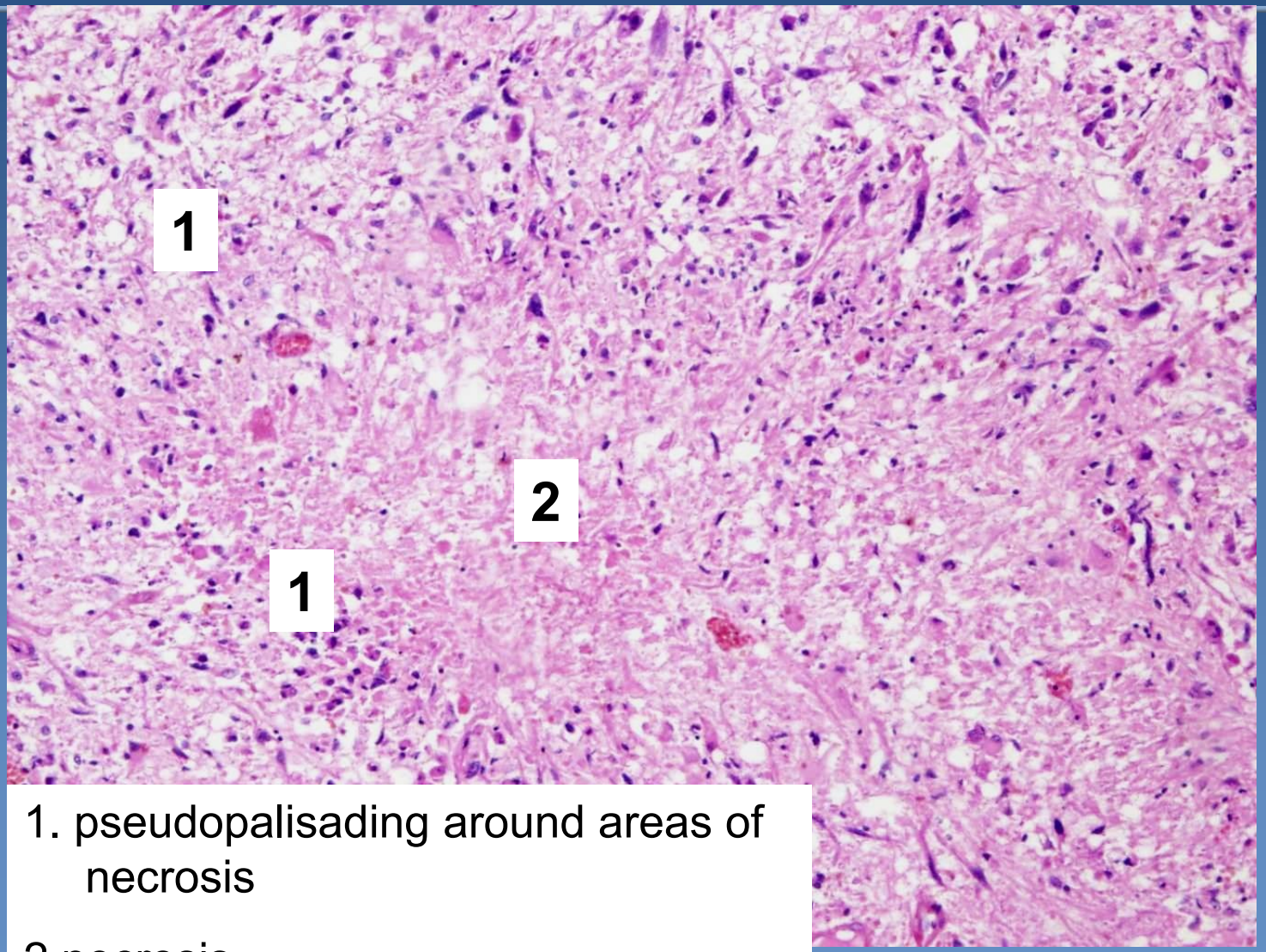
Glioblastoma



1 psudopalisading around areas of necrosis

2 necrosis

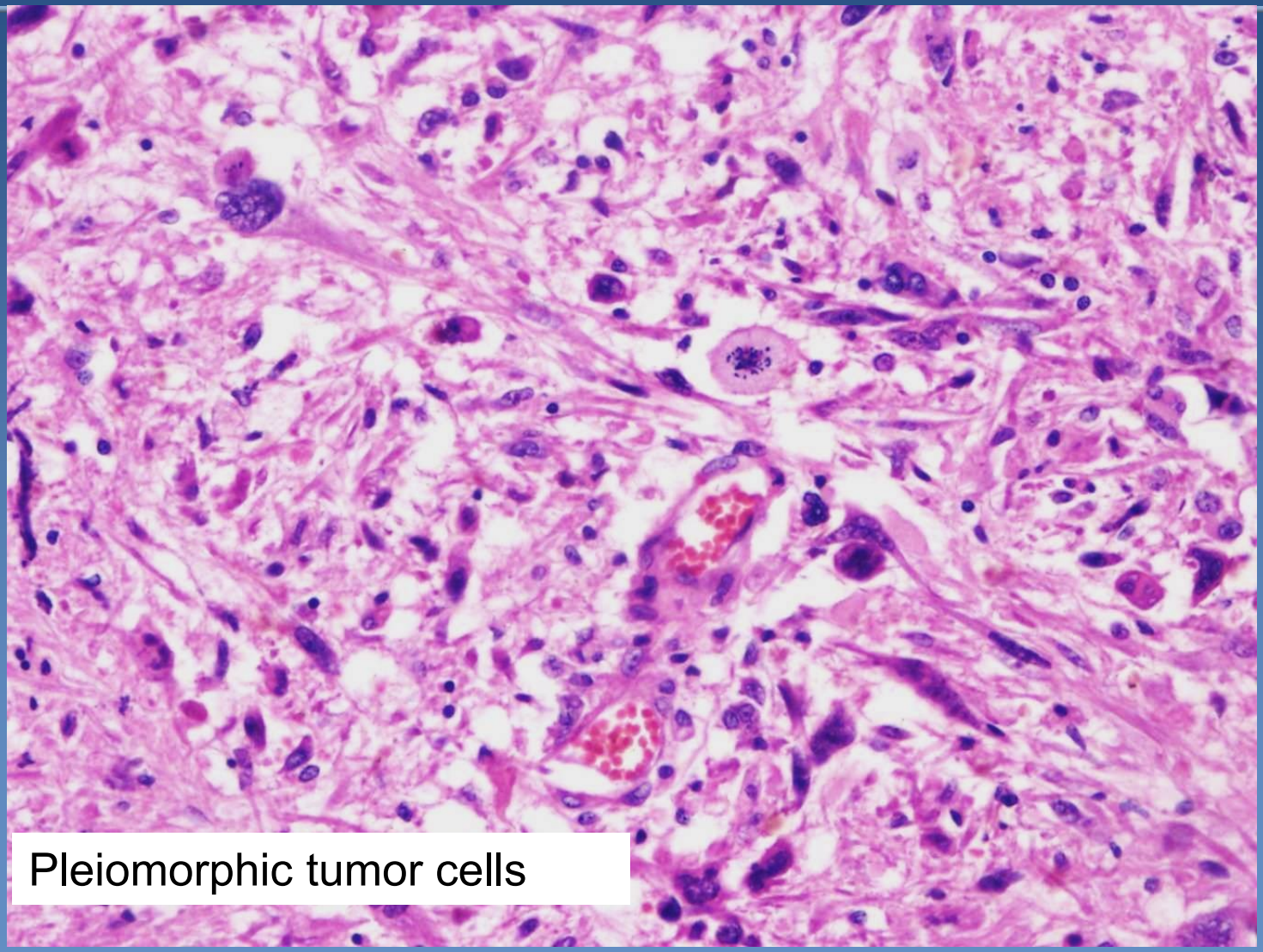
Glioblastoma



1. pseudopalisading around areas of necrosis

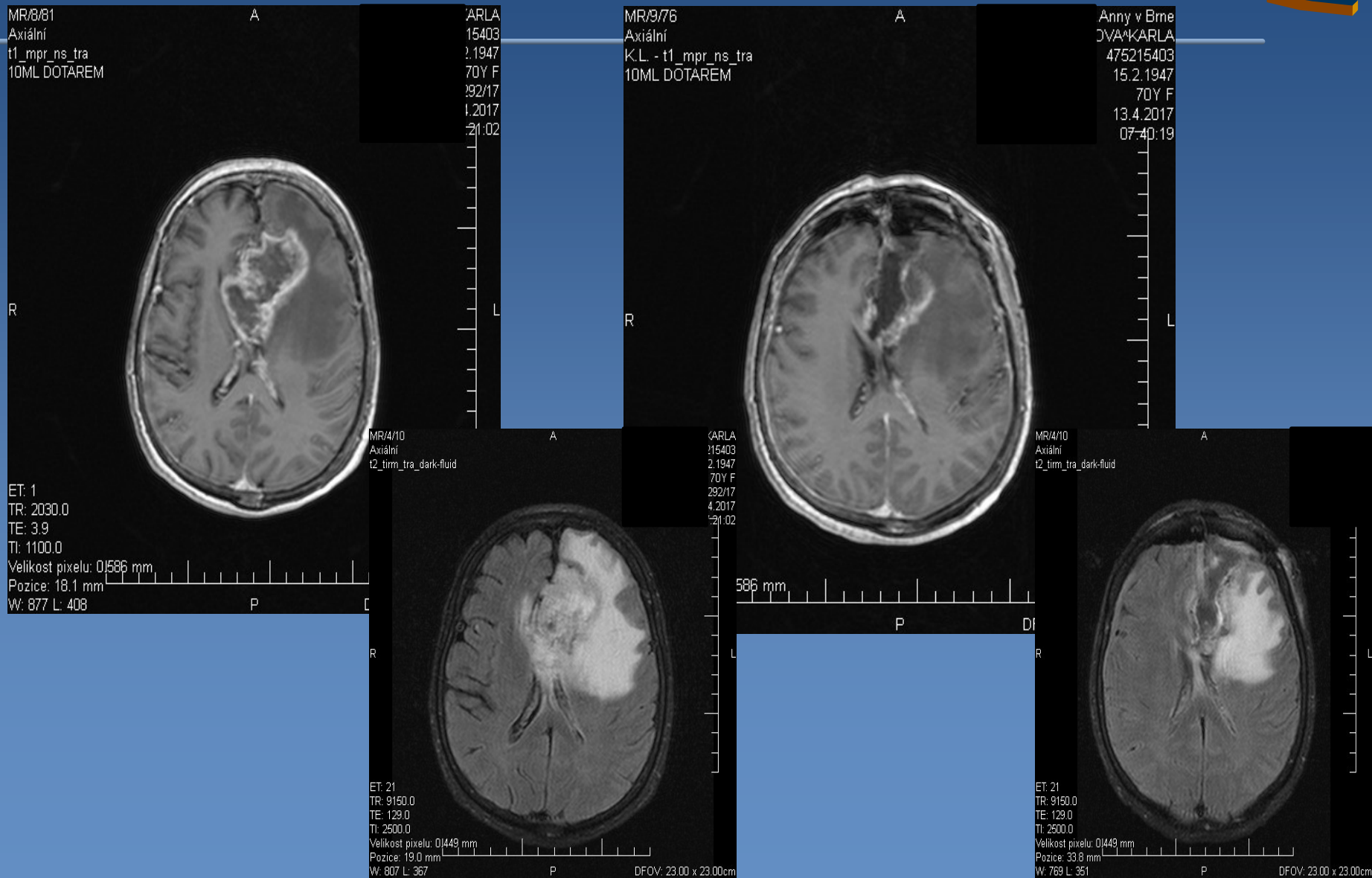
2 necrosis

Glioblastoma



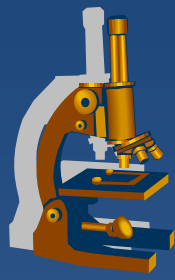
Pleiomorphic tumor cells

Glioblastoma - resection



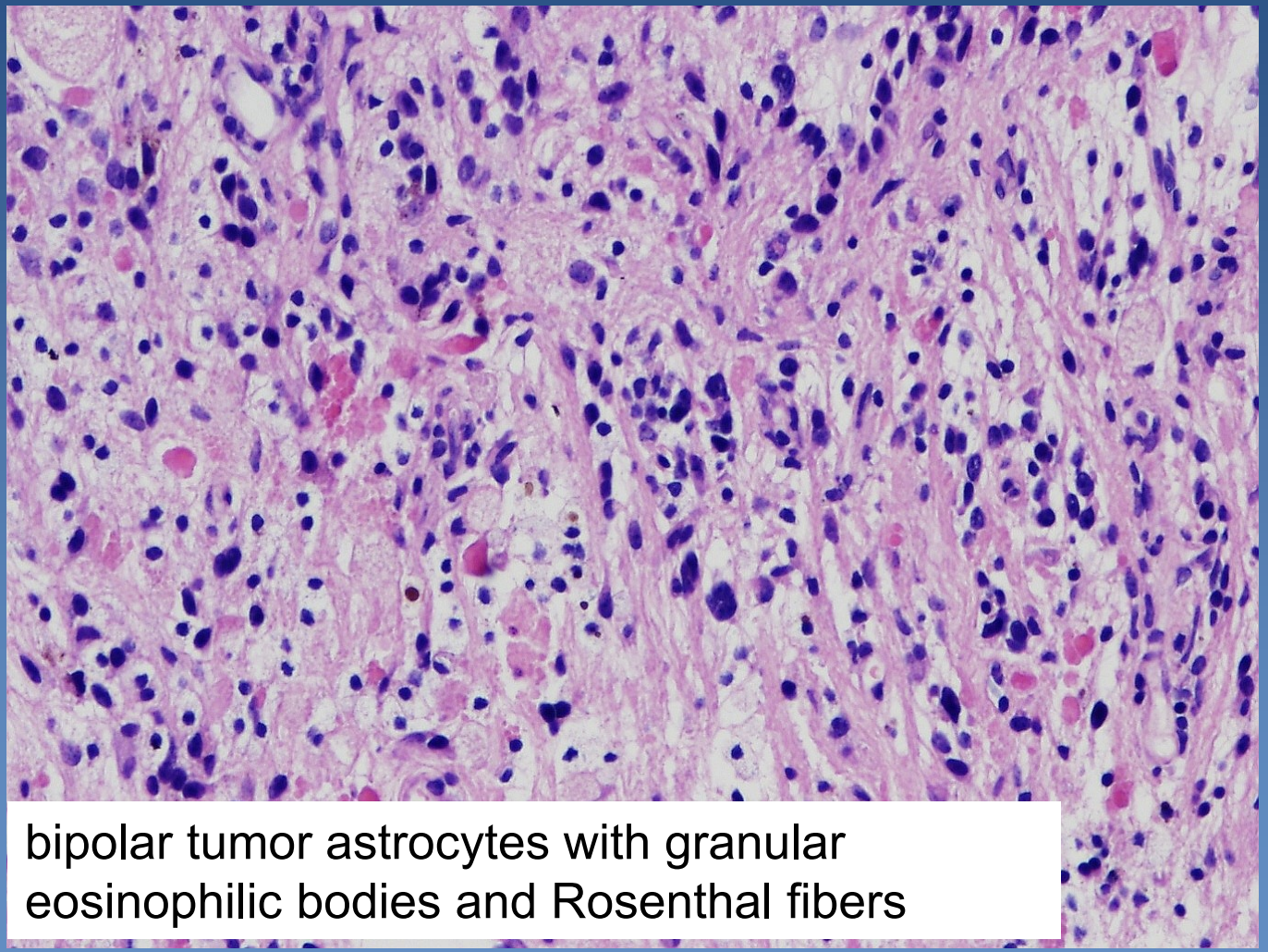
Astrocytic tumors

Pilocytic astrocytoma



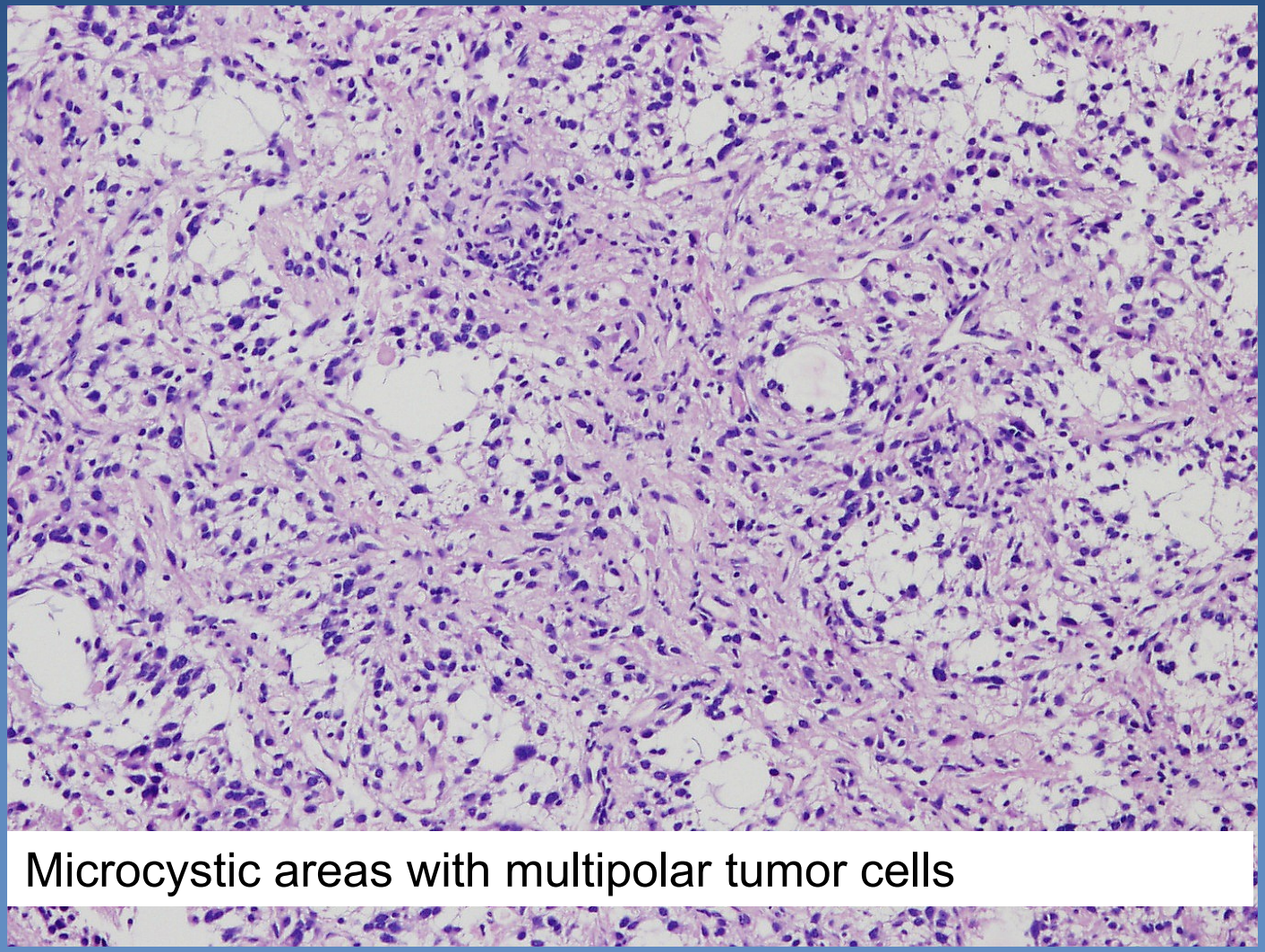
- **WHO grade I, demarcated tumor**
- **grows very slowly**
- growth begins in childhood - clinical signs manifest around age of 20 (and later); in cerebellum or near III. and IV. ventricle, resection posssible
- **micro:**
  - ⇨ ***biphasic structure solid / cystic***
    - compact region with bipolar tumor astrocytes with eosinophilic Rosenthal fibers
    - microcystic, sparsely cellular areas with multipolar tumor cells with granular eosinophilic bodies and eosinophilic globules
  - ⇨ *degenerative atypia and calcification*
  - ⇨ *infrequent mitosis, sm. nuclear pleiomorphism and hyperchromasia*
  - ⇨ *glomeruloid vascular endothelial proliferation often*
  - ⇨ *small necrosis possible*

Pilocytic astrocytoma



bipolar tumor astrocytes with granular eosinophilic bodies and Rosenthal fibers

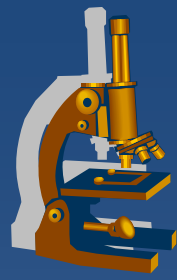
Pilocytic astrocytoma



Microcystic areas with multipolar tumor cells

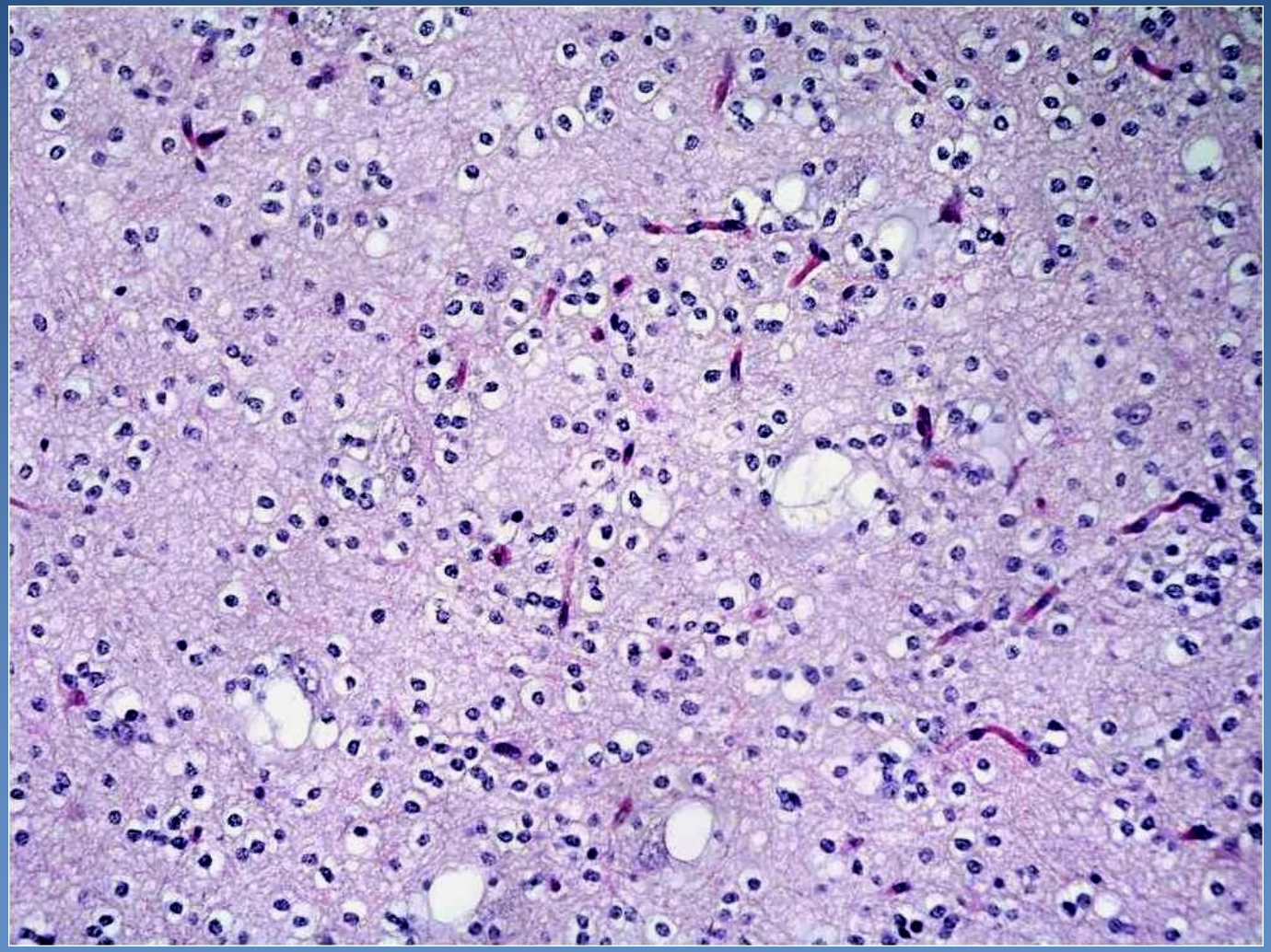
Oligodendroglial tumors

Oligodendroglioma

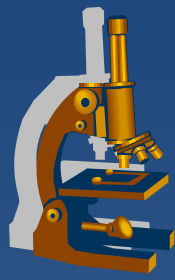


- **WHO G2**
- **typical genetic changes**
- **in adults; slow growth**
- **Micro:**
  - ⇨ ***uniform tumor cells with round nuclei and perinuclear halos***
  - ⇨ ***microcalcifications (X-ray)***
  - ⇨ *areas of mucoid degeneration*
  - ⇨ ***abundant branching capillaries***

Oligodendroglioma

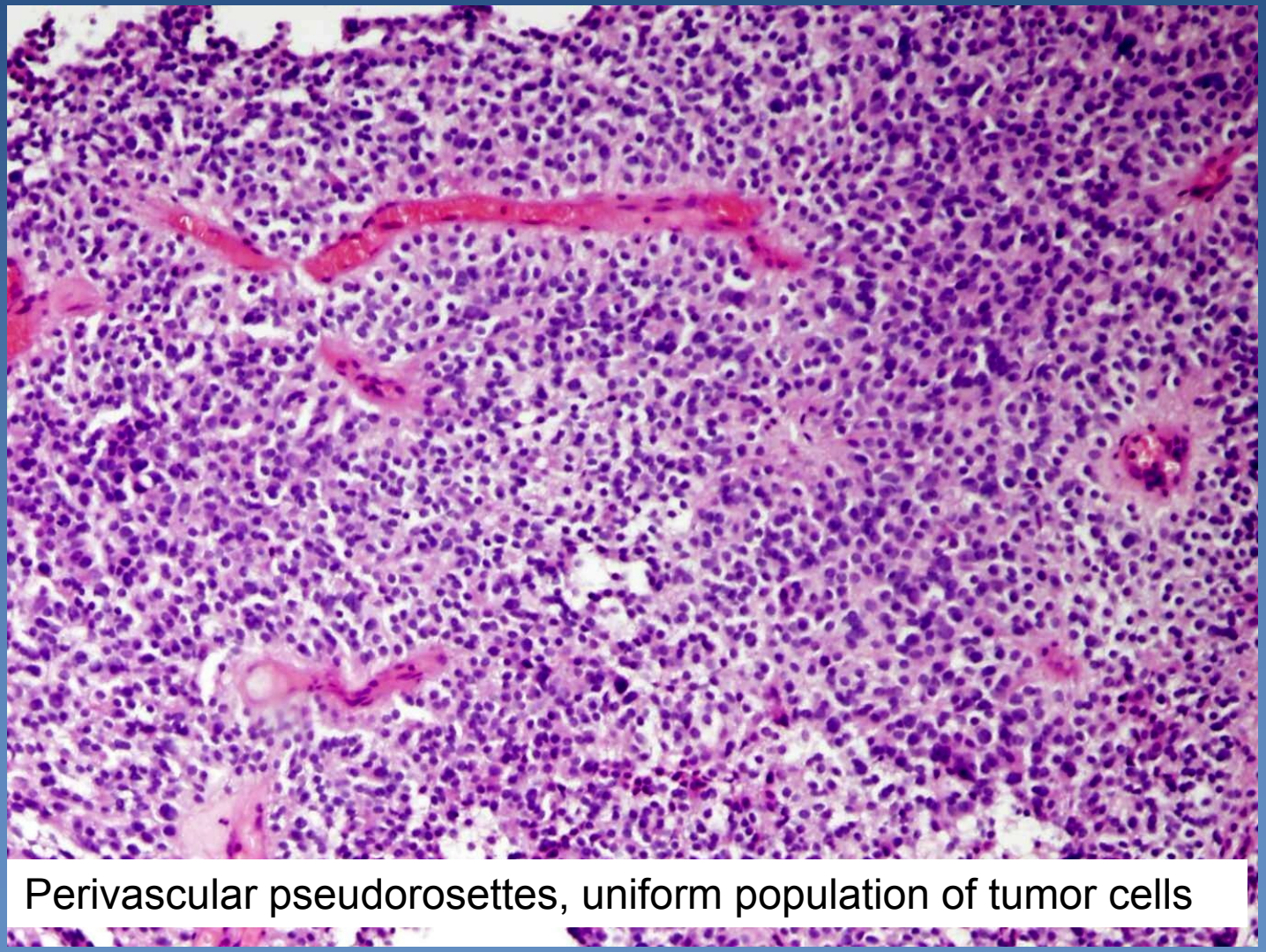


Ependymoma WHO G2



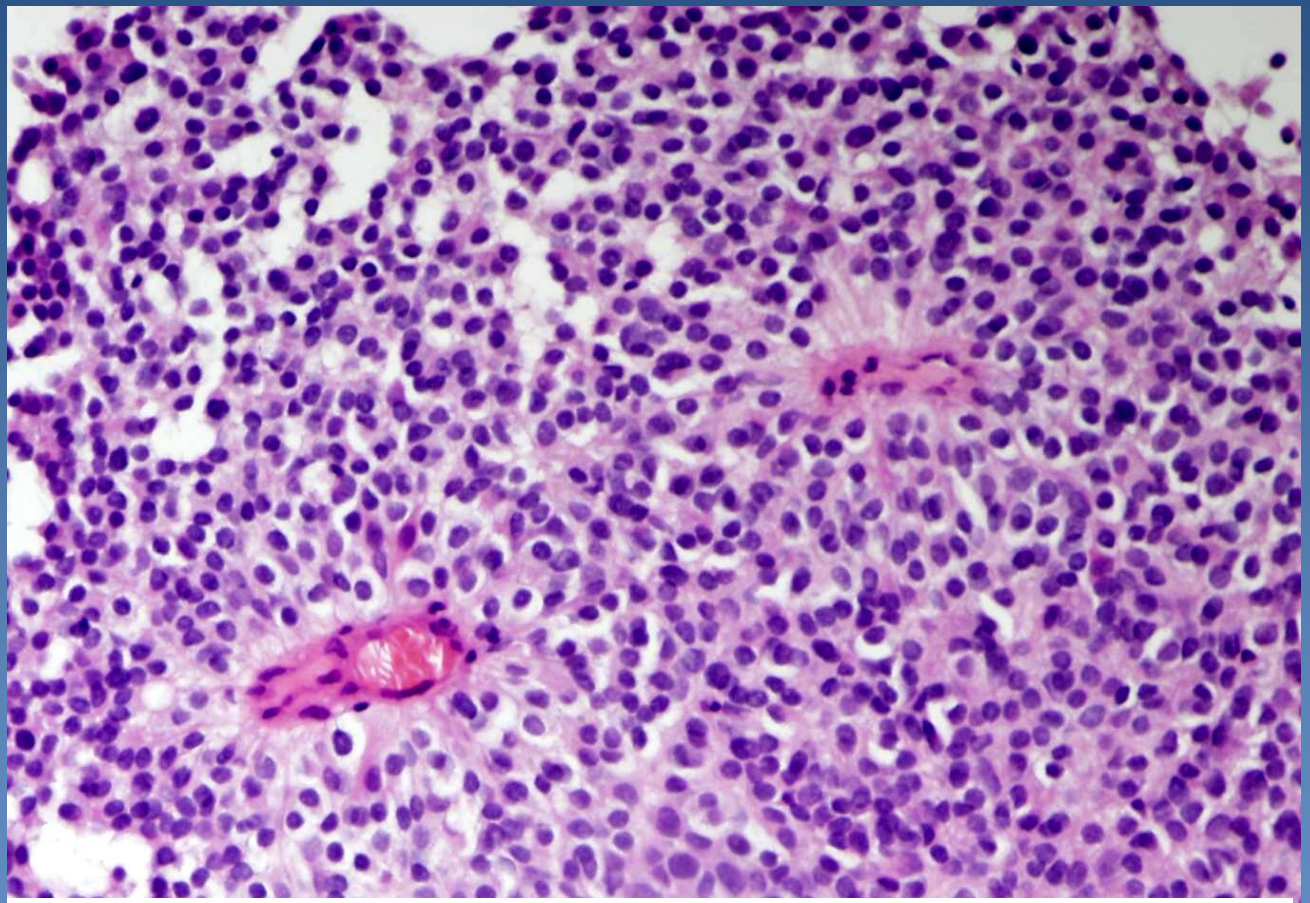
- **grade II (WHO)**
- **in children - usually around IV. vetricle, in adults - spinal cord, with neurofibromatosis type 2**
- **hydrocephalus**
- **micro:**
  - ⇨ *fusiform cells with long processes,uniform round to oval nuclei*
  - ⇨ *fine fibrillary background*
  - ⇨ *canalicular formations, perivascular pseudorosettes*
  - ⇨ *sporadic or no mitotic figures*

Ependymoma



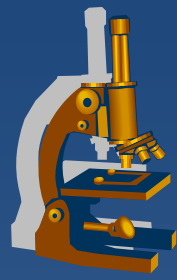
Perivascular pseudorosettes, uniform population of tumor cells

Ependymoma



Perivascular pseudorosettes, uniform population of tumor cells

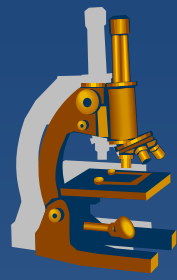
Tumors of the choroid plexus



- Choroid plexus papilloma (WHO G1)
- Atypical choroid plexus papilloma (WHO G2)
- Choroid plexus carcinoma (WHO G3)

- more common in children
- usually lateral ventricles
- exophytic tumors
- hydrocephalus

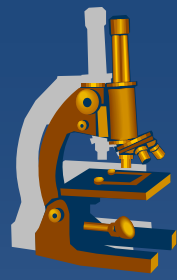
Embryonal tumors



- **Primitive aggressive malignant tumors of childhood**
- **Tumors "of small blue cells" grade IV**
  - ***Medulloblastoma***
  - *Atypical teratoid/rhabdoid tumor*
  - *Supratentorial primitive neuroectodermal tumor*
  - *Ependymoblastoma*
  - *Retinoblastoma*
  - *…*

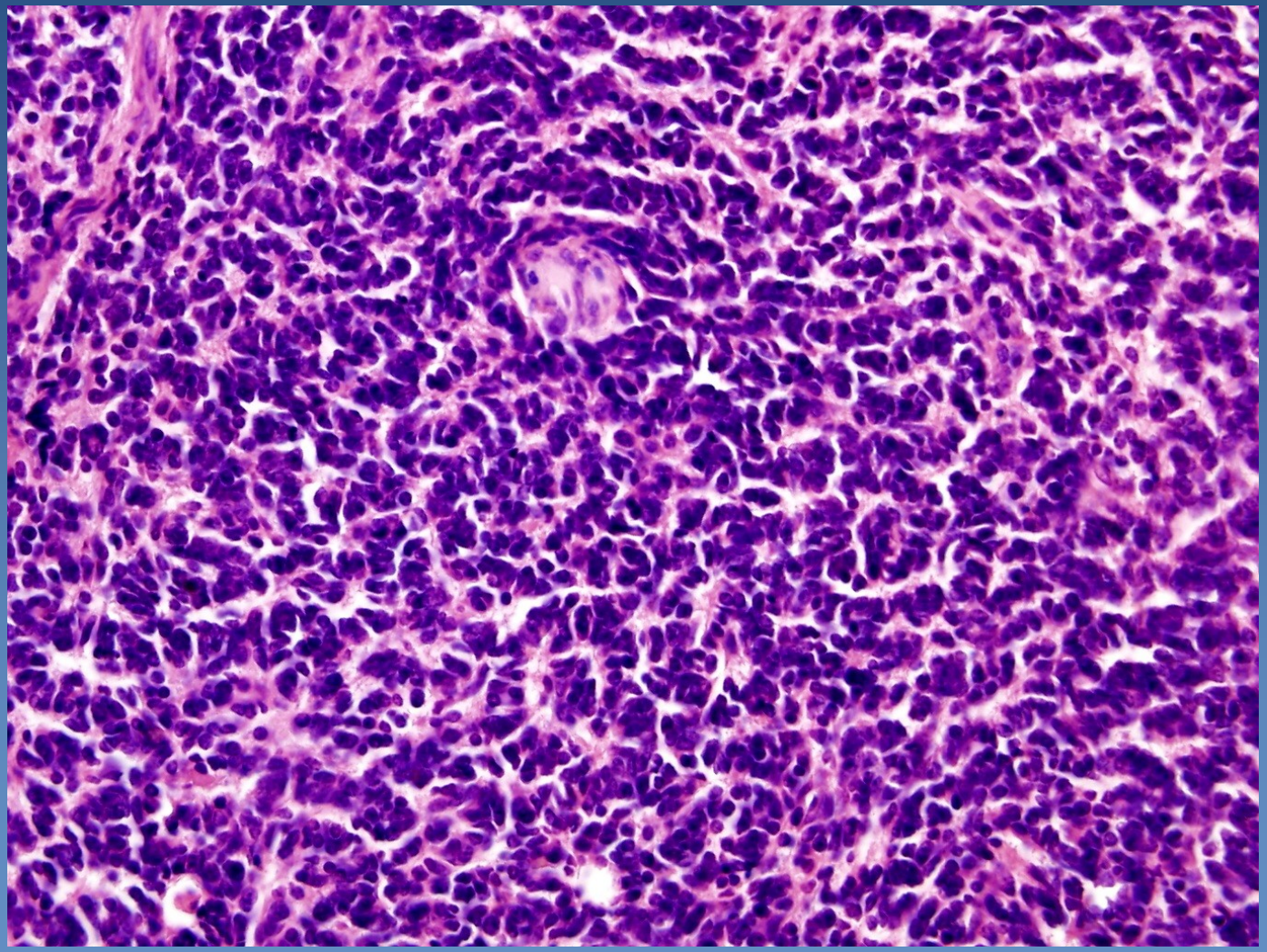
Embryonal tumors

Medulloblastoma

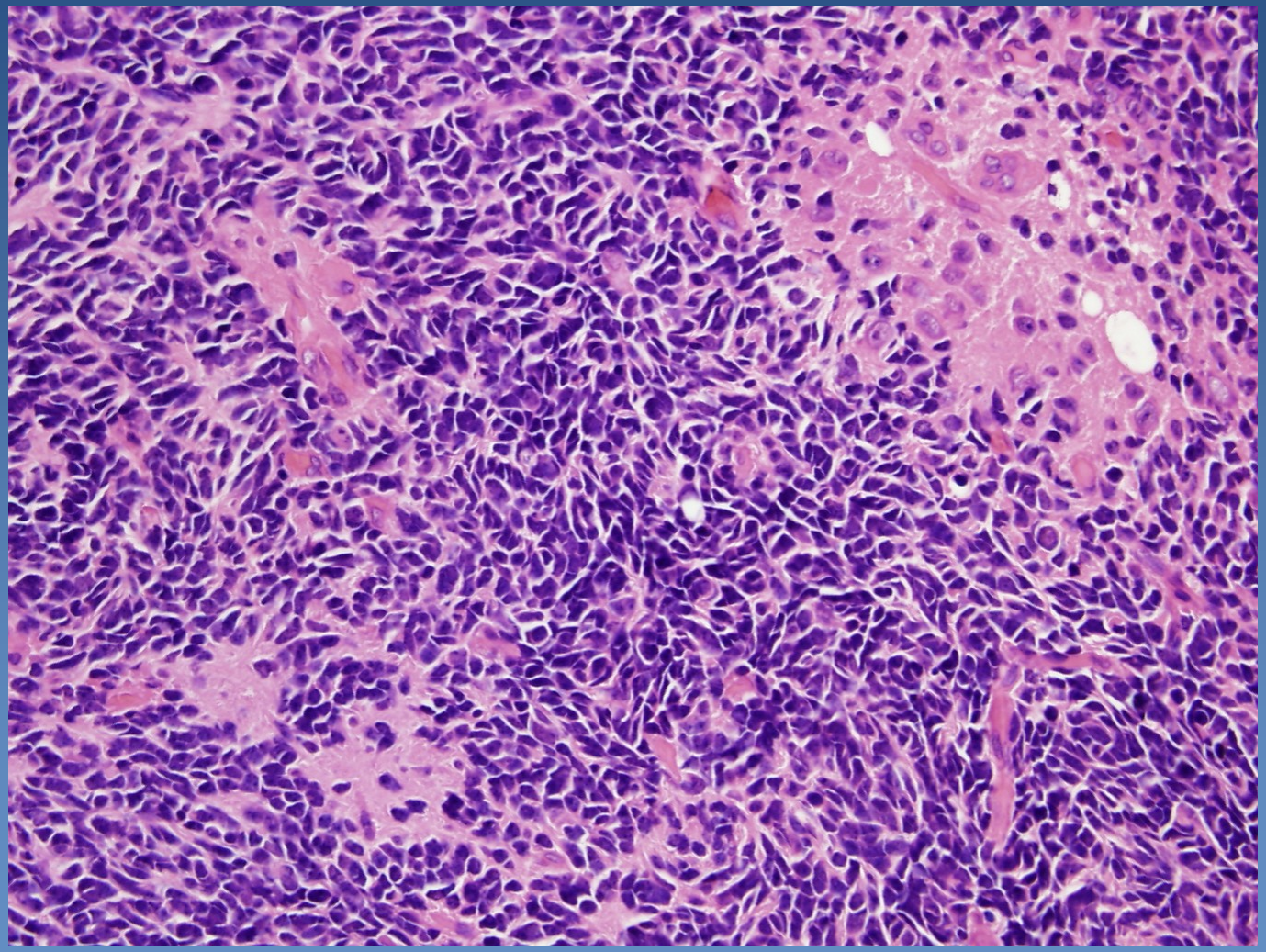


- **WHO G4**
- **tumor of first two decades of life**
- **4 genetic groups with different biological behaviour**
- **highly malignant but radiosensitive**
- **in cerebellum, midline in children**
  - ⇨ *local infiltration, meningeal and CSF spread → hydrocephalus*
  - ⇨ *gross – focal pink/grey tumor*
- **micro:**
  - ⇨ *highly cellular*
  - ⇨ *small hyperchromatic nuclei, carrot-shaped*
  - ⇨ *neuroblastic Homer-Wright's rosettes*
  - ⇨ *high mitotic activity*
  - ⇨ *differentiation to neuronal / other cells possible*

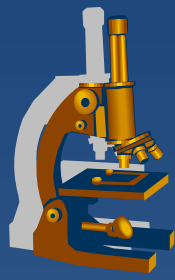
Medulloblastoma



Medulloblastoma

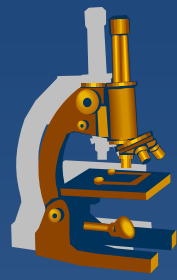


Mixed glioneural tumors



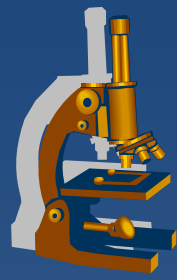
- associated with farmacoresistant epilepsy
- demarcated, low grade, G1
- ganglioglima

Tumors of the meninges



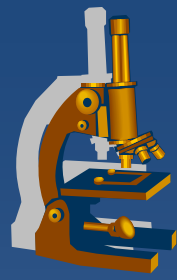
- common tumors
- mostly in older adults
- meningiomas most common
- others
  - ***solitary fibrous tumor***
  - ***mesenchymal tumors***
  - ***lymphomas***
  - ***metastases***

Tumors of the meninges



- **Meningioma (G1)**
- Atypical meningioma G2,
  - ⇨ ***more common mitotic activity***
- Anaplastic meningioma G3
  - ⇨ ***possible metastasis***
- Surgery
- in incomplete resection, G2, G3 - radiotherapy

Tumors of the meninges
Meningioma

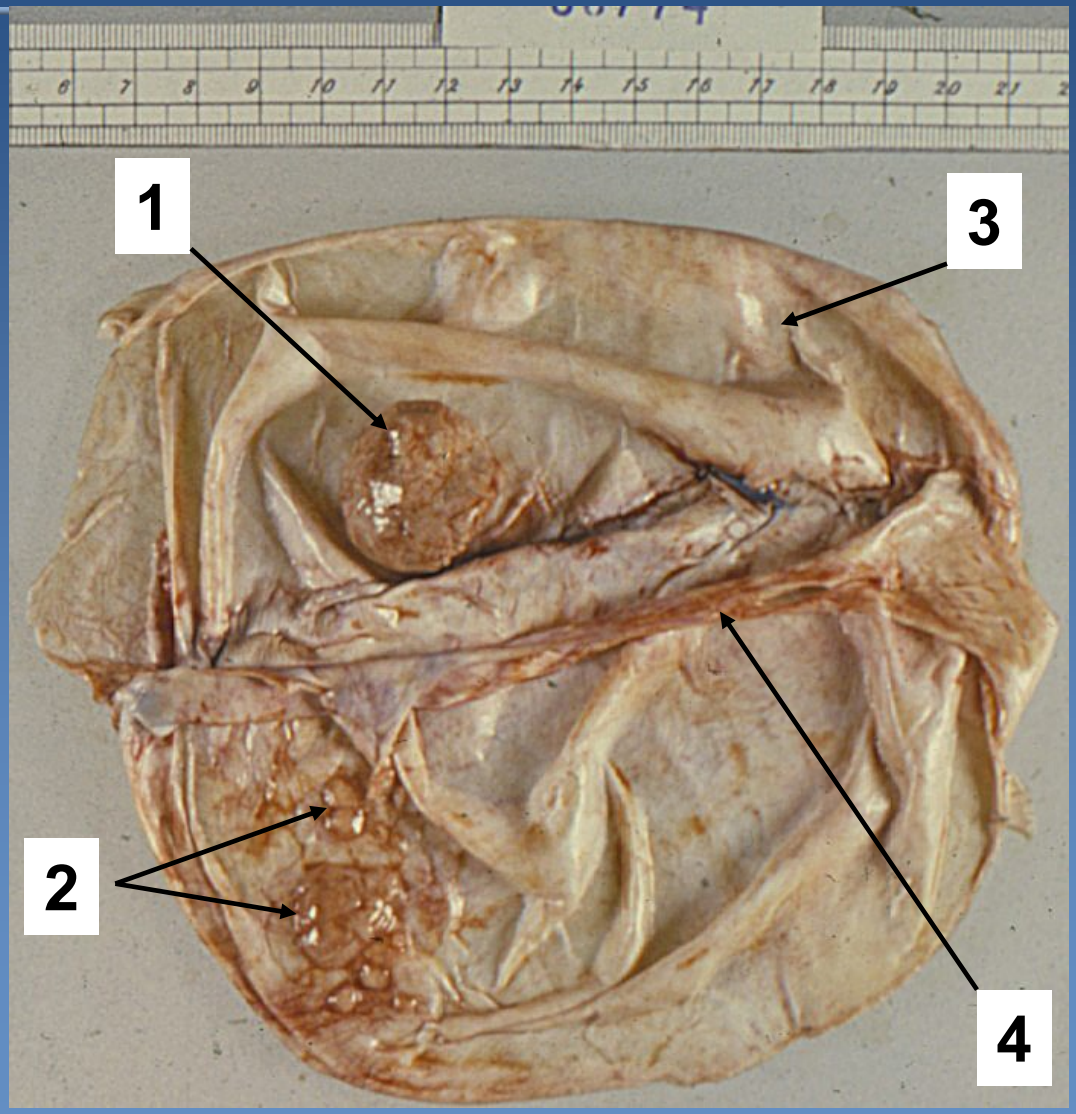


- **20% of all intracranial tumors, adults**
- **predominantly on the hemispheral convexity**
- **origin from arachnoidal cap cells**

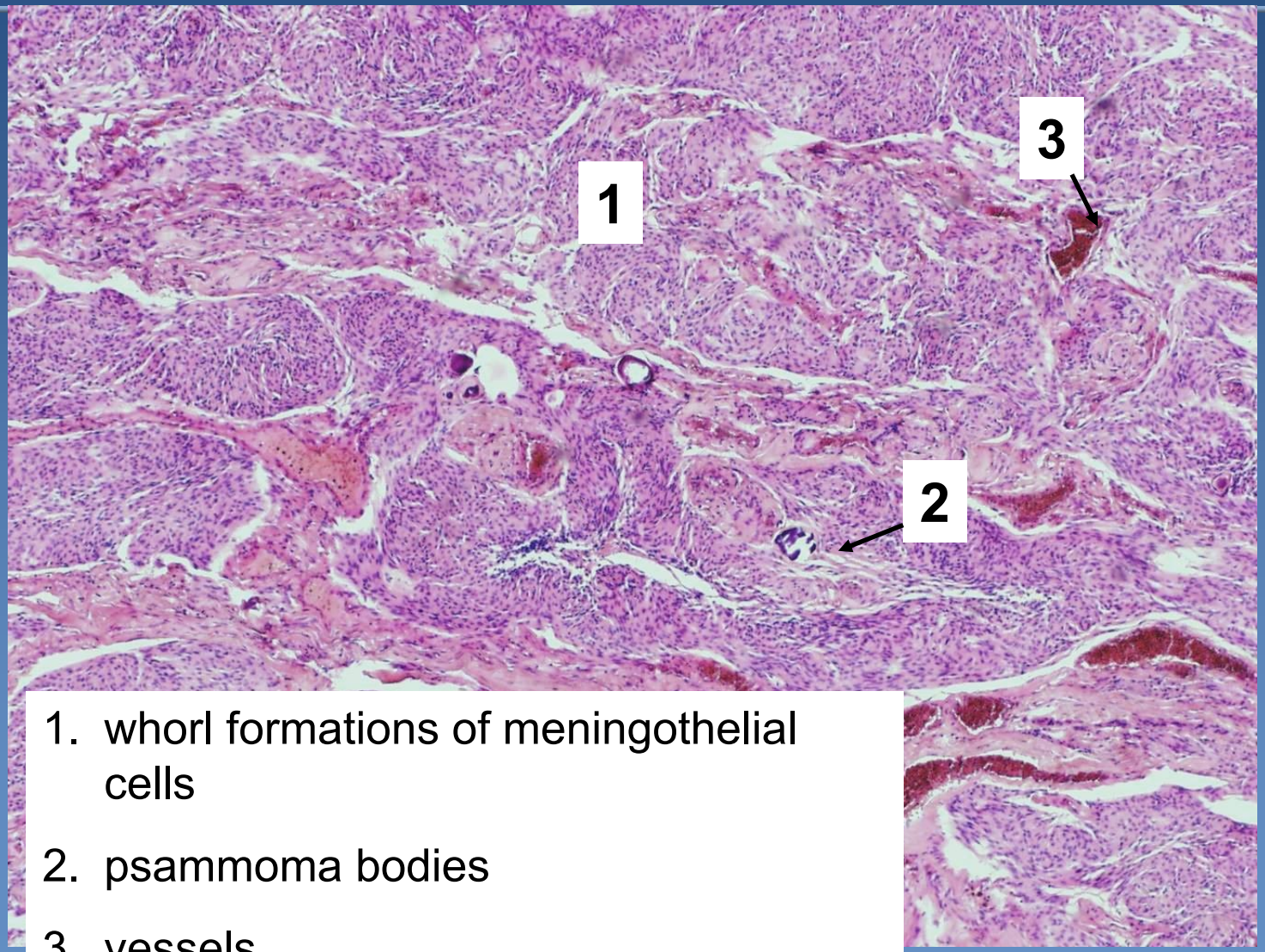
- **gross:**
  - ⇨ *usually solitary , well demarcated, firm, whorl-like pattern on cut surfaces*
  - ⇨ *attached to the dura, cortical compression, rare skull invasion*
- **micro:**
  - ⇨ *highly variable*
  - ⇨ *whorls, bundles*
  - ⇨ *common laminated calcific concretions – psammoma bodies (X-ray)*

Meningioma

1. Lobular meningioma
2. Flat meningiomas
3. Dura mater
4. Falx cerebri

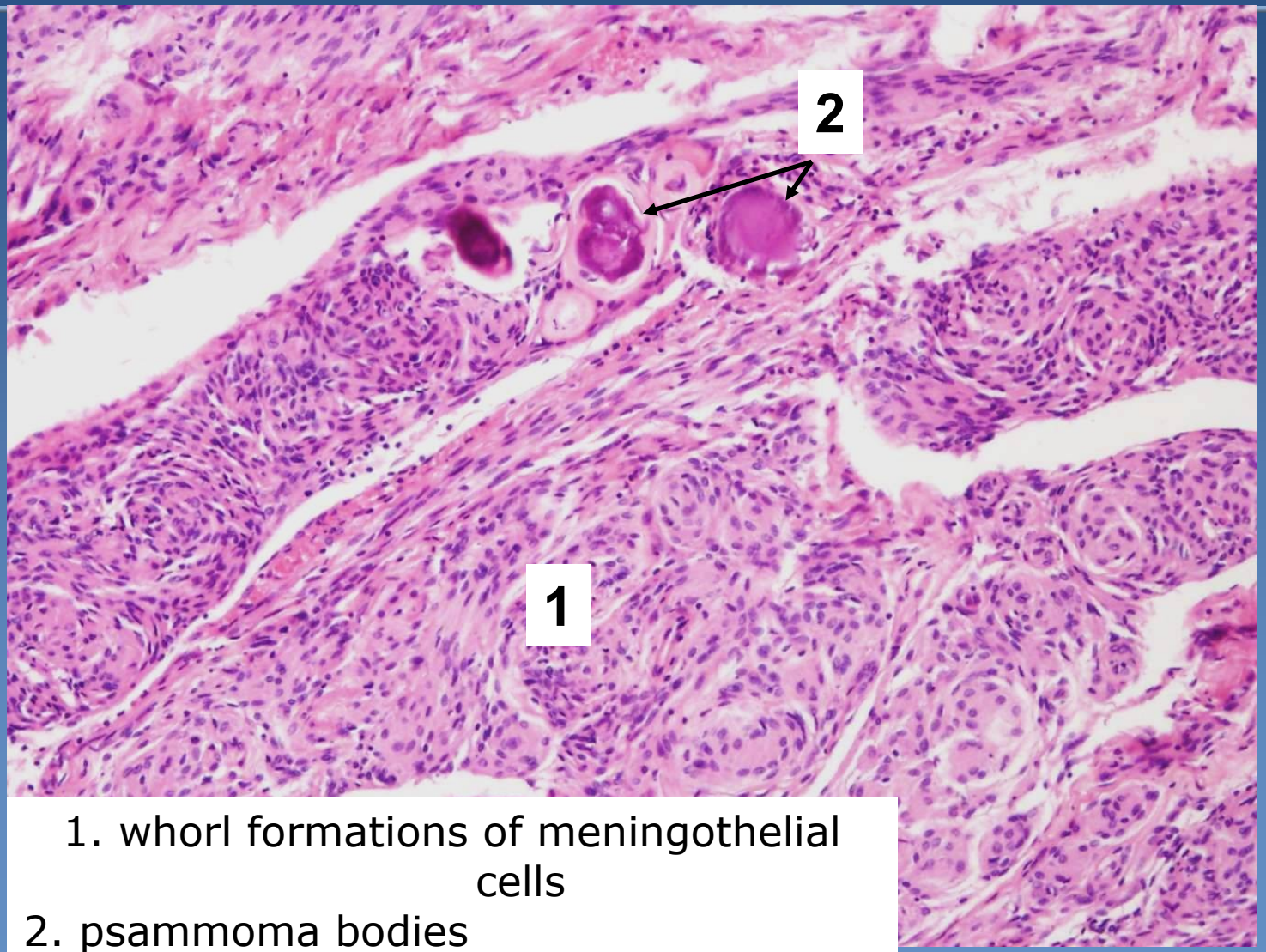


Meningioma



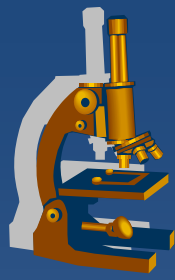
1. whorl formations of meningothelial cells
2. psammoma bodies
3. vessels

Meningioma

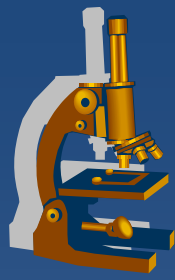


1. whorl formations of meningothelial cells
2. psammoma bodies

Craniopharyngeoma WHO G1

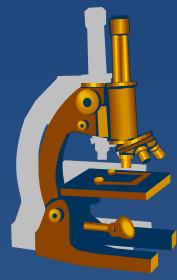


- children + young adults
- from Rathke‘s pouch rests
- suprasellar cystic mass
- chiasma opticum defects
- endocrine dysregulations
- neurosurgical resection
- possible relaps after incomplete resection
- keratinising squamous cell epithelium



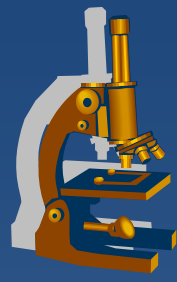
Peripheral nerve sheat tumors

Benign tumors



- **Schwannoma**
- **neurofibroma (solitary; multiple - neurofibromatosis type 1)**
- perineurioma
- neurothecoma
- granulosa cell tumor

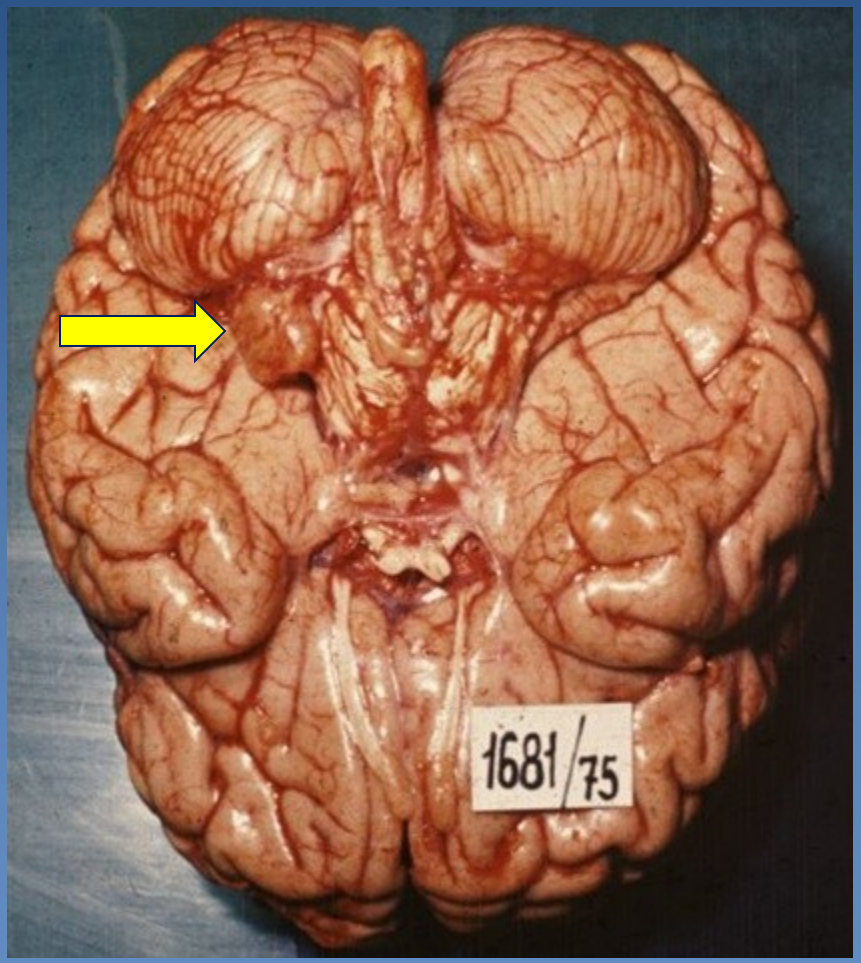
Schwannoma

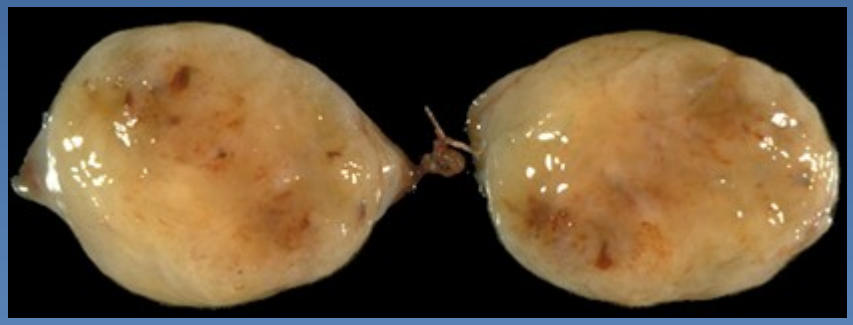


- **intracranial - cerebellopontine angle – VIII. nerve „acoustic neuromas**
- **compression (excitation, later loss of function)**
- in connection with **peripheral nerve**

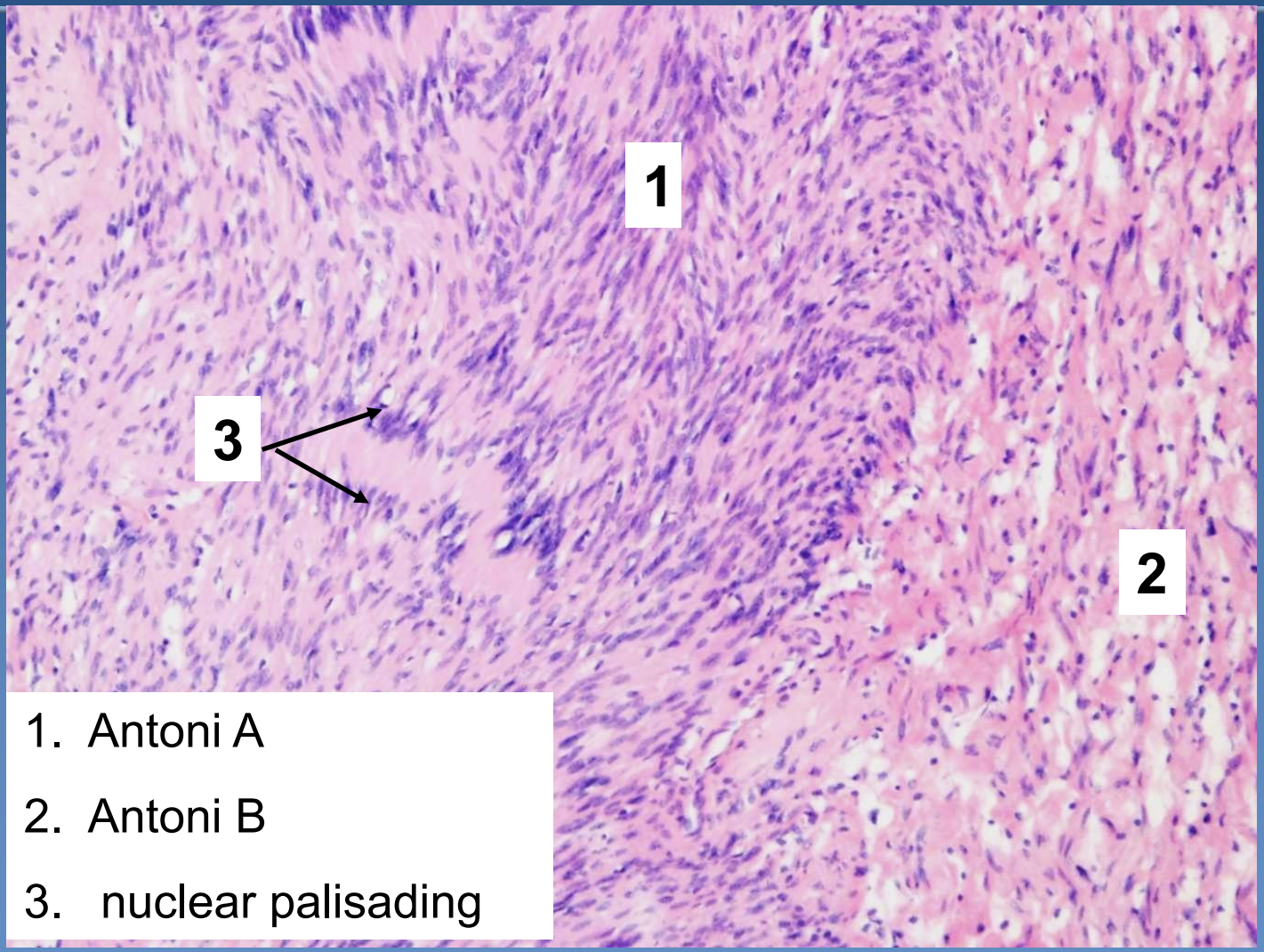
- **gross:**
  - ⇨ *well-circumscribed encapsulated lesion, may be attached to the nerve*
- **micro:**
  - ⇨ ***cellular areas of densely packed spindle cells (Antoni A pattern, Verocay bodies – nuclear palisading)***
  - ⇨ ***intermixed with looser, myxoid regions (Antoni B pattern)***

Schwannoma



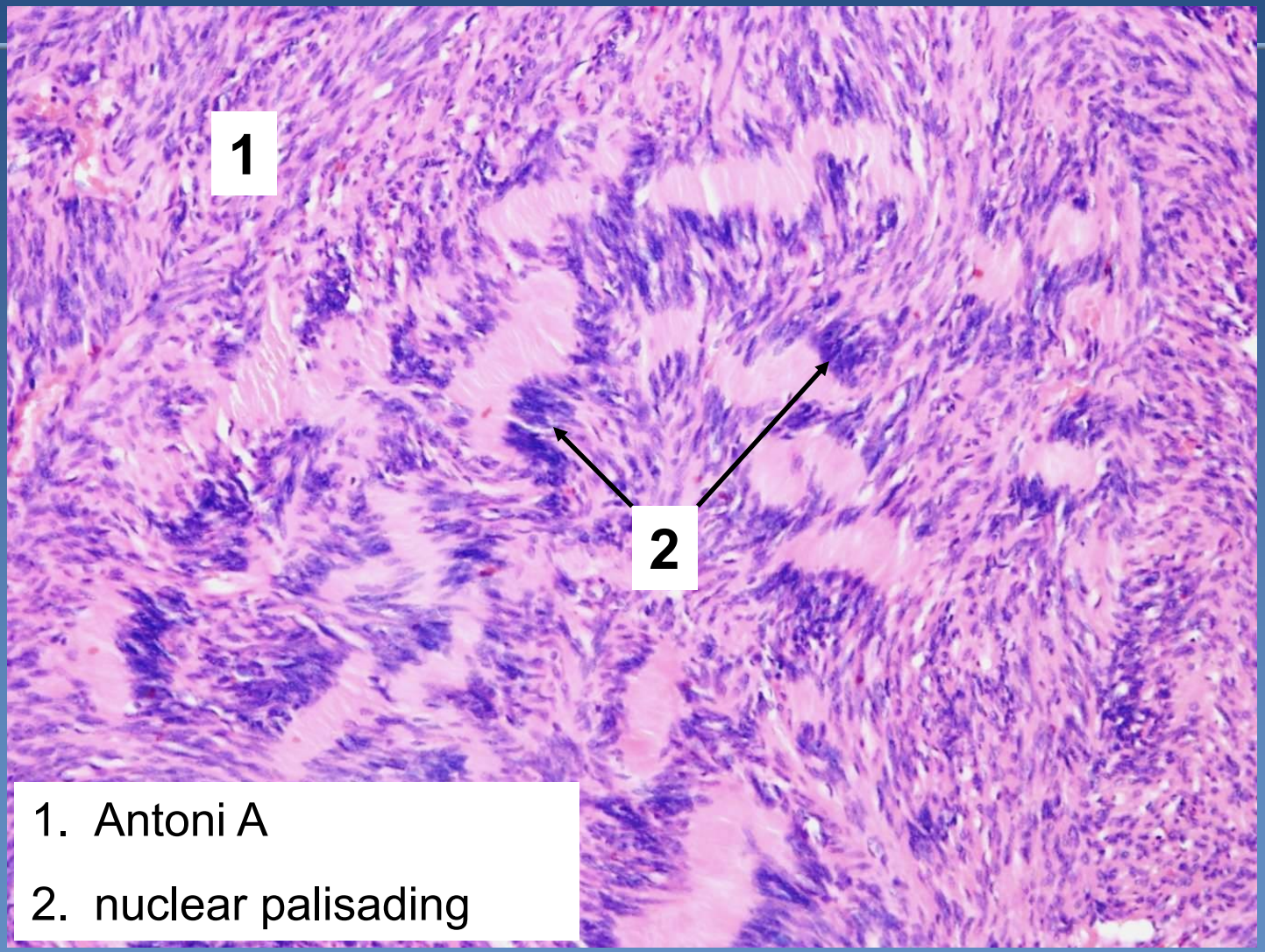


Schwannoma



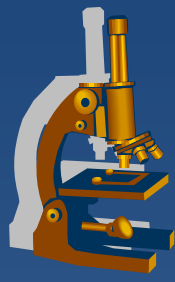
1. Antoni A
2. Antoni B
3. nuclear palisading

Schwannoma



1. Antoni A
2. nuclear palisading

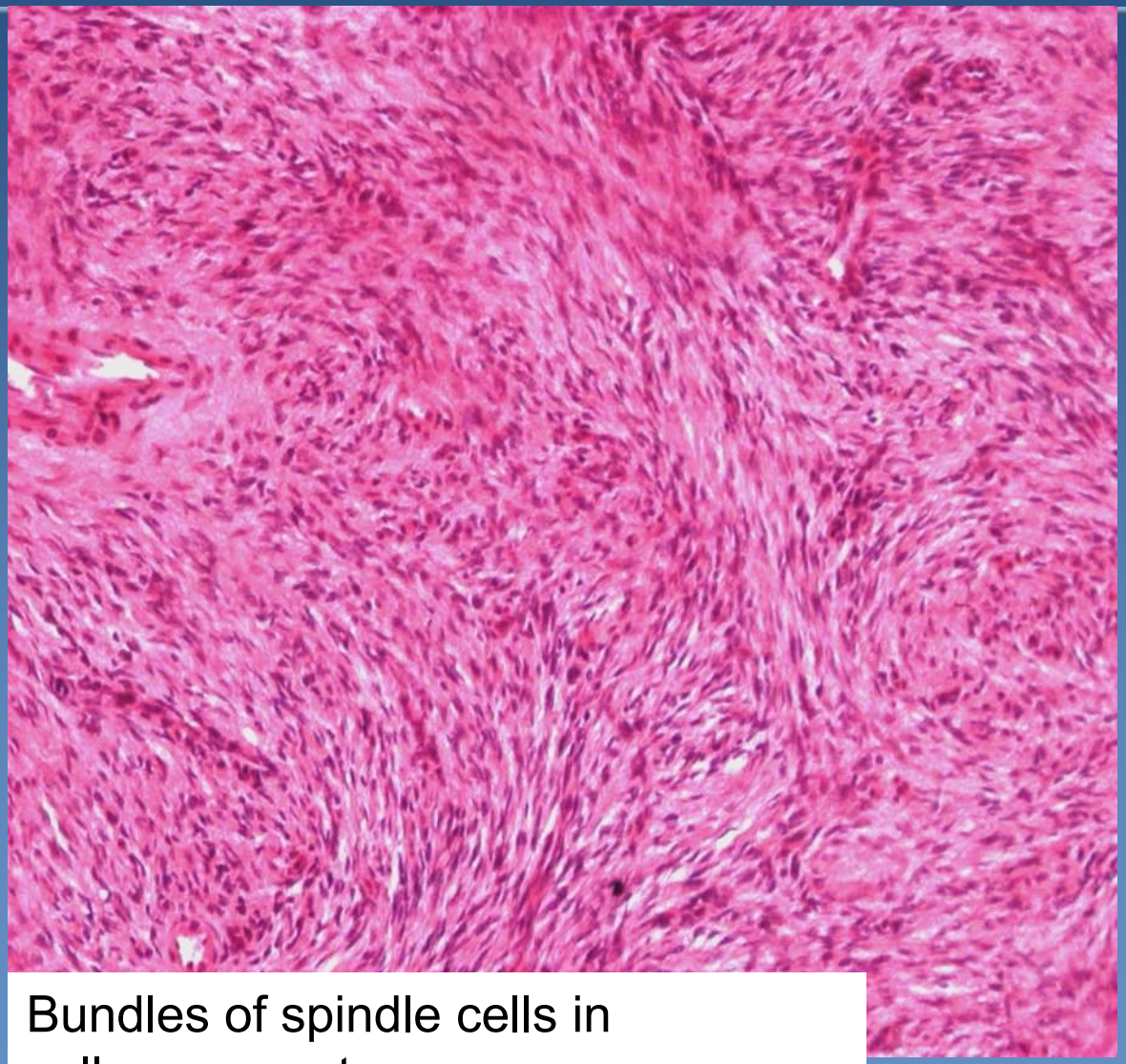
Neurofibroma



- **peripheral nerve sheath tumor**
- **solitary x multiple (neurofibromatosis I. , II. type)**
- **cutaneous x plexiform** *(along nerves)*

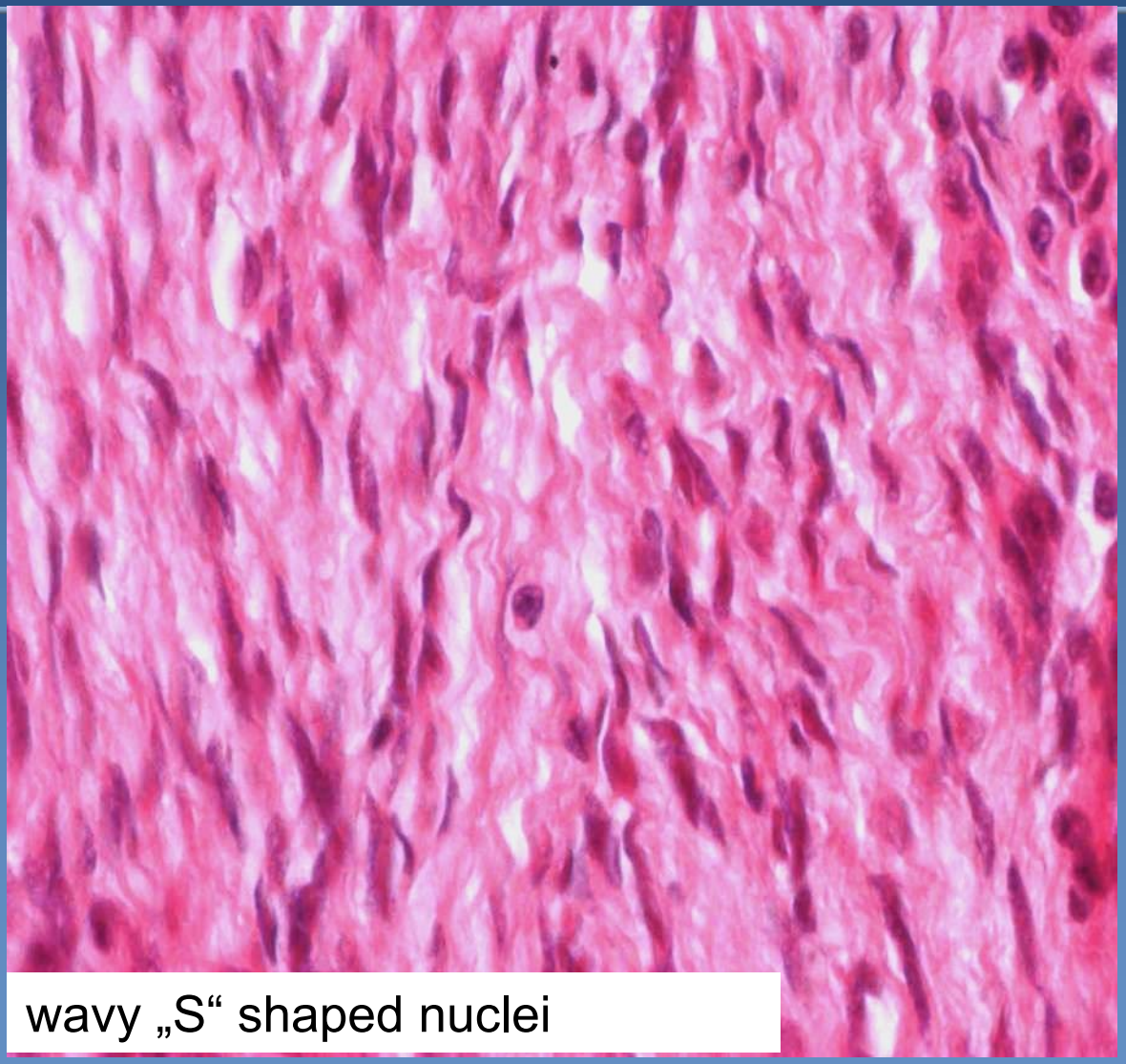
- **gross:**
  - ⇨*unencapsulated soft roundish nodules*
- **micro:**
  - ⇨***spindle cells, „S“ and „C“ shaped***
  - ⇨***extracellular loose myxoid or collagenous matrix***
  - ⇨***sporadic small vascular lumina***

neurofibroma



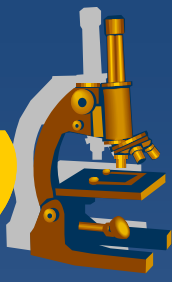
Bundles of spindle cells in collagenous stroma

neurofibroma



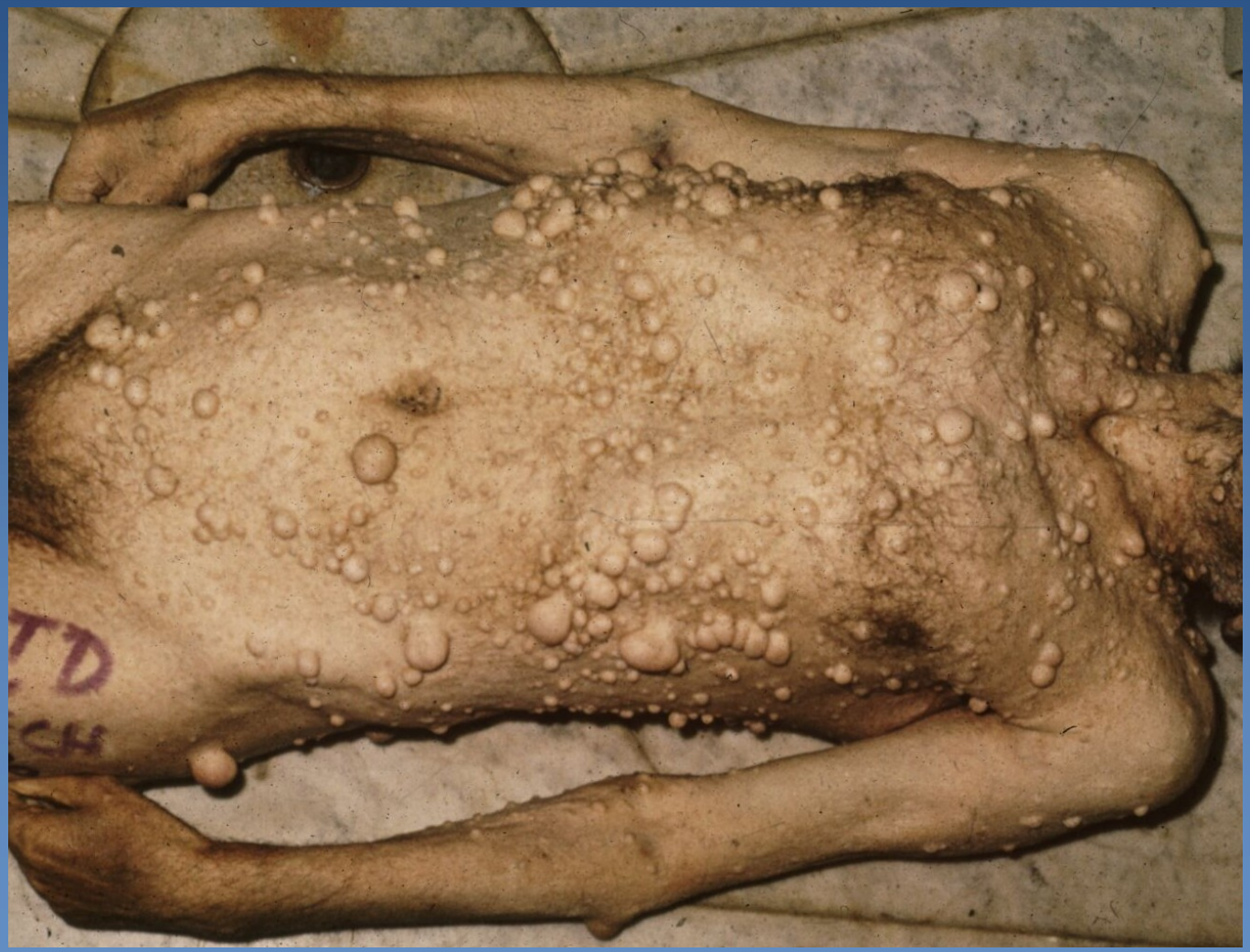
wavy „S“ shaped nuclei

Neurofibromatosis (type I)

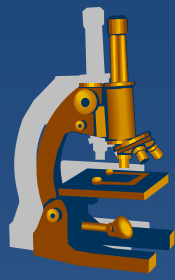


- von Recklinghausen‘s disease
  - ⇨ *AD, frequency 1:3000, chromosome 17, defect of tumor suppressor gene*
- **multiple neurofibromas, mostly on skin ,** in any localisation - retroperitoneum, orbit, tongue, GIT, melanin-containing variants
- **hyperpigmented skin lesions** (café-au-lait spots), **pigmented iris hamartomas** (Lisch nodules)
- **in approx. 3% of patients malignant transformation**
- ↑ **risk of development of other tumors** *(optic gliomas, meningiomas, pheochromocytomas)*

Neurofibromatosis (type I)



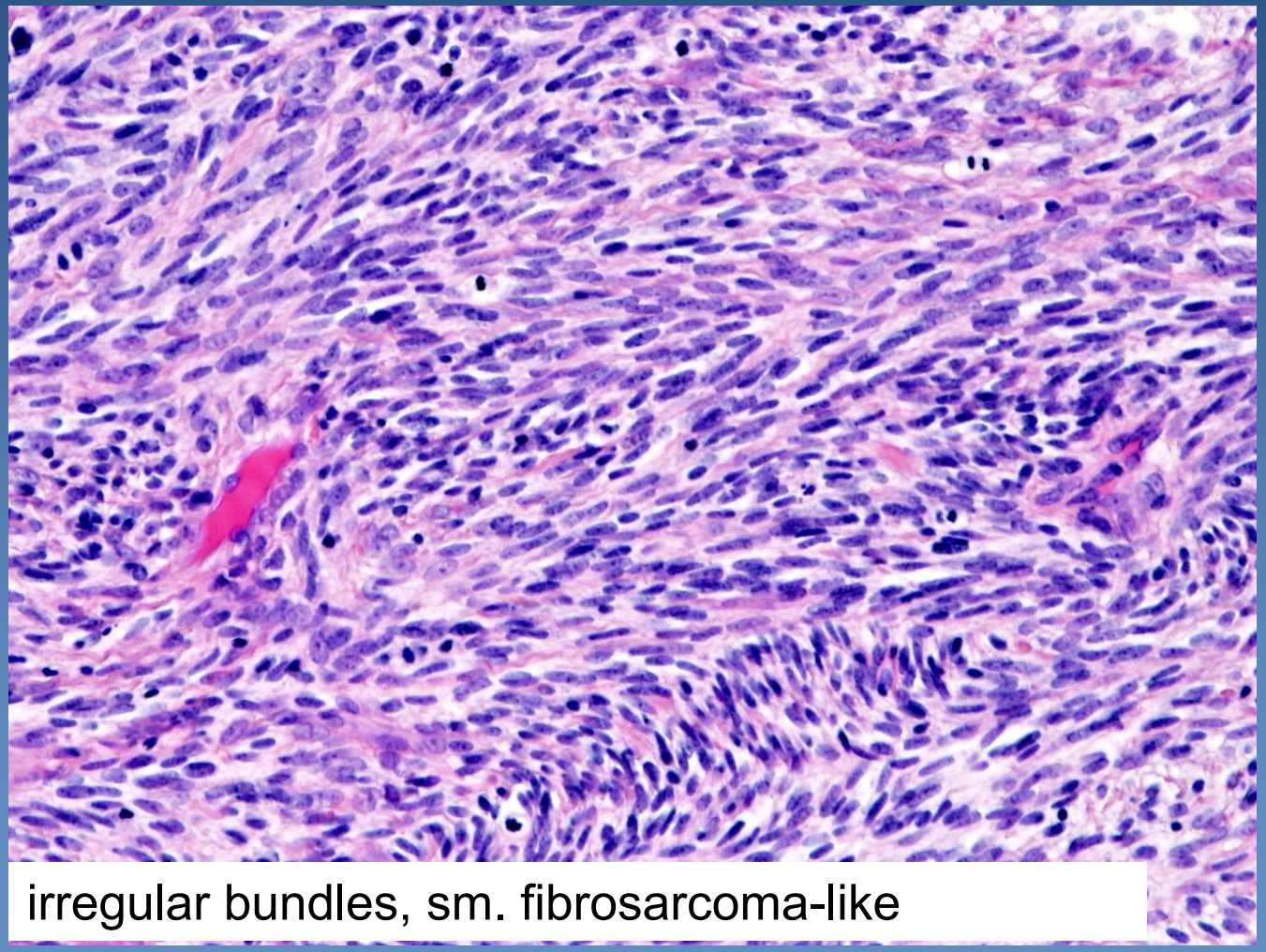
Malignant tumors



- **malignant peripheral nerve sheath tumor (MPNST)**
  - *„neurogennic sarcomas“ arising from the peripheral nerve sheath*
  - *50% occur in patients with neurofibromatosis type 1, adults*
  - *agressive, recurrent, metastases (lung, bones)*
  - *gross: foci of necrosis, hemorrhage*
  - *micro: fibroblast-like cells with elongated nuclei, frequent mitotic figures, areas of necrosis*

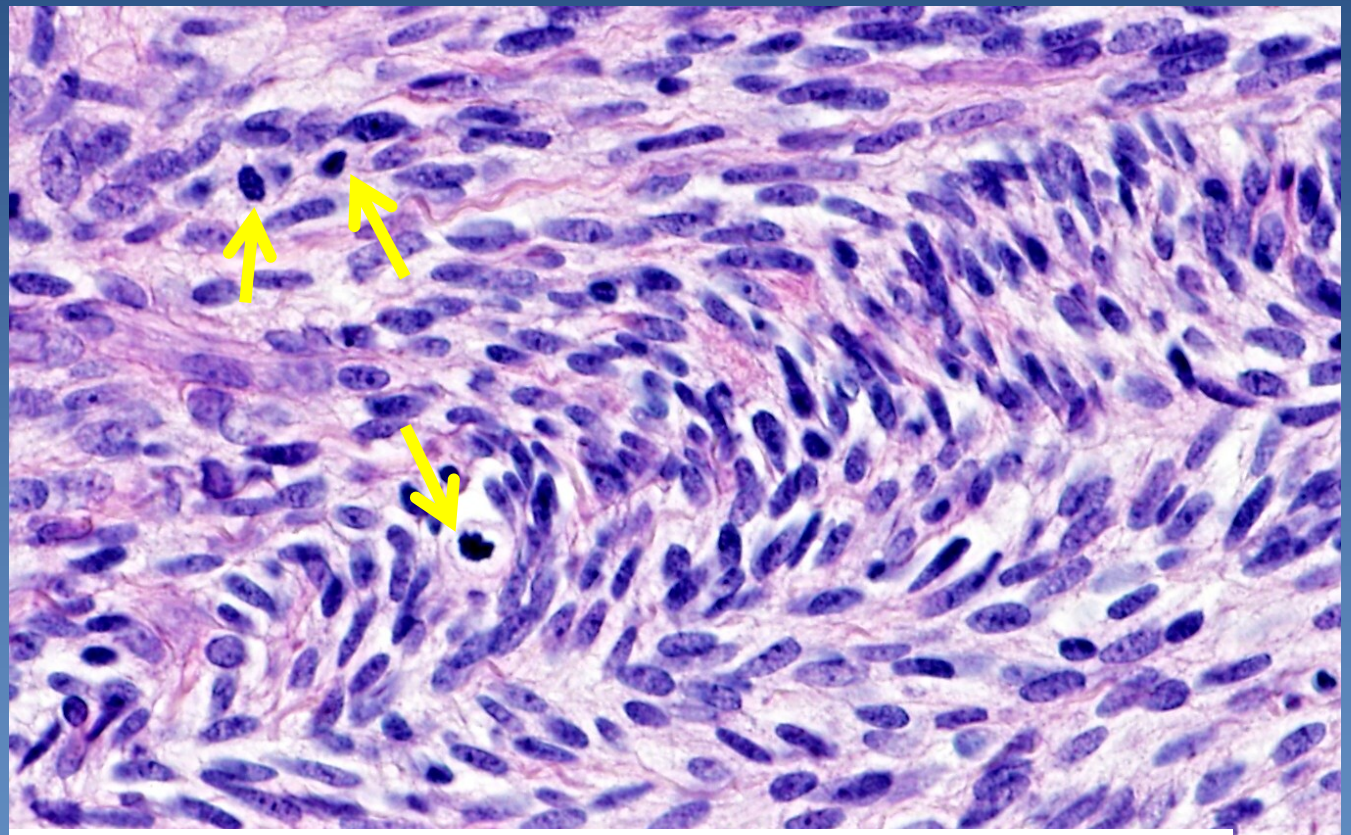
- **primitive neuroectodermal tumors (PNET)**
  - *bone tumor*

MPNST



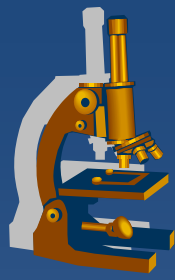
irregular bundles, sm. fibrosarcoma-like

MPNST



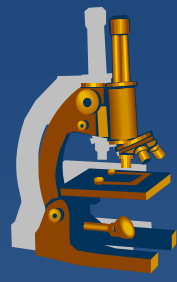
Hyperchromatic nuclei of spindle cells

Mitoses (arrows)



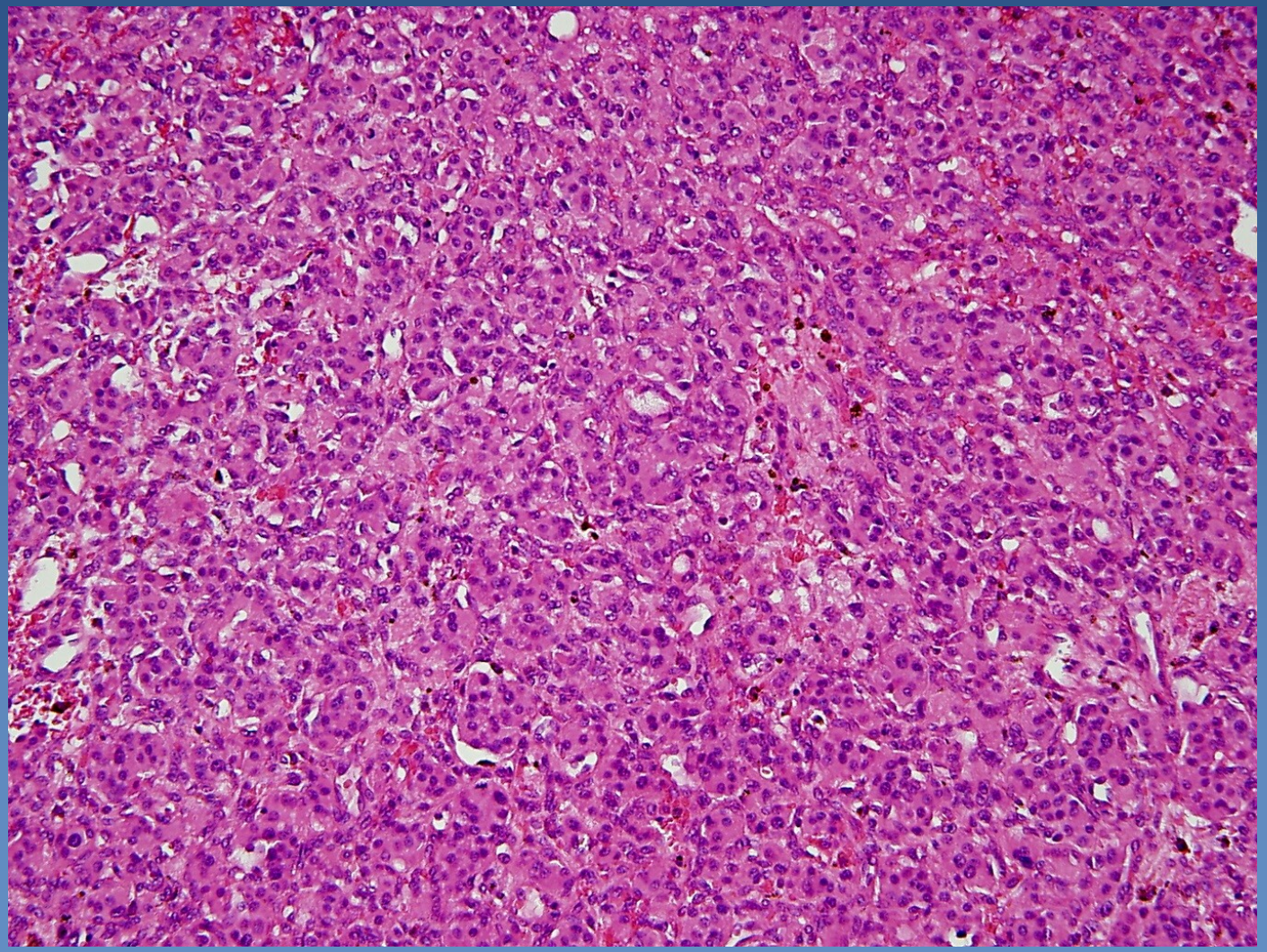
TUMORS OF THE AUTONOMIC NERVOUS SYSTEM

Tumors of the parasympathetic system

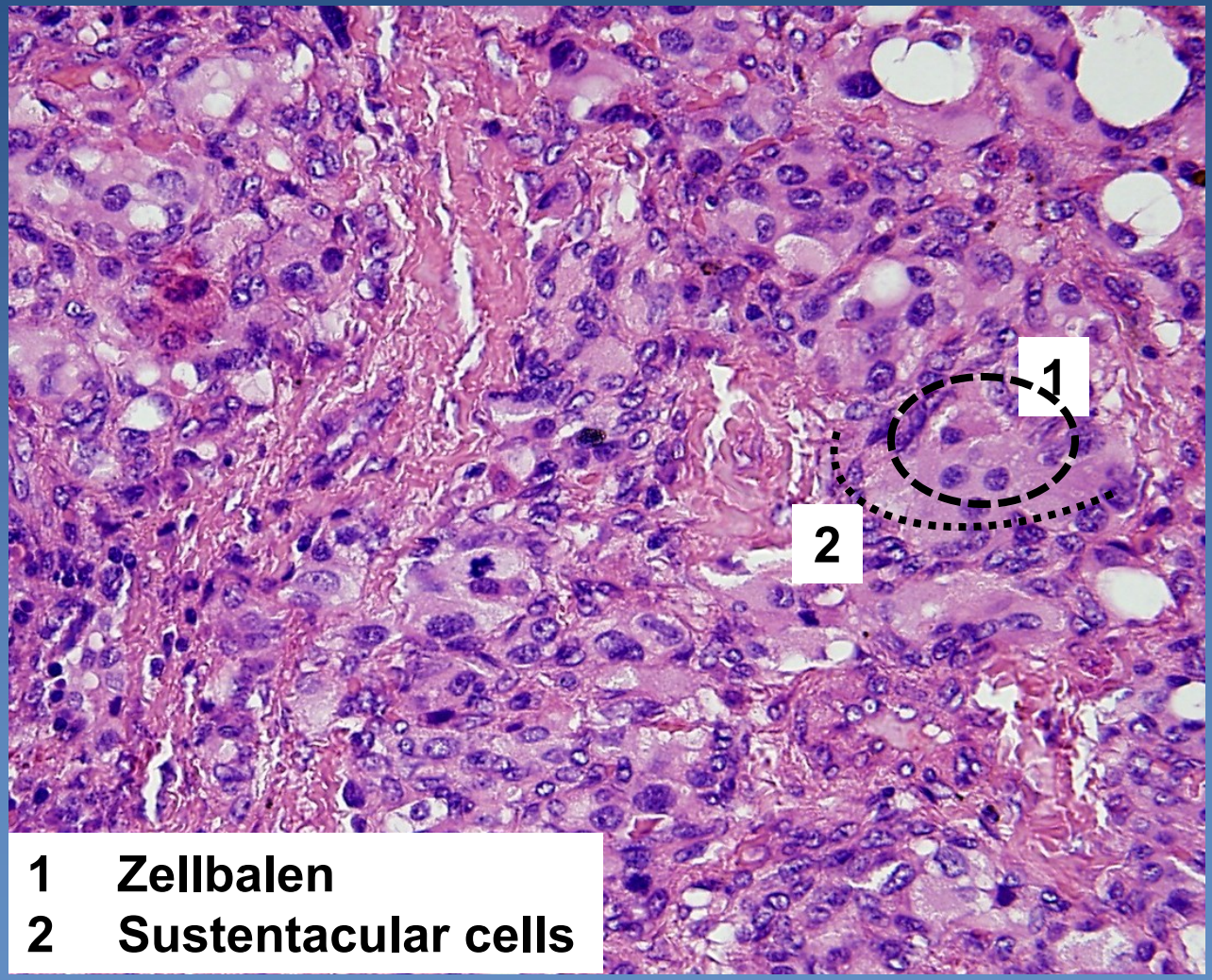


- **paraganglioma, chemodectoma**
  - ⇨ ***originate from extraadrenal paraganglia***
    - glomus tympanicum and jugulare, vagal bodies, carotid bodies, laryngeal, aorticopulmonary
      - pressure changes: ↓P_aO_2, ↑P_aCO_2 a ↑pH → reflex stimulation of respiratory and cardiovascular system
  - ⇨ ***micro:***
    - organoid (solid alveolar) formation ofcells:
      - chief cells - polygonal to oval; in distinctive cell nests, „Zellballen“)
      - **supporting (sustentacular) spindle cells**
    - separated by thin fibrovascular stroma

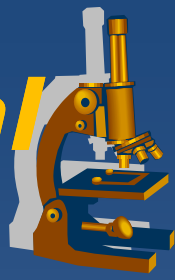
Paraganglioma



Paraganglioma

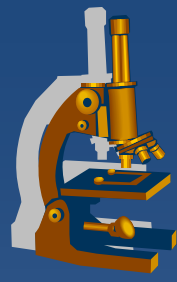


Tumors of the sympatoadrenal system



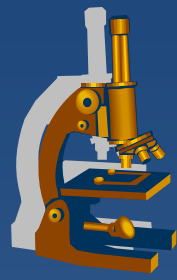
- **Paragangliomas**
- **Pheochromocytoma**
  - ***Adrenal medullary paraganglioma***
  - ***Gross*:, circumscribed lessions, usually confined to the adrenal , yellow-tan (hemorrhage, necrosis)**
  - ***10% associated with familial syndromes (MEN 2A,2B,..), 10% extra-adrenal, in adrenal location 10% bilateral, 10% biologically malignant)***
- **Neuroblastoma → ganglioneuroblastoma→ ganglioneuroma**
  - *spontaneous or chemotherapy-induced maturation*
  - *even regression possible*
  - *variable prognosis, according to age and stage*

Neuroblastoma



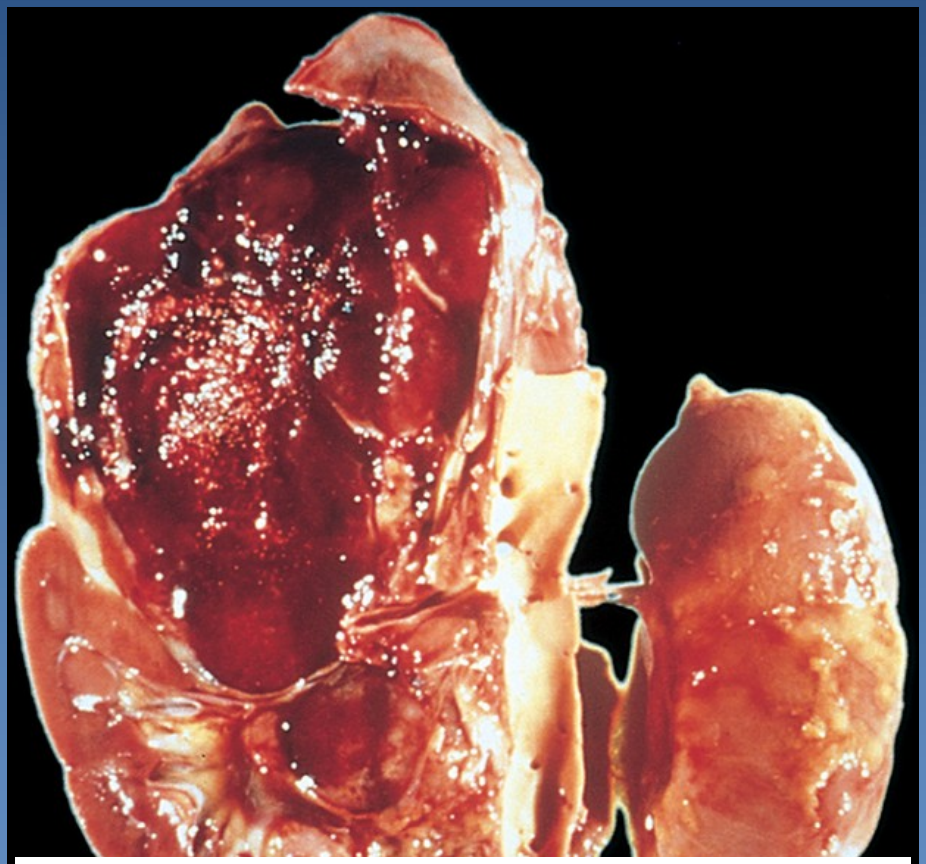
- most common extracranial solid tumor in chidhood
- usually sporadic, 1% germline mutation of ALK (anaplastic lymphoma kinase)-gene
- mostly in adrenal medulla, paravertebral sympathetic ganglia
- large tumors haemorrhagic, necrotic

Neuroblastoma



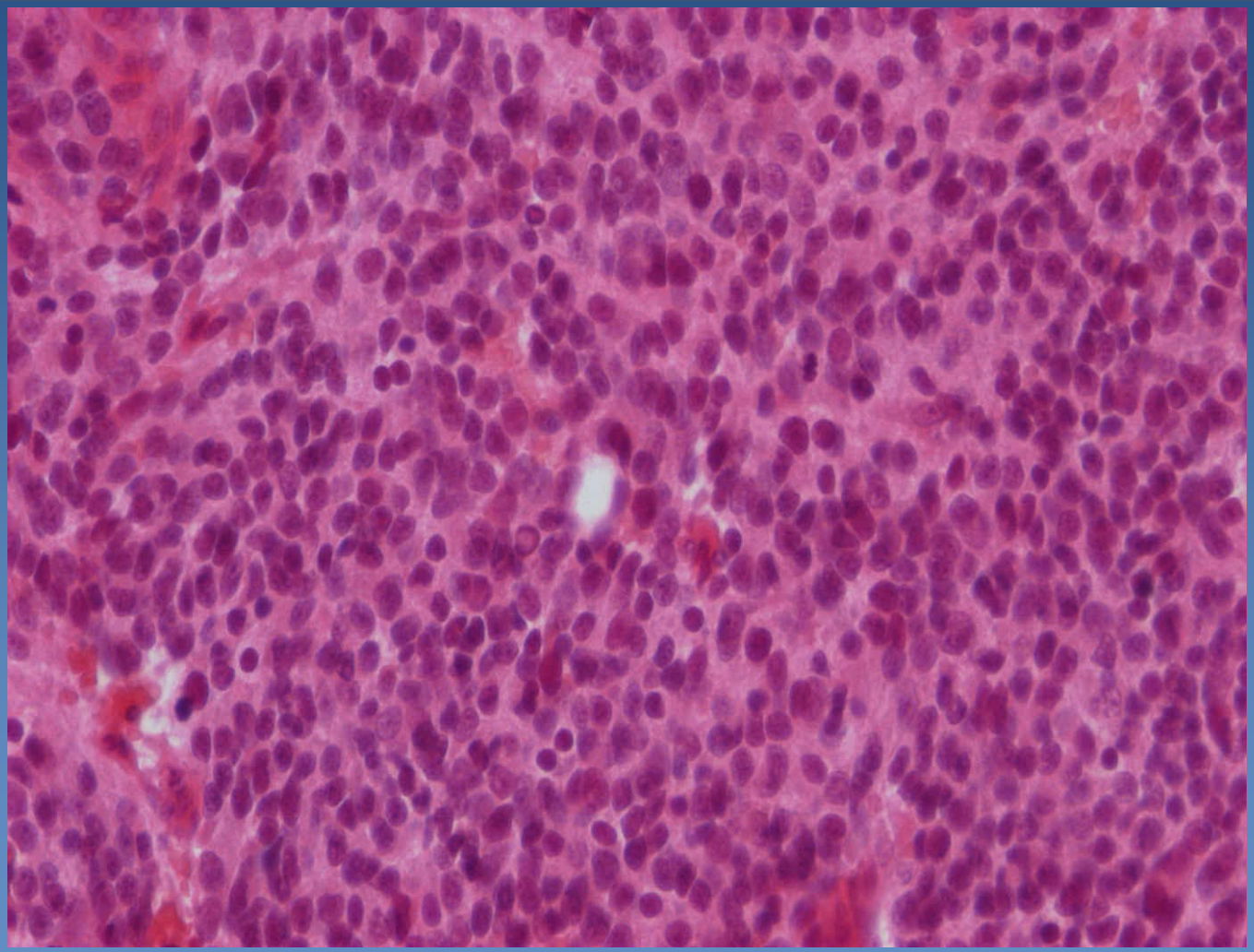
- Micro:
  - ⇨ *small round cells, hyperchromatic nuclei („small blue cells“)*
  - ⇨ *extracellular eosinophilic fibrillary stroma*
  - ⇨ *Homer-Wright rosettes*
  - ⇨ *commonly high mitotic acitivity, caryorrhexis*

Neuroblastoma



Necrotic haemorrhagic adrenal tumor

Neuroblastoma



Neuroblastoma