Pathology of the Nervous System

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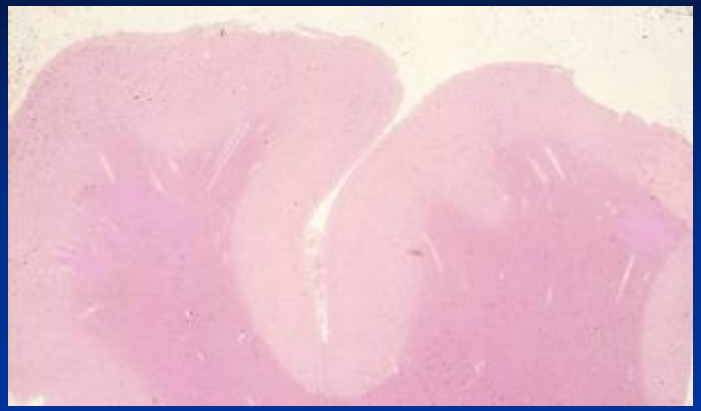
- Introduction
- Increased intracranial pressure
- Vascular and circulatory disorders
- Trauma
- Infections
- Tumors
- Demyelinating diseases
- Degenerative diseases
- Developmental Abnormalities



Hematoxylin and Eosin

Luxol fast-blue-PAS

Bielschowsky

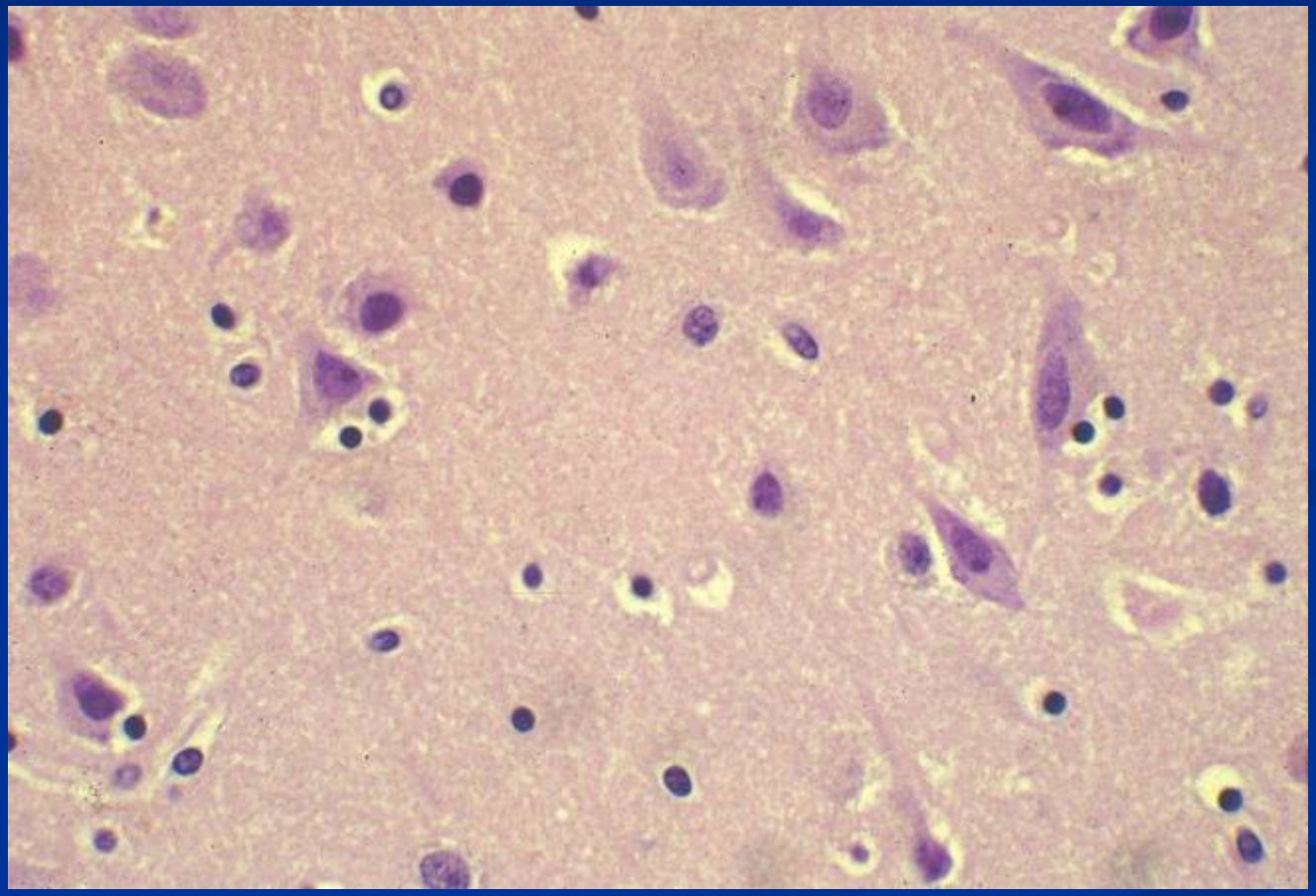
Cell types

1. Neuron: functions in neural transmission, most vulnerable cell, limited regeneration
2. Astrocyte: major reactive cell of CNS forms 'scar'
3. Oligodendrocyte: highly vulnerable, limited proliferation, forms myelin sheath
4. Ependymal cell: vulnerable, limited regeneration, lines ventricles (ependymal granulations)
5. Microglial cell: monocyte/macrophage (bone marrow) derived phagocytic cell, antigen presentation, producer of cytokines, inflammatory cell

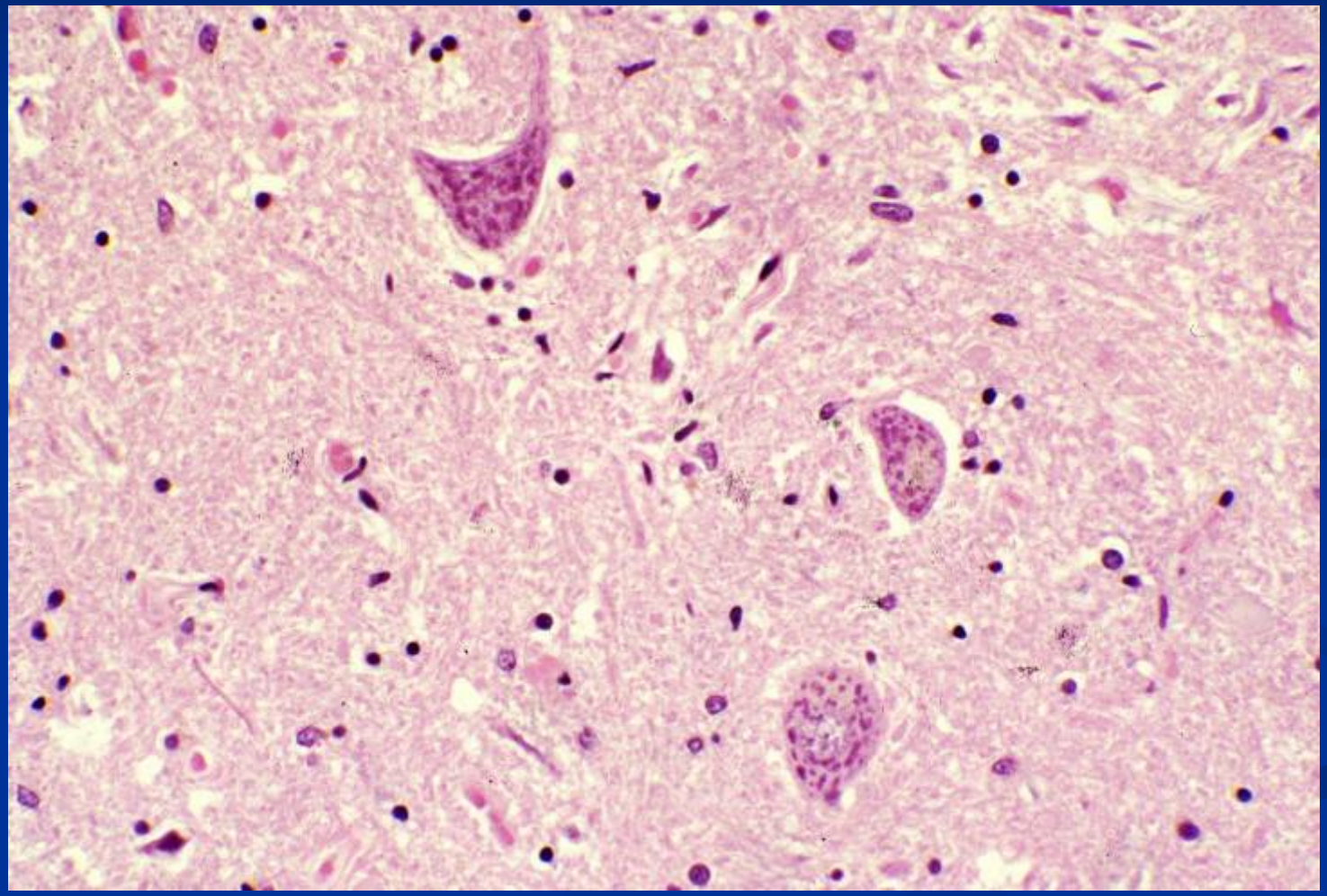
Introduction

- Cellular reactions of the central nervous system
  - Neurons: permanent
    - Axonal retraction (axonal spheroids)
    - Ischemic cell changes
    - Atrophy and degeneration
    - Intraneuronal deposits and inclusions (neurodegenerative diseases)
  - Glia: proliferate, form glial 'scar'

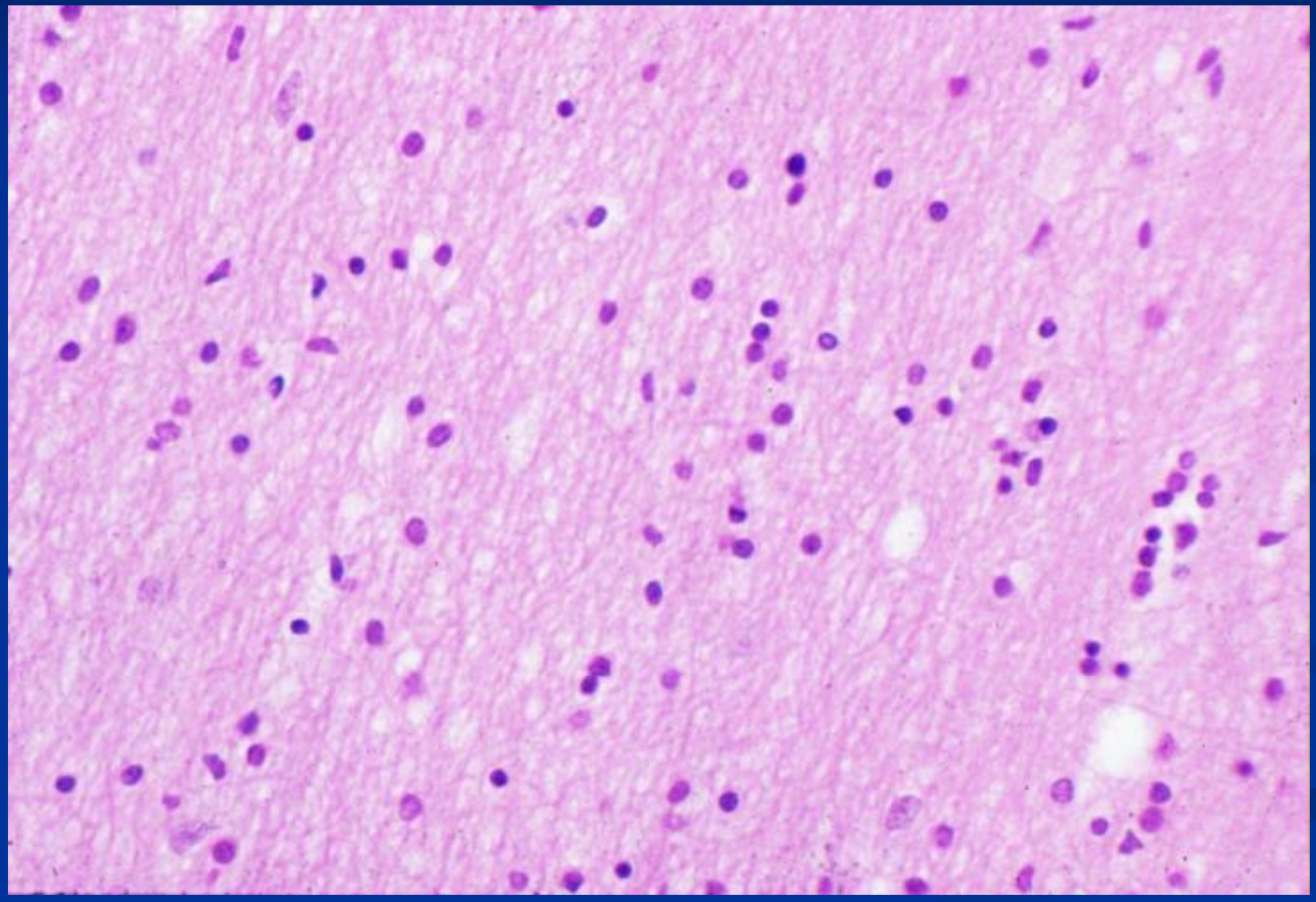
Gray Matter



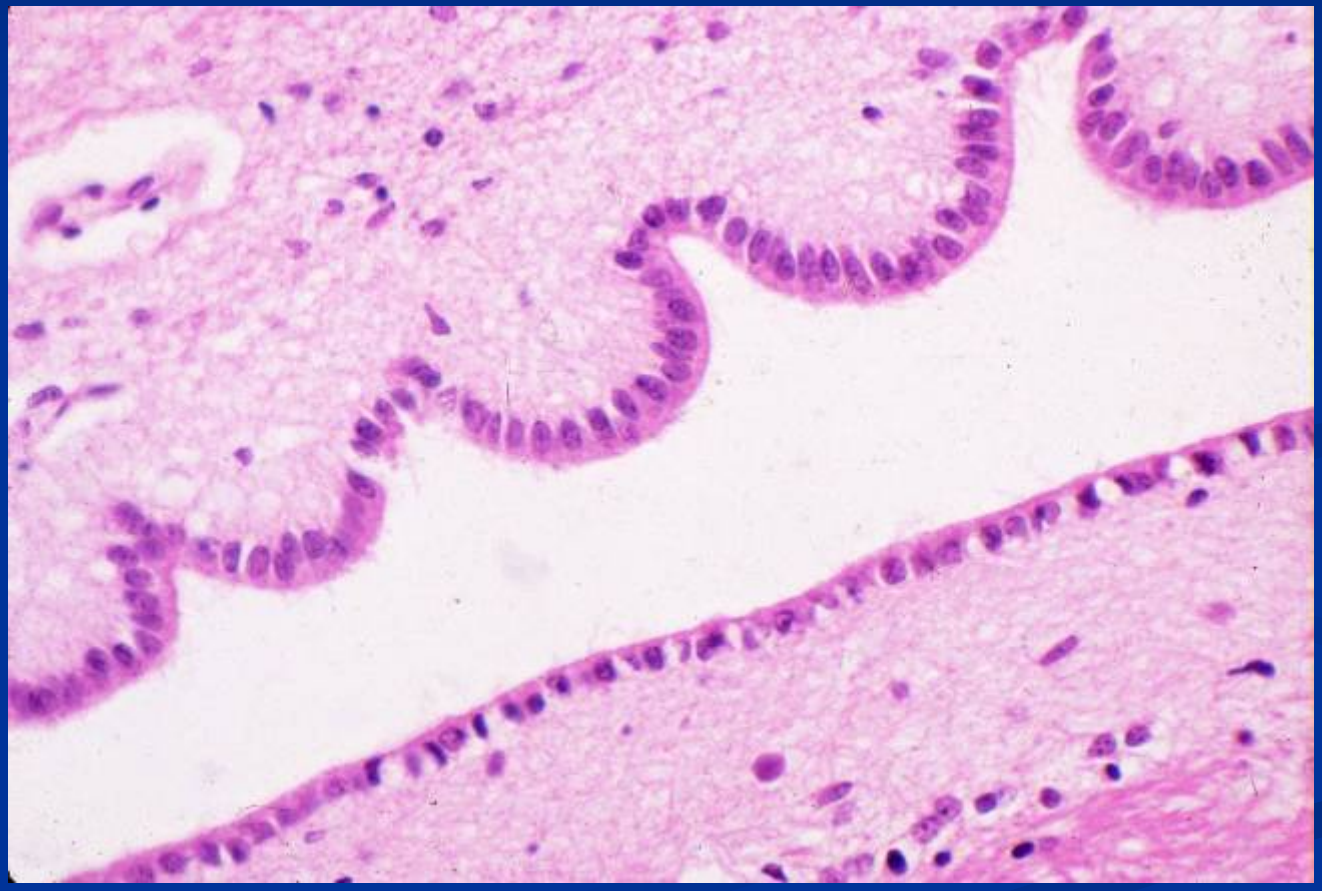
Nissl substance



White Matter



Ventricular lining



Mechanisms of dysfunction causing disease

- Pathophysiological (toxic/metabolic)
- Structural
  - Focal lesions correlate with localizing symptoms
  - System degenerations correlate with functionally localizing symptoms (ie motor neuron disease)
- Increased intracranial pressure (generalized or focal), can cause global symptoms or brain herniation since the volume of the brain is fixed by the skull

Increased intracranial pressure

Headache

Vomiting

Decreased Level of Consciousness

Papilledema

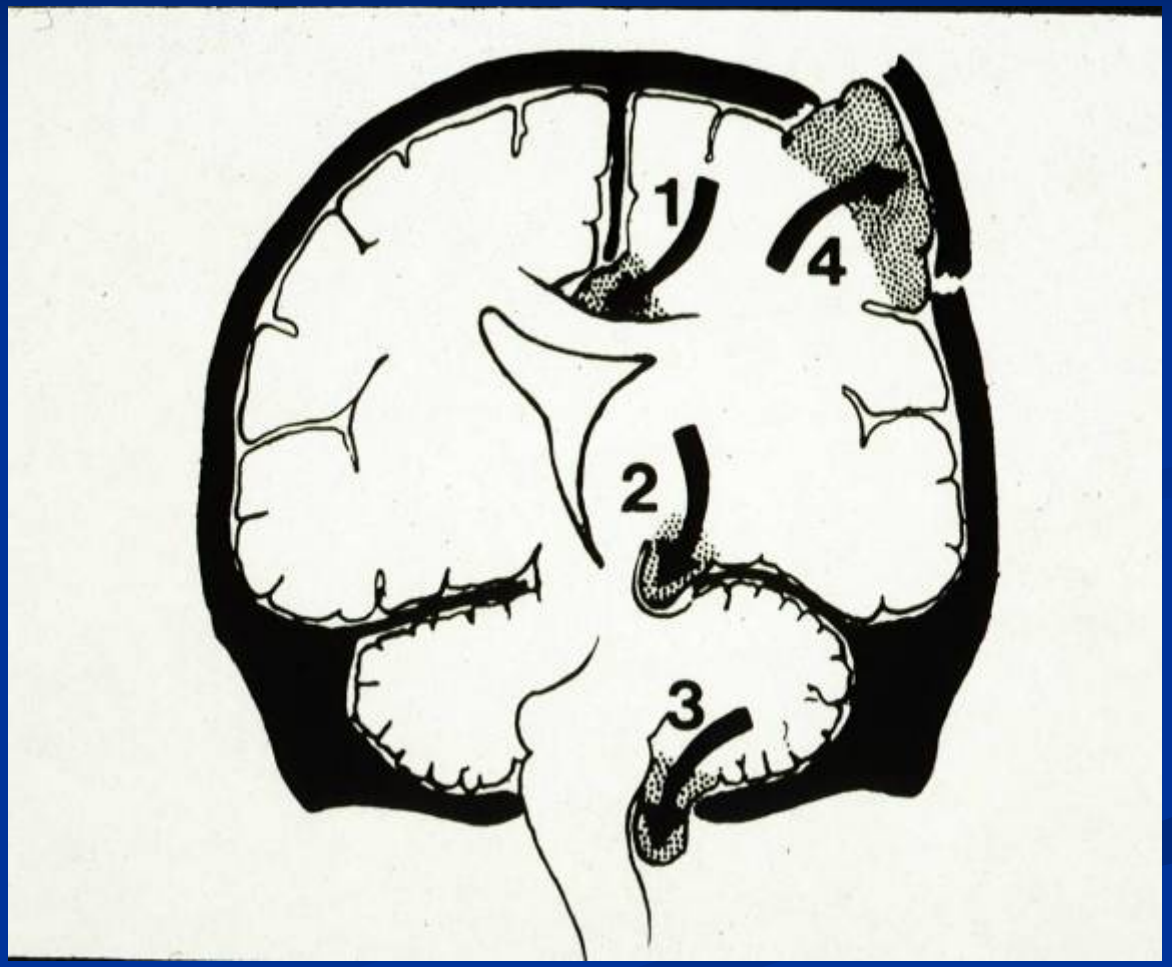
Herniation

Causes of Cerebral Edema

- Generalized (frequently cytotoxic)
  - Hypoxia
  - Toxins
  - Encephalitis
  - Trauma
- Focal (often vasogenic)
  - Infarction
  - Injury/contusion
  - Mass—neoplastic, infectious (cerebral abscess), hematoma

TYPES OF HERNIATION

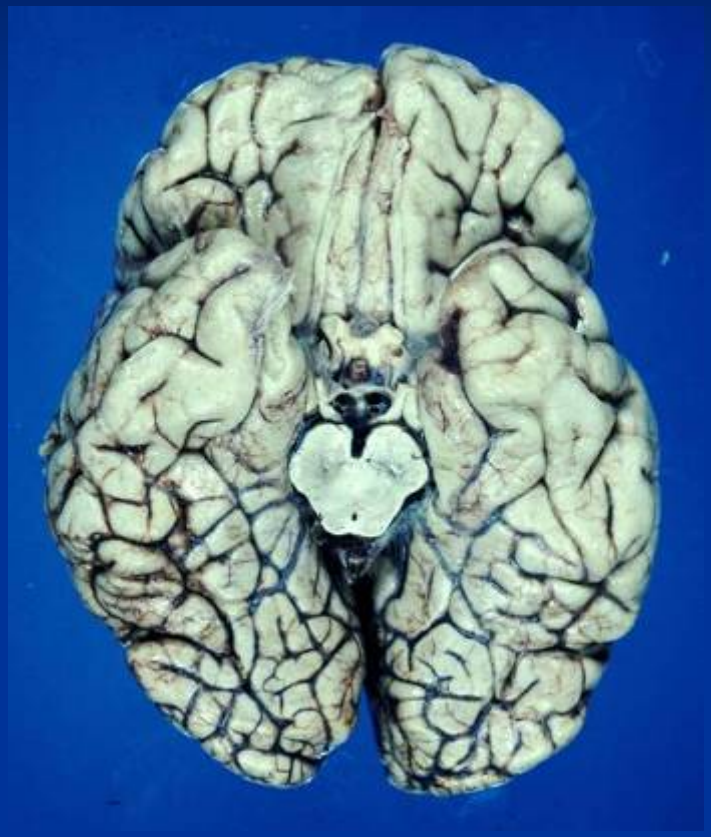
1. Subfalcine (cingulate)
2. Transtentorial (uncal)
3. Tonsillar (foramen magnum)
4. Extracranial



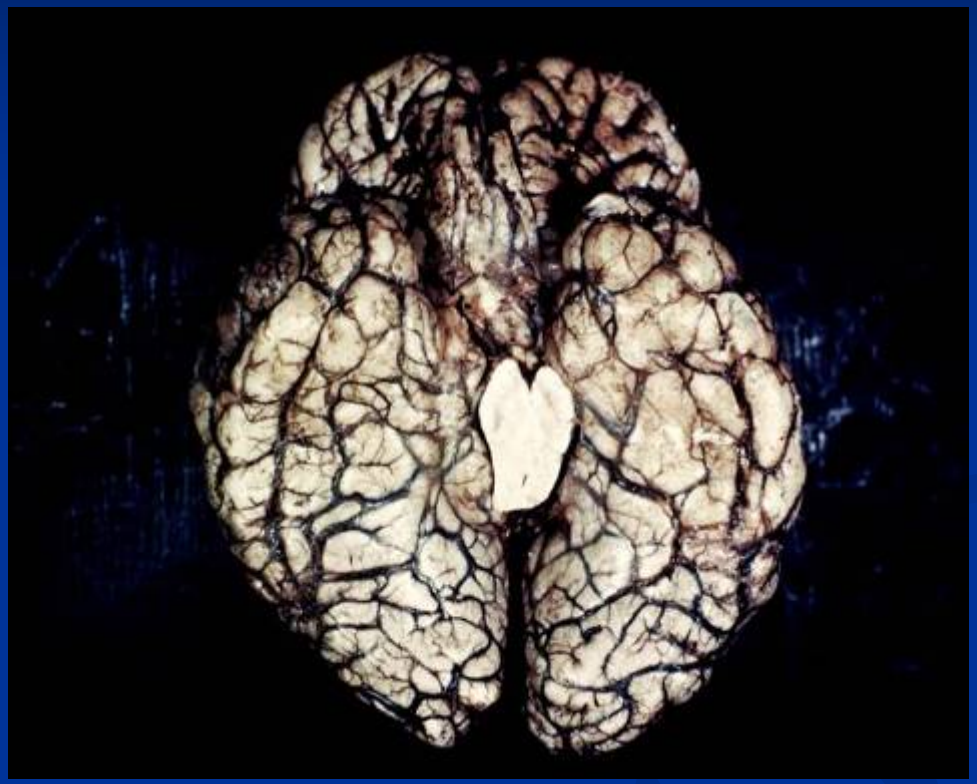
TRANSTENTORIAL (UNCAL) HERNIATION

- SHIFT OF THE BRAIN FROM THE MIDDLE TO THE POSTERIOR FOSSA THROUGH THE TENTORIAL INCISURA
- MAY BE UNILATERAL OR "CENTRAL"
- SECONDARY EFFECTS INCLUDE:
  - Compression of the third cranial nerve(s)
  - Duret hemorrhages in midline rostral brainstem
  - Compression of the contralateral cerebral peduncle (Kernohan's notch)
  - Compression of the posterior cerebral artery with infarction of the medial occipital lobe

UNCAL HERNIATION

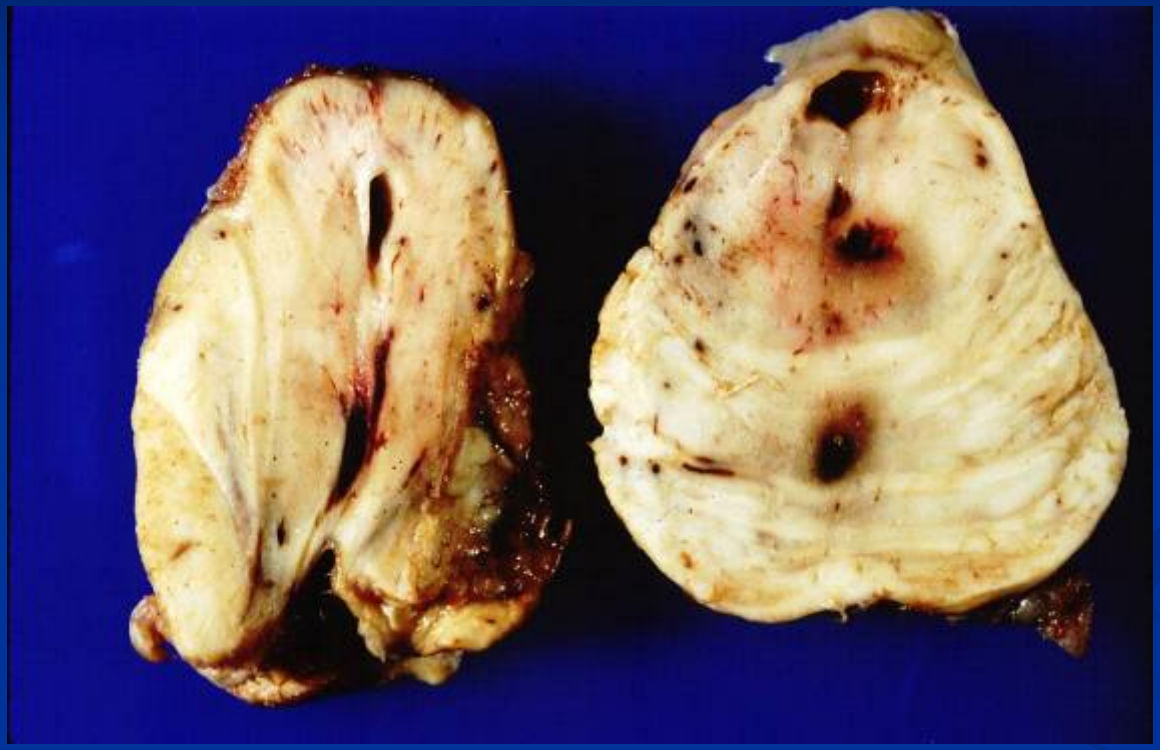


Normal uncus



Herniated right uncus

DURET HEMORRHAGES



Midline Duret hemorrhages plus Kernohan's notch in the right cerebral peduncle

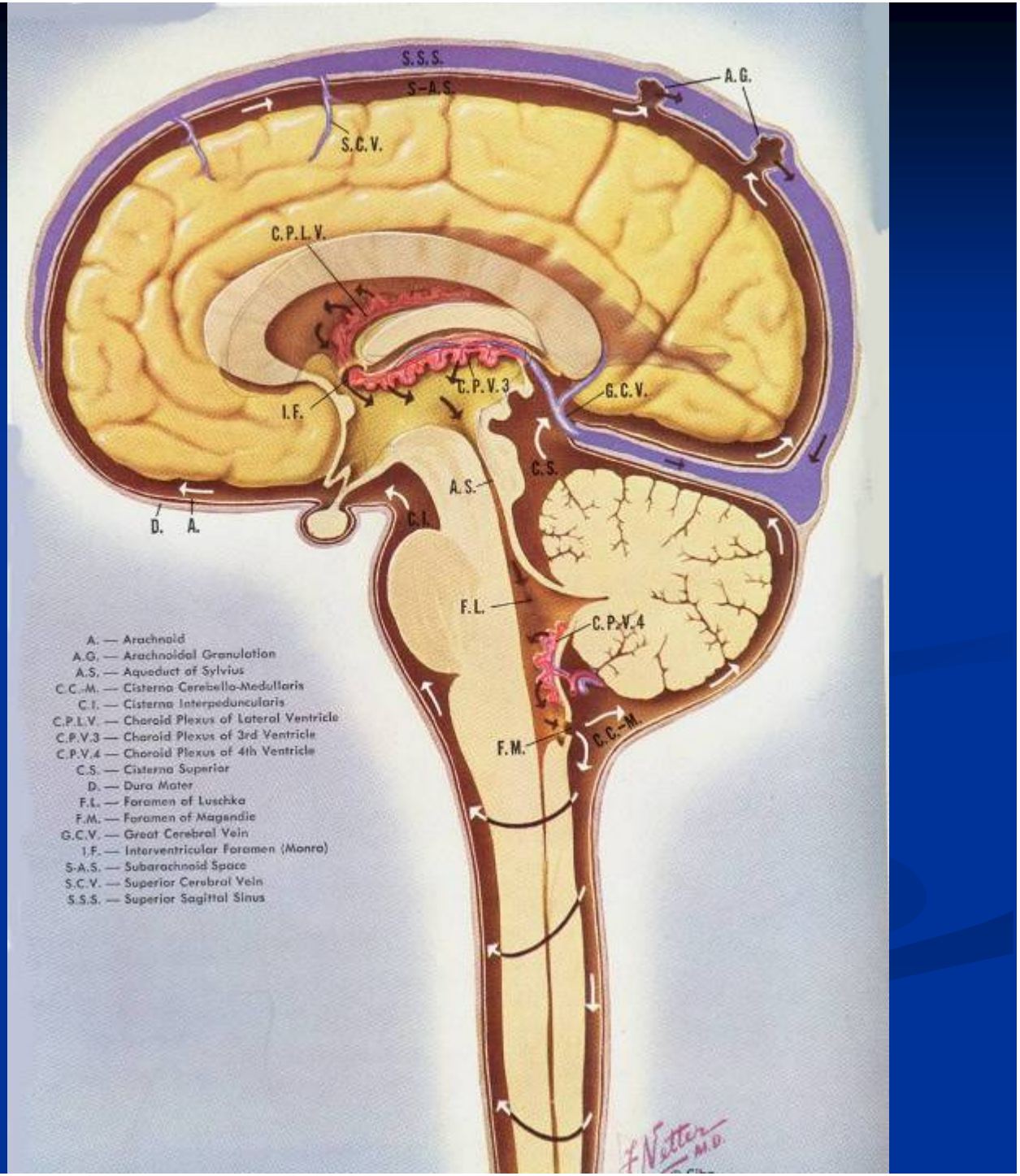
HYDROCEPHALUS

DILATATION OF THE VENTRICULAR SYSTEM

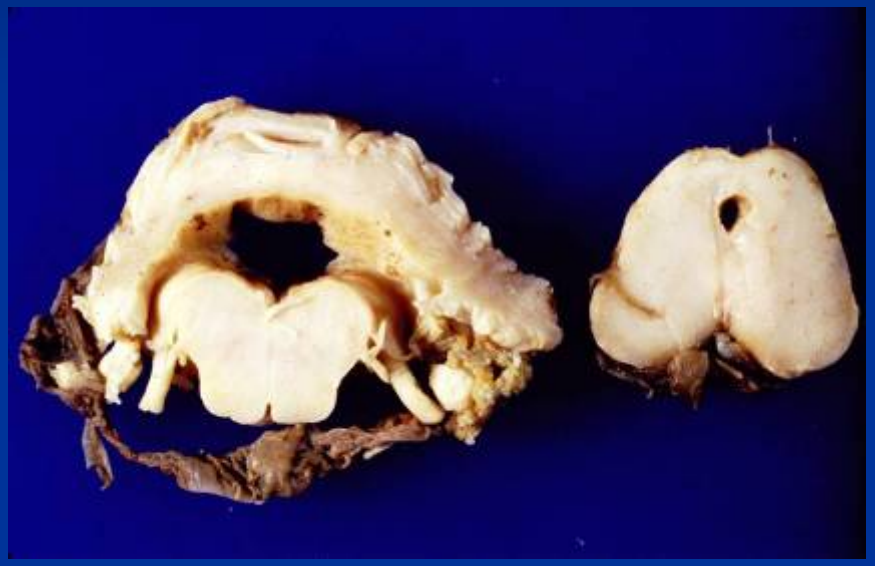
NONCOMMUNICATING: Due to obstruction within the ventricular system, e.g., tumor, aqueductal stenosis

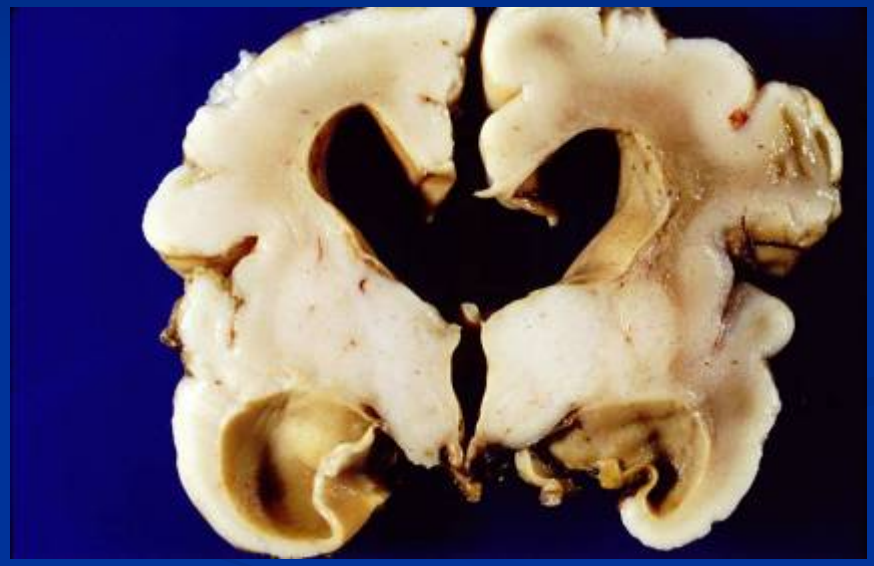
COMMUNICATING: Due to obstruction of CSF flow in the subarachnoid space with decreased reabsorption

CSF FLOW


S.S.S.
S-A.S.
A.G.
S.C.V.
C.P.L.V.
C.P.V.3
G.C.V.
I.F.
C.S.
A.S.
D.
A.
C.I.
F.L.
C.P.V.4
F.M.
C.C.-M.
A. — Arachnoid
A.G. — Arachnoidal Granulation
A.S. — Aqueduct of Sylvius
C.C.-M. — Cisterna Cerebello-Medullaris
C.I. — Cisterna Interpeduncularis
C.P.L.V. — Choroid Plexus of Lateral Ventricle
C.P.V.3 — Choroid Plexus of 3rd Ventricle
C.P.V.4 — Choroid Plexus of 4th Ventricle
C.S. — Cisterna Superior
D. — Dura Mater
F.L. — Foramen of Luschka
F.M. — Foramen of Magendie
G.C.V. — Great Cerebral Vein
I.F. — Interventricular Foramen (Monro)
S-A.S. — Subarachnoid Space
S.C.V. — Superior Cerebral Vein
S.S.S. — Superior Sagittal Sinus

COMMUNICATING HYDROCEPHALUS





Dilatation of the entire ventricular system including the aqueduct and fourth ventricular foramina. There is thickening and scarring of the meninges, secondary to previous subarachnoid hemorrhage

Summary: Microscopic and gross brain abnormalities

- Cell types: Function and proliferative capacity
- Mechanisms of CNS dysfunction:
  - Pathophysiological "invisible" lesions: metabolic, toxic
  - Structural "visible" abnormalities: mass, edema, hydrocephalus, cytologic abnormalities.
- Increased intracranial pressure
  - Causes of cerebral edema: focal and generalized
  - Types of herniation: cingulate, uncal, tonsillar
  - Hydrocephalus: non-communicating and communicating

Vascular and Circulatory Disorders

Ischemia/Infarction

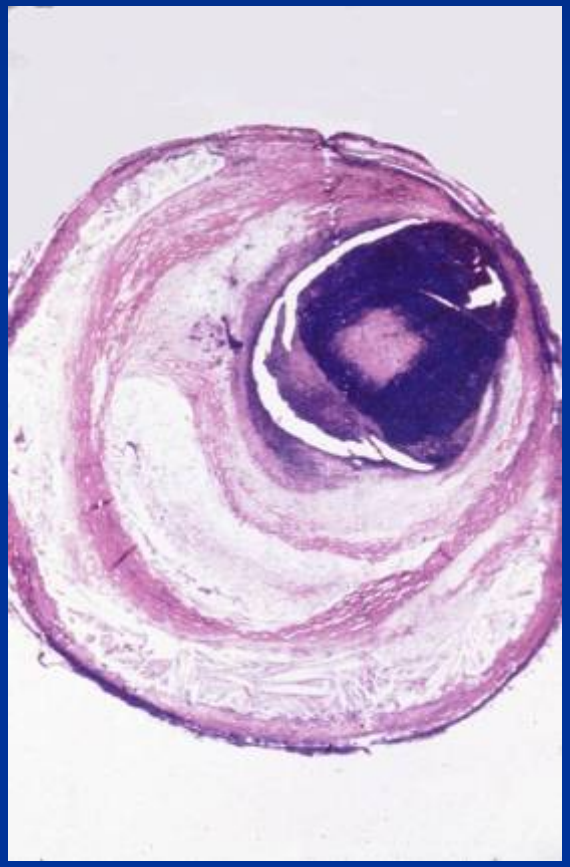
Transient Ischemic Attacks

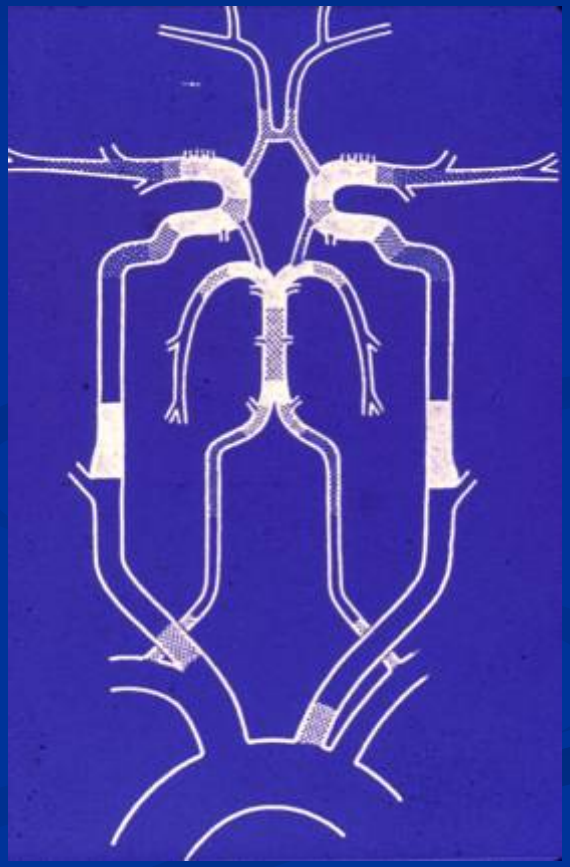
Hemorrhage

Stroke: Ischemia/Infarct

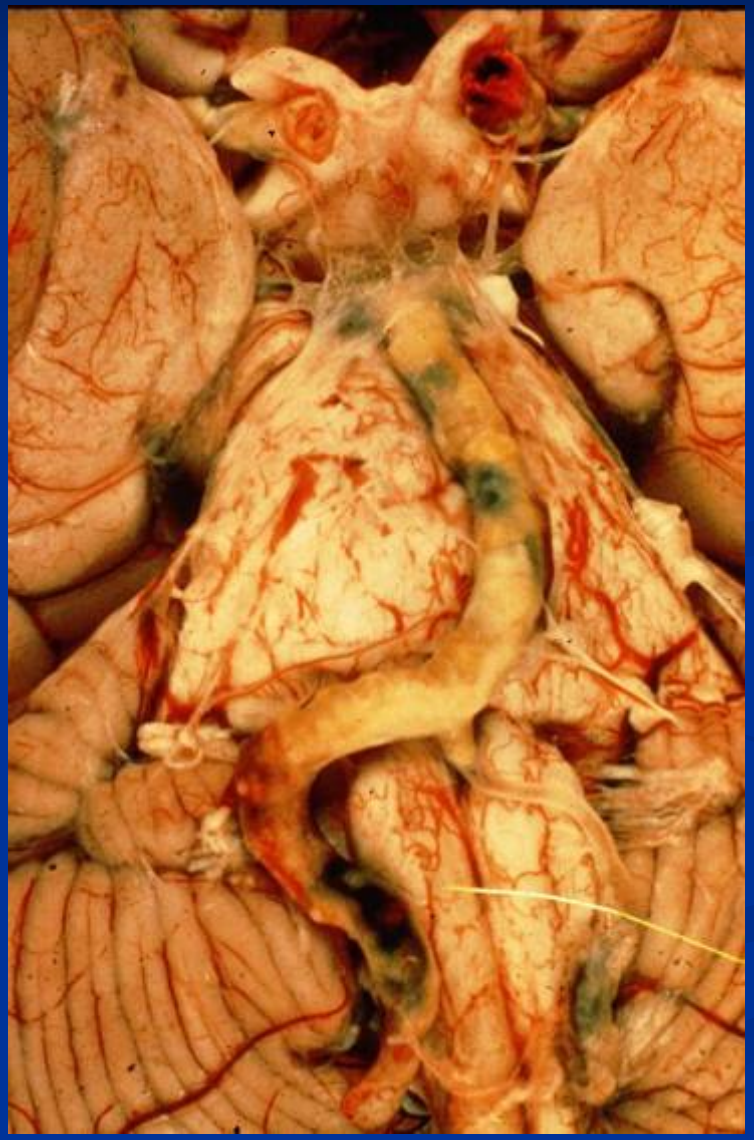
- Atherosclerosis: Narrowing
- Thrombosis: Damages vessel, infarcts are non-hemorrhagic
- Embolism: Heart valves, plaques (frequently hemorrhagic)
- Vasospasm: Rare, but common after subarachnoid hemorrhage
- Hypertensive vasculopathy: Lacunar infarcts

RISK FACTORS
atherosclerosis

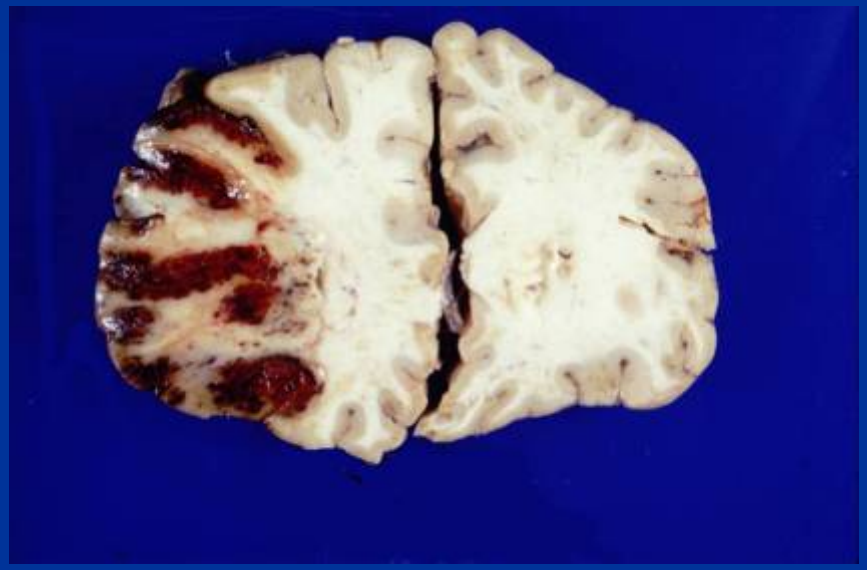




RISK FACTOR: atherosclerosis



EMBOLIC INFARCTS TYPICALLY ARE HEMORRHAGIC



RISK FACTORS: hypertension (lacunar infarcts)

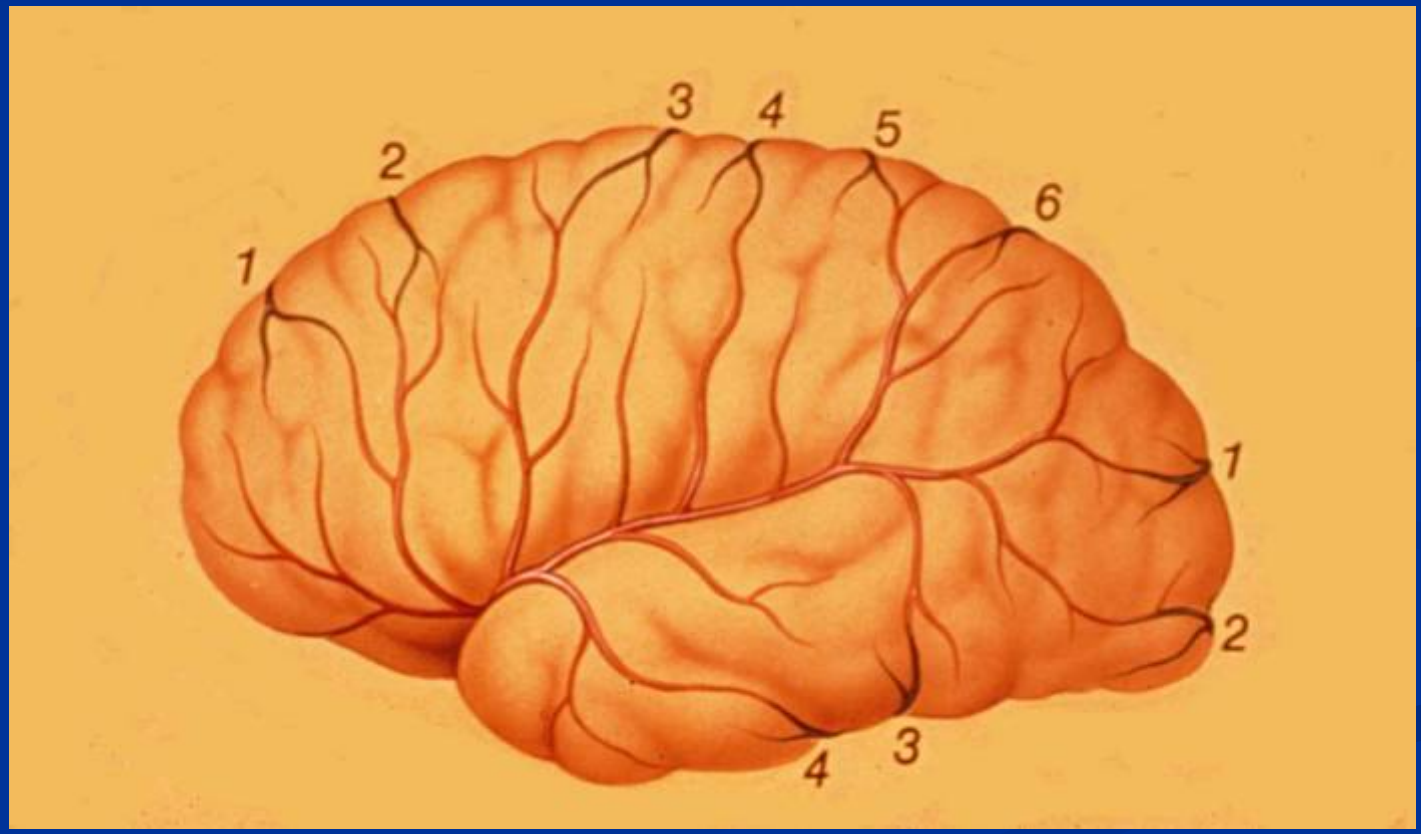
Lacunar infarct of the pons

Lacunar infarct of the globus pallidus

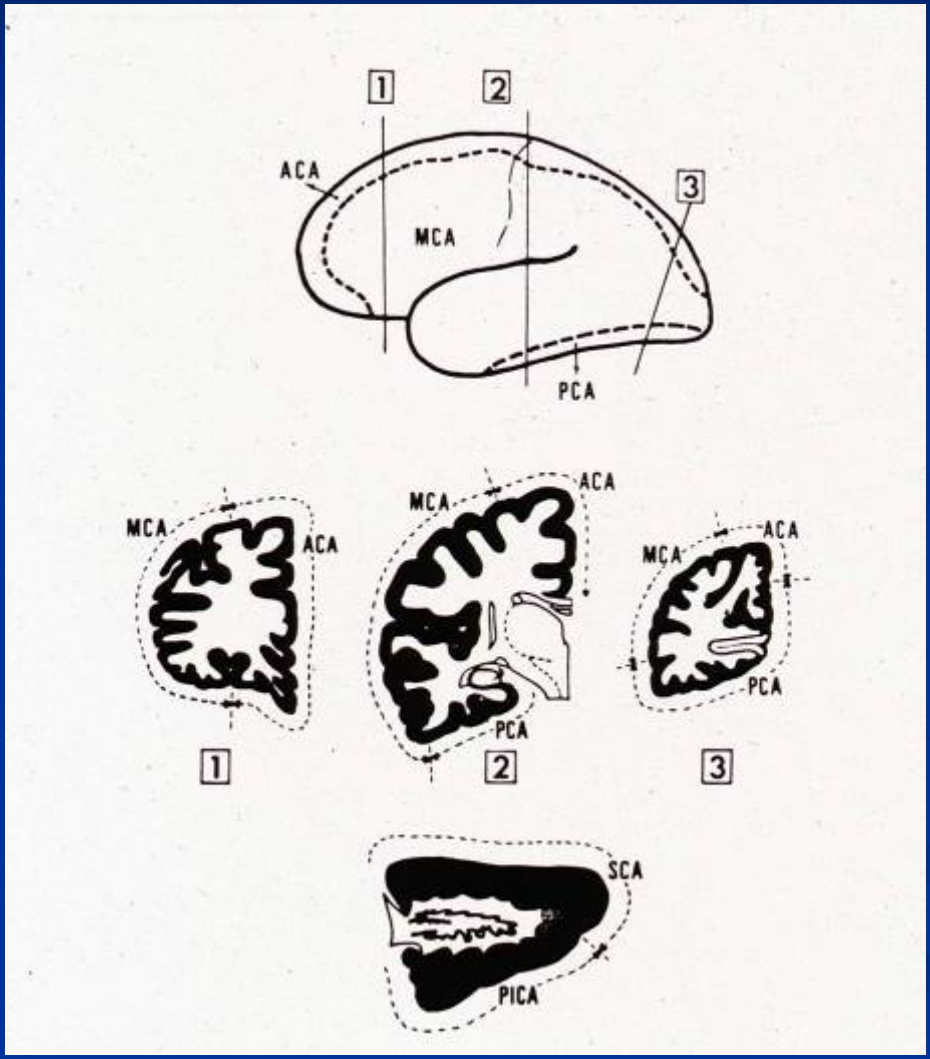
Other causes of ischemia

- Systemic Hypotension: Results in watershed infarcts
- Hypoxia or Anoxia: Lack of oxygen or poor perfusion after MI results in watershed infarcts and/or damage in vulnerable regions, ie hippocampus and cerebellum
- Venous thrombosis: Rare, causes hemorrhagic infarcts, consider coagulopathy

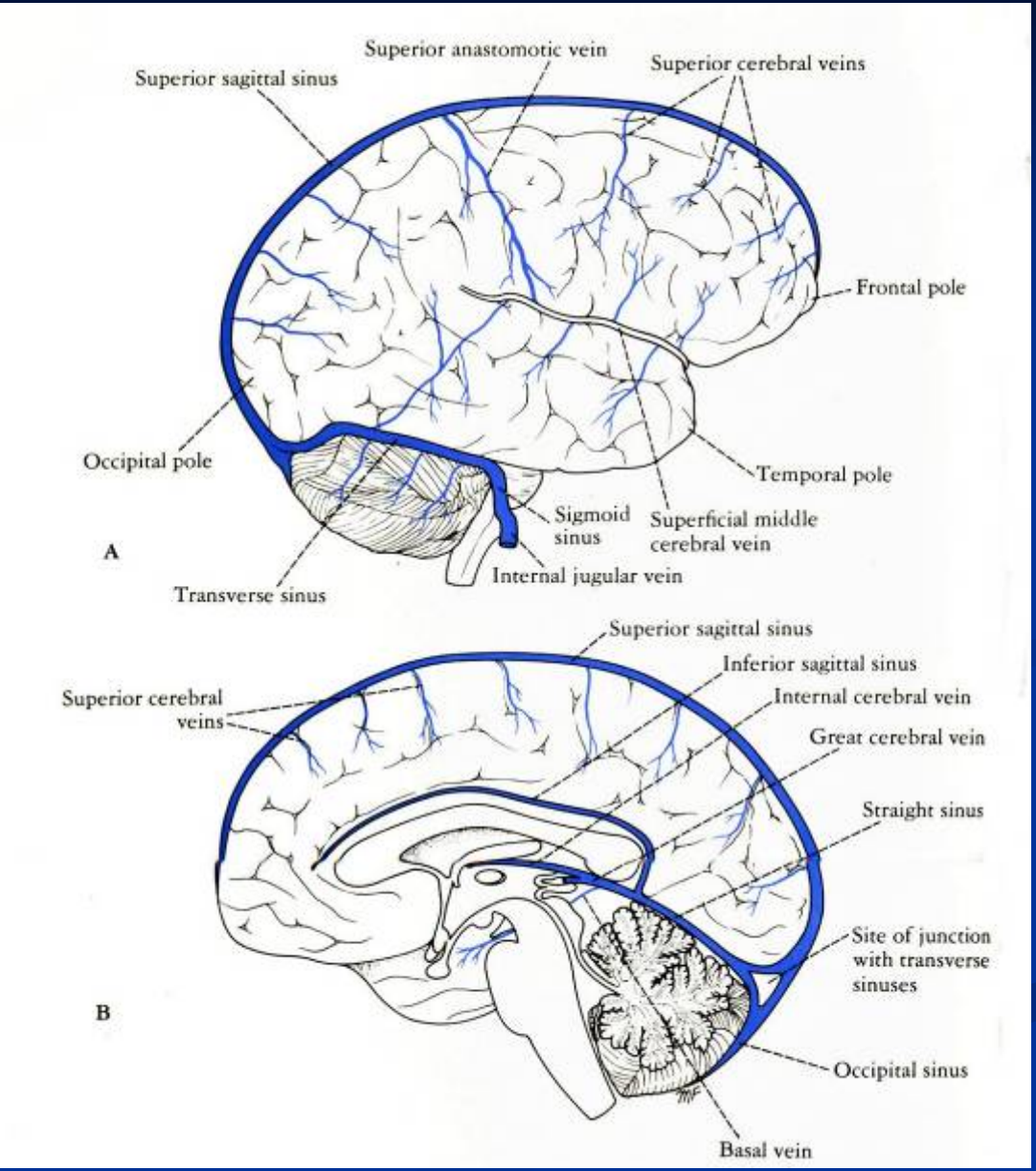
ANASTOMOSES BETWEEN TERMINAL BRANCHES OF MAJOR CEREBRAL ARTERIES



VASCULAR WATERSHEDS

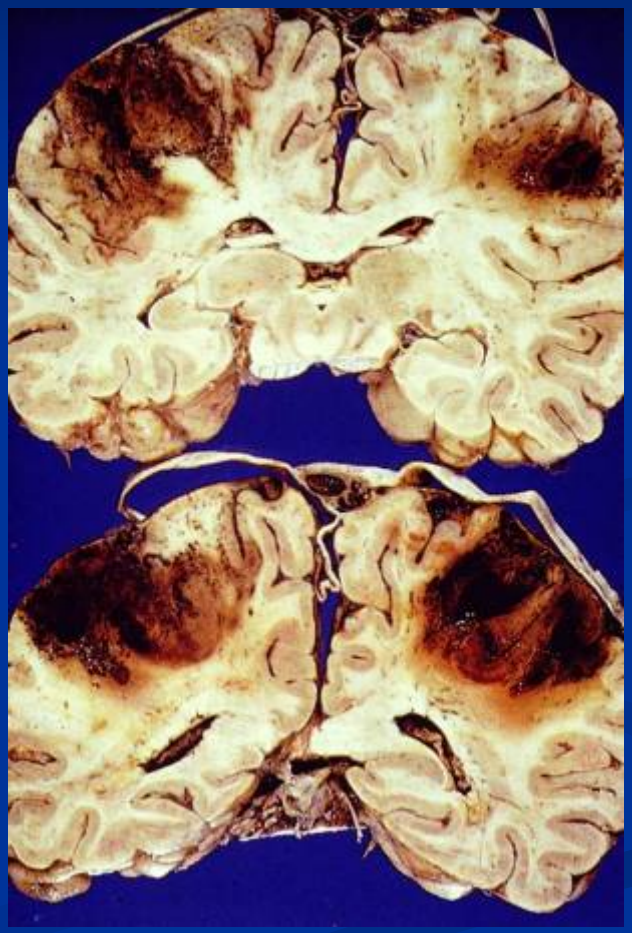


VENOUS CIRCULATION



VENOUS INFARCTION

- Venous infarction usually results from venous sinus thrombosis
- Risk factors include a number of states that result in hyperviscosity or increased coagulability
- Grossly they are very hemorrhagic



Transient Ischemic Attacks

- Lasts less than 24 hours by definition
- Attributed to transient embolization
- Occurs in patients with atherosclerotic stenosis
- Harbinger of cerebral infarction

Summary: Strokes due to ischemia/infarction

- Large vessel atherosclerotic disease (non-hemorrhagic)
- Embolic (hemorrhagic)
- Hypertensive (hemorrhages and lacunes)
- Vasospasm (2° to subarachnoid hemorrhage)
- Watershed infarcts: hypotension and hypoxia
- Venous thrombosis (rare, hemorrhagic)
- TIA: clears in 24 hours -by definition, often associated with large vessel disease

Strokes Due to Hemorrhage

Hypertension

Aneurysms

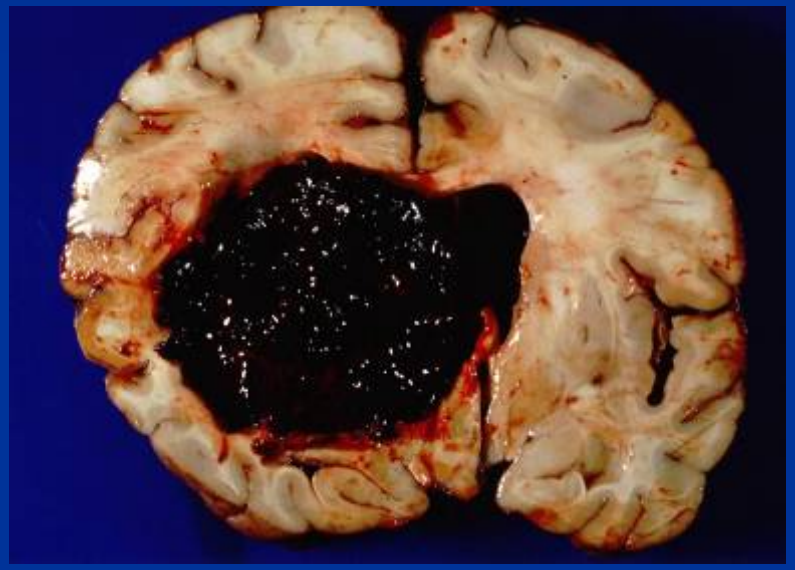
Vascular Malformations

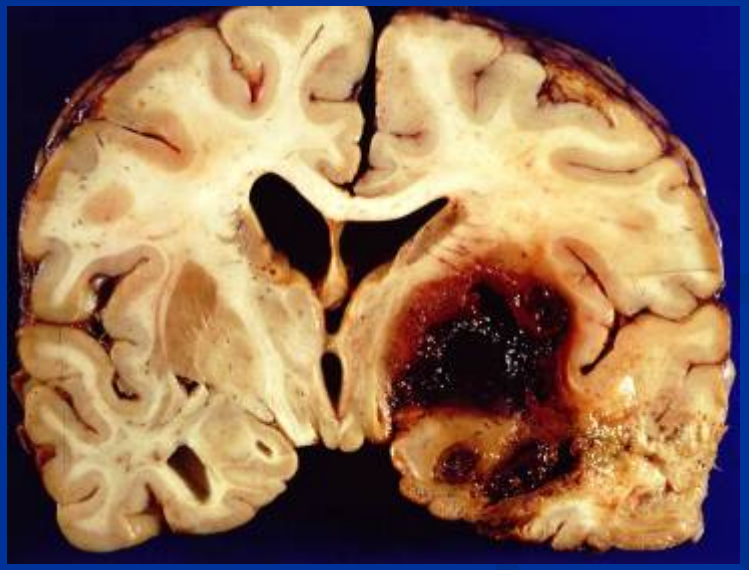
Bleeding Diathesis

Trauma

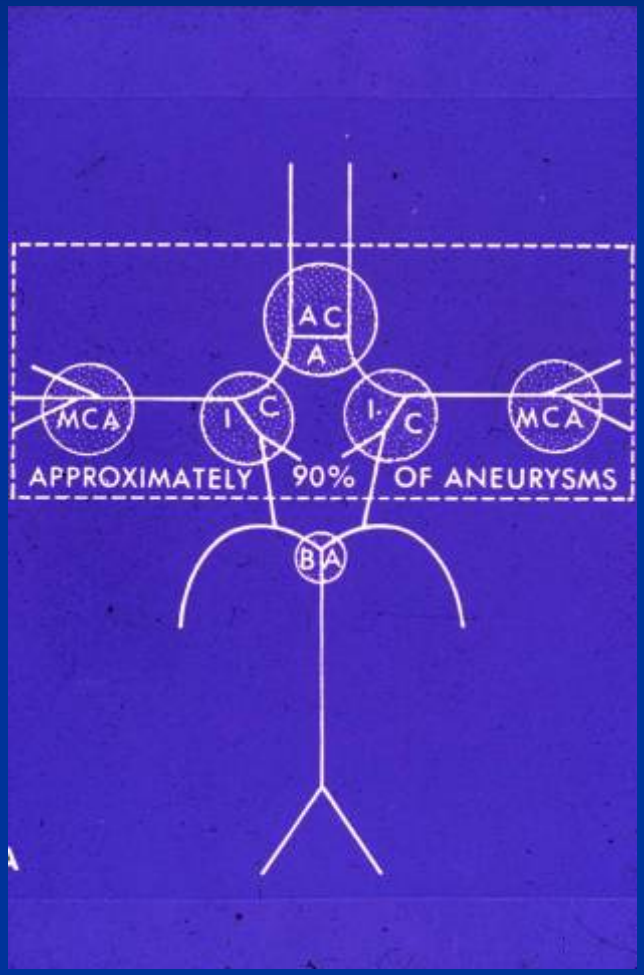
HYPERTENSIVE HEMORRHAGE

lenticulostriate arteries



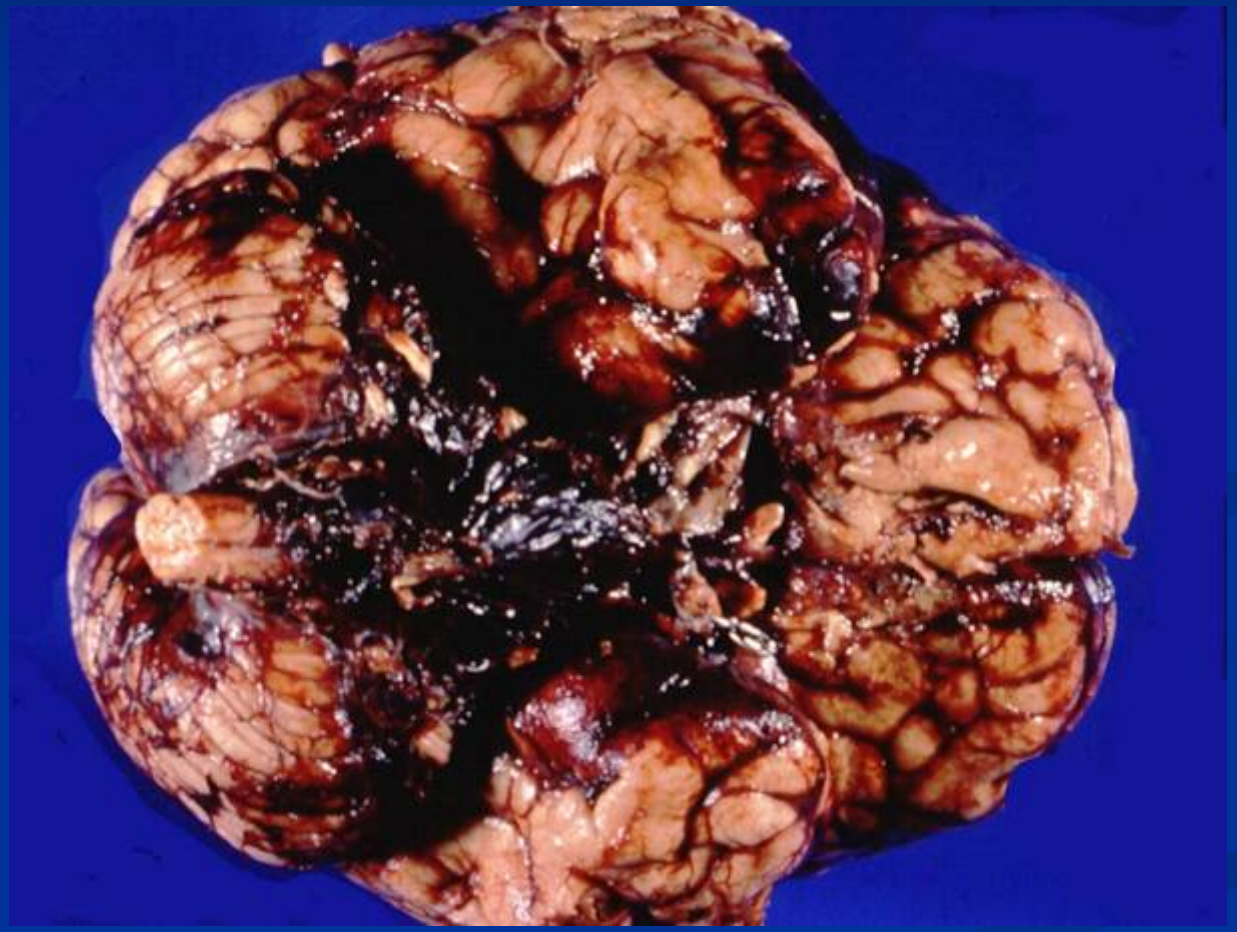


SACCULAR ANEURYSMS

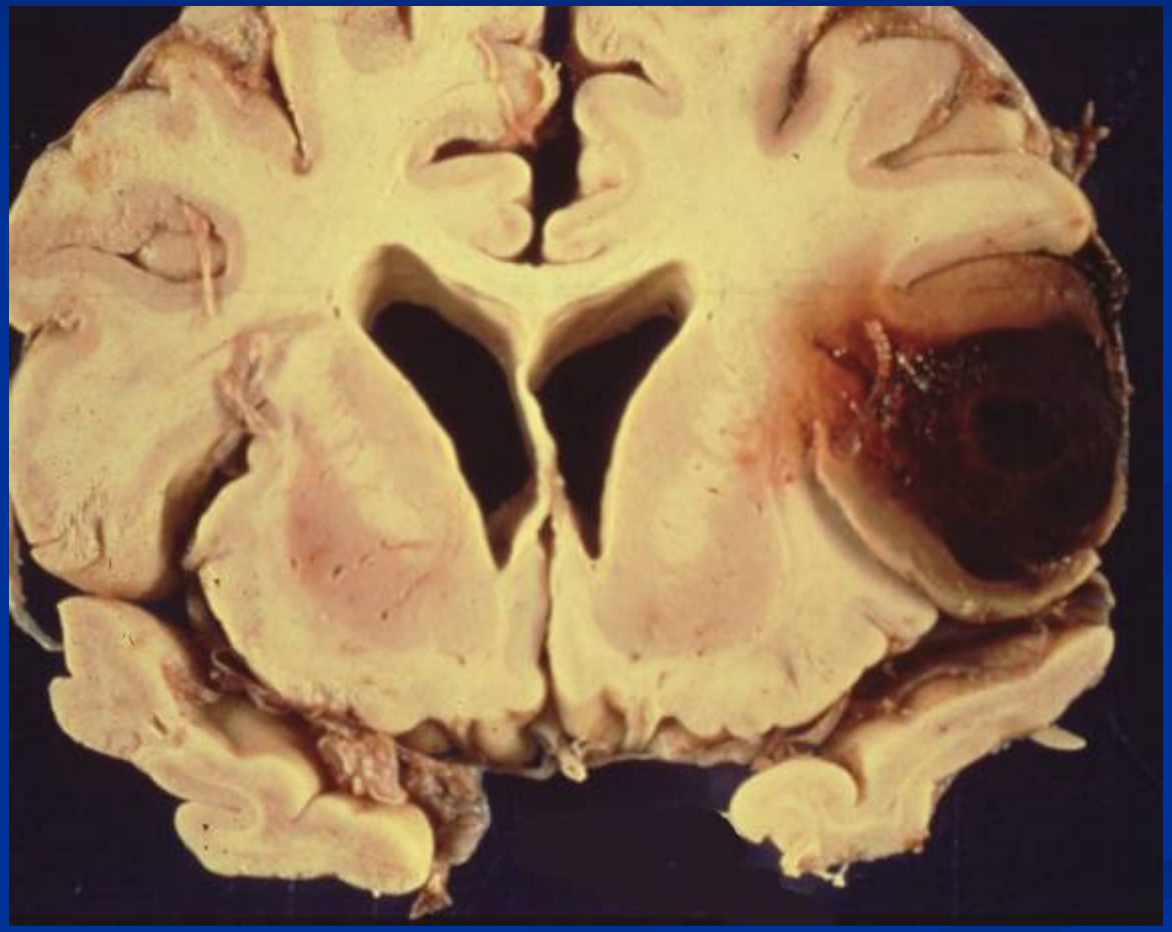


SUBARACHNOID HEMORRHAGE

rupture of saccular (berry) aneurysm



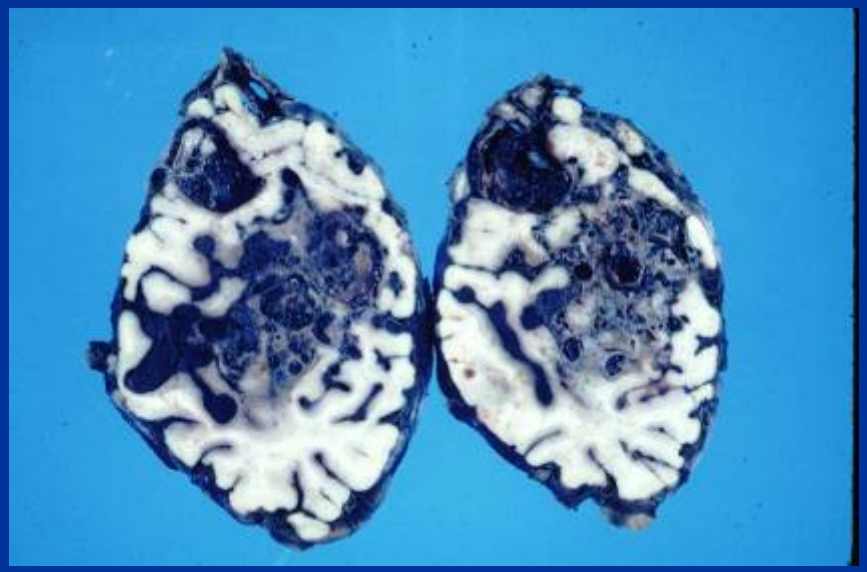
MYCOTIC ANEURYSM

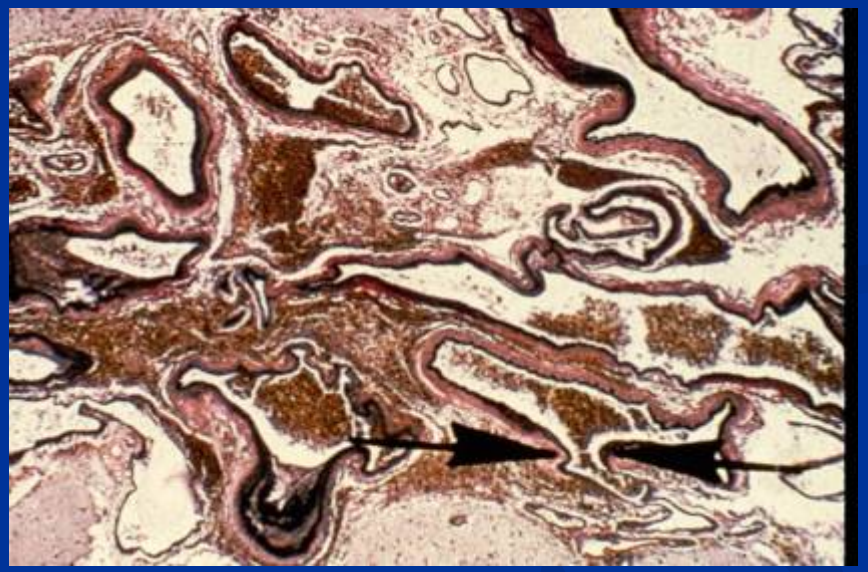


(bacterial)

VASCULAR MALFORMATION AS A SOURCE OF HEMORRHAGE

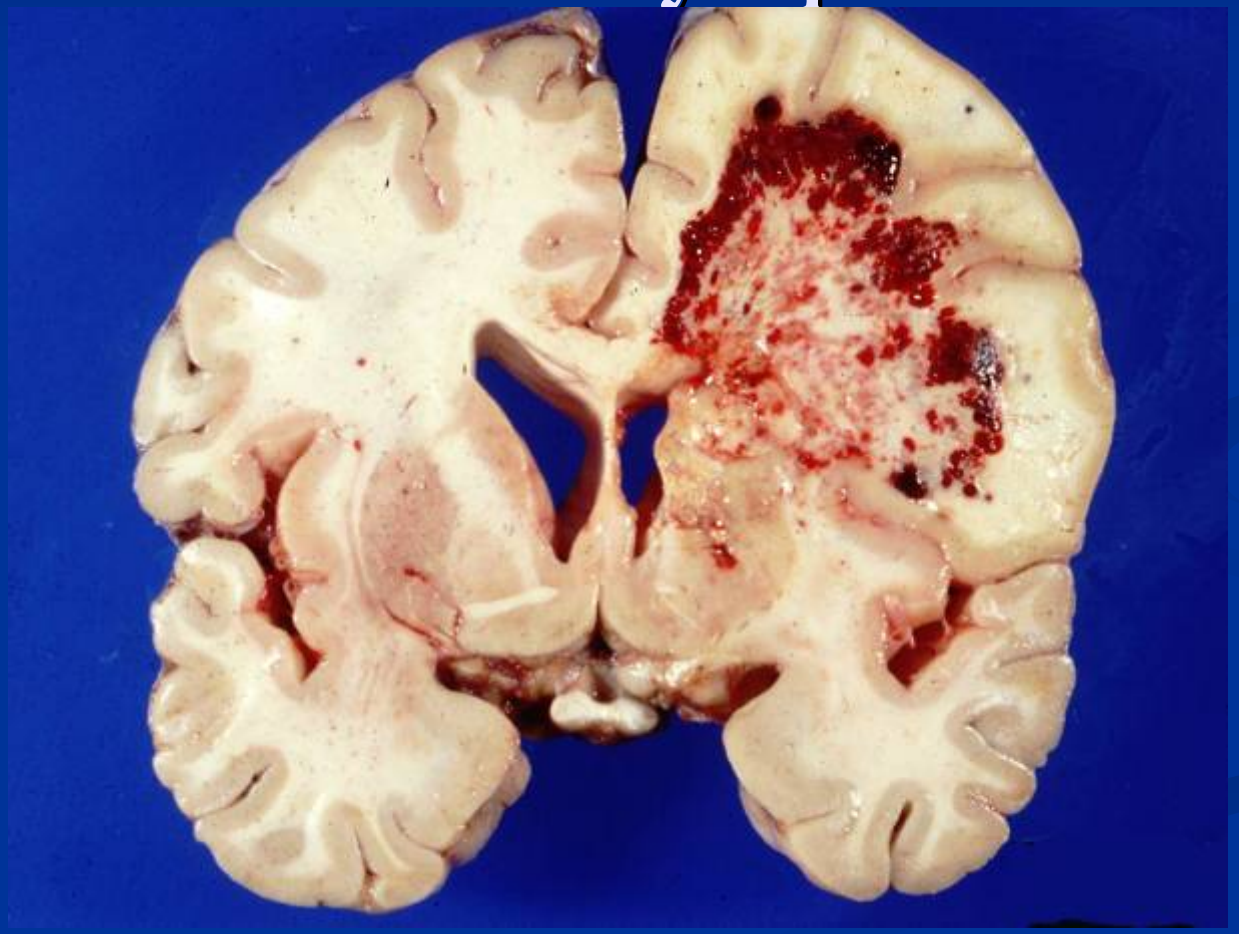
arteriovenous malformation (AVM)





BLOOD DYSCRASIAS AS A CAUSE OF HEMORRHAGE

thrombocytopenia



Summary: Strokes due to hemorrhage

- Hypertension: Most common cause of brain hemorrhage, sites include basal ganglia, pons, cerebellum and cerebral white matter
- Aneurysms:
  - Berry aneurysm: Most common type, causes **SAH**
  - Mycotic aneurysm: Rare, parenchymal bleed, bacterial
  - Atherosclerotic: Rarely bleed, may cause mass effect, fusiform
- Vascular malformations and clotting abnormalities

Closed Head Injury

Concussion

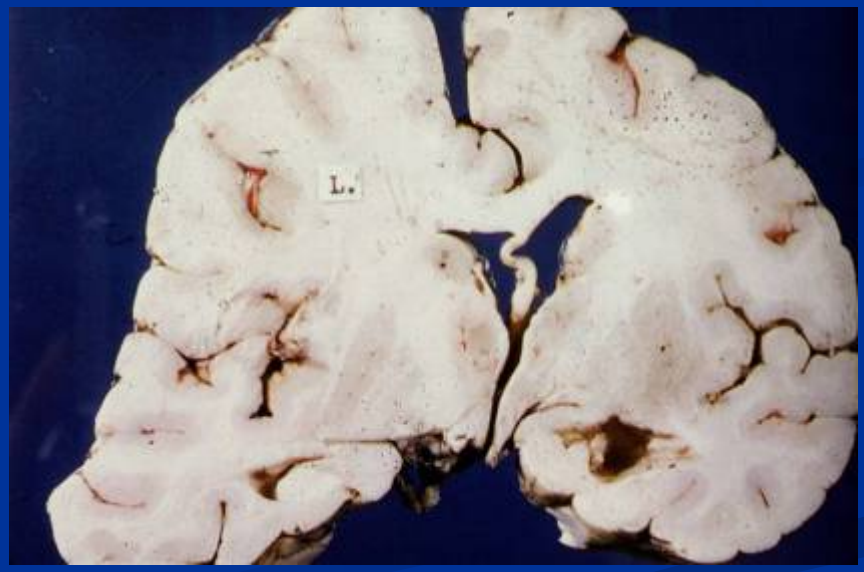
- Immediate and temporary disturbance of brain function.
  - Grading (1. ***mild***: no LOC/smpt <15 min, 2. ***mod***: no LOC/smpt >15min, 3. ***severe***: any LOC)
- Cause
  - Shearing of axons
- Signs: Amnesia, confusion, headache, visual disturbances, nausea, vomiting, dizziness

Closed Head Injury

- **Epidural hematoma**: Middle meningeal artery tear (temporal bone fracture), accumulates rapidly (arterial)
- **Subdural hematoma**: Shearing of bridging veins, accumulate in hours to days (rarely weeks+)
- **Subarachnoid hemorrhage**: Occurs with contusions or intraparenchymal hemorrhage (also with berry aneurysms)

TRAUMA AS A CAUSE OF HEMORRHAGE

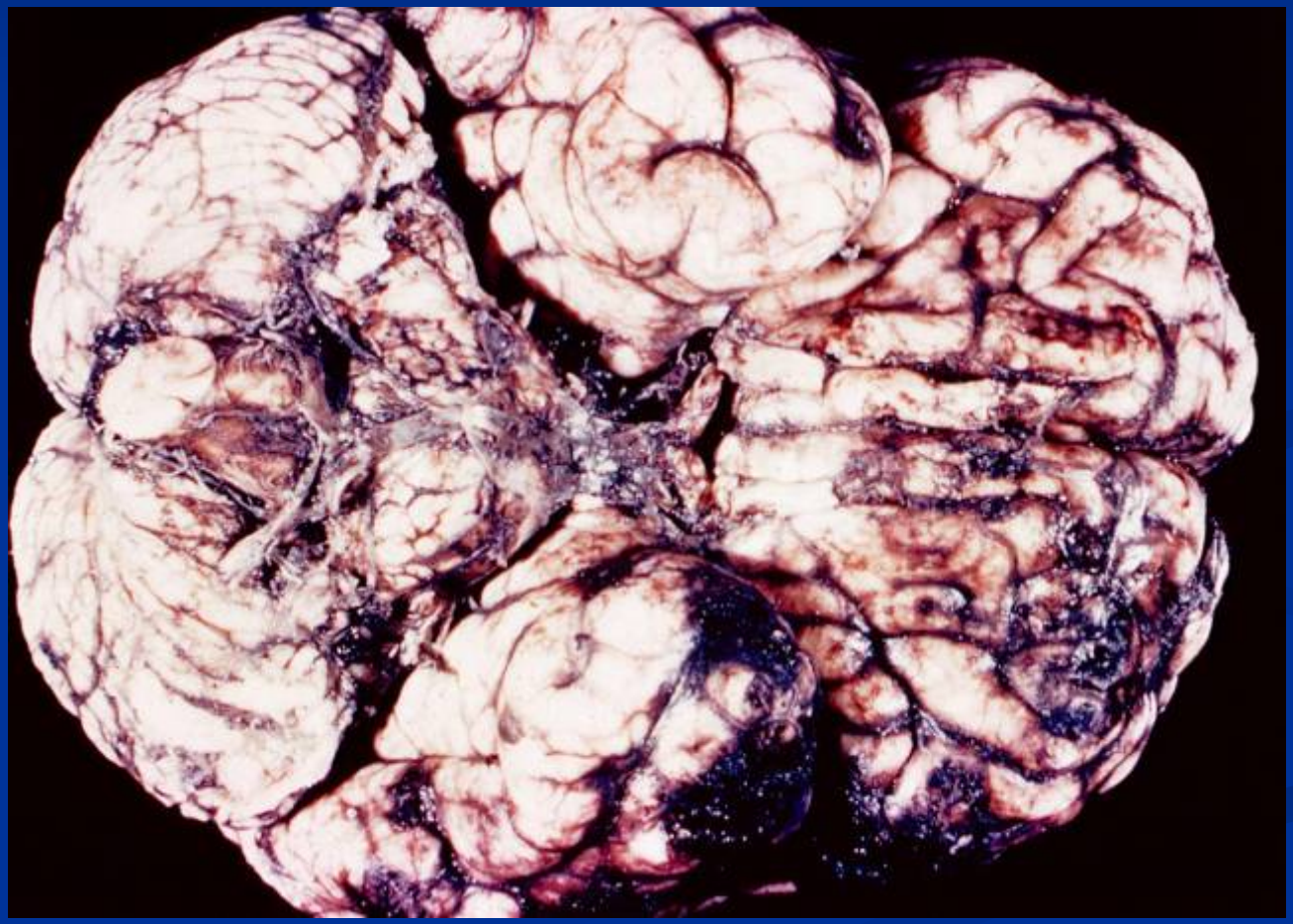
subdural hematoma



Closed Head Injury

- **Contusions**: Brain against bone, coup (at site of impact)/contrecoup (side opposite impact)
- **Intracerebral hemorrhage**: Shearing of brain vessels, high impact
- **Diffuse Axonal Injury**: Shearing of axons results in post-traumatic neurologic deficits
- **Cerebral Edema**: Occurs with and without an obvious structural lesion
  - Note: Can occur without evidence of hemorrhage

TRAUMA AS A CAUSE OF HEMORRHAGE: contusions



Other traumatic injuries

- Penetrating injuries: Bullets, bone fragments, result in laceration with the potential for infection
- Spinal cord injury: Fractures, vertebral dislocation, penetrating injury, the spinal cord may be crushed or the site of hemorrhage

Summary: Trauma

- Closed head injuries:
  - Sites (epidural, subdural, subarachnoid, parenchymal) and typical etiology
  - Contusion, hemorrhage, diffuse axonal injury, edema
- Penetrating injuries:
  - Causes and risks (infection)
  - Spinal cord injuries

Infections

- Meningitis
  - Bacterial
  - Tuberculous
  - Fungal
  - Viral
- Cerebral abscess
- Subdural empyema
- Cerebritis
- Viral encephalitis

Infections: Route of entry

- Hematogenous (most common)
  - Localized source: abscess, heart valve, lung infection
  - Other: mosquitos, needles
- Direct implantation (trauma)
- Local extension (ear infection→ abscess)
- Axonal transport (rabies, HSV)

Meningitis

- Inflammation of the meninges
  - Fever
  - Headache
  - Stiff neck
  - Decreased level of consciousness
- Bacterial (purulent)
- Tuberculous (granulomatous)
- Fungal (granulomatous)

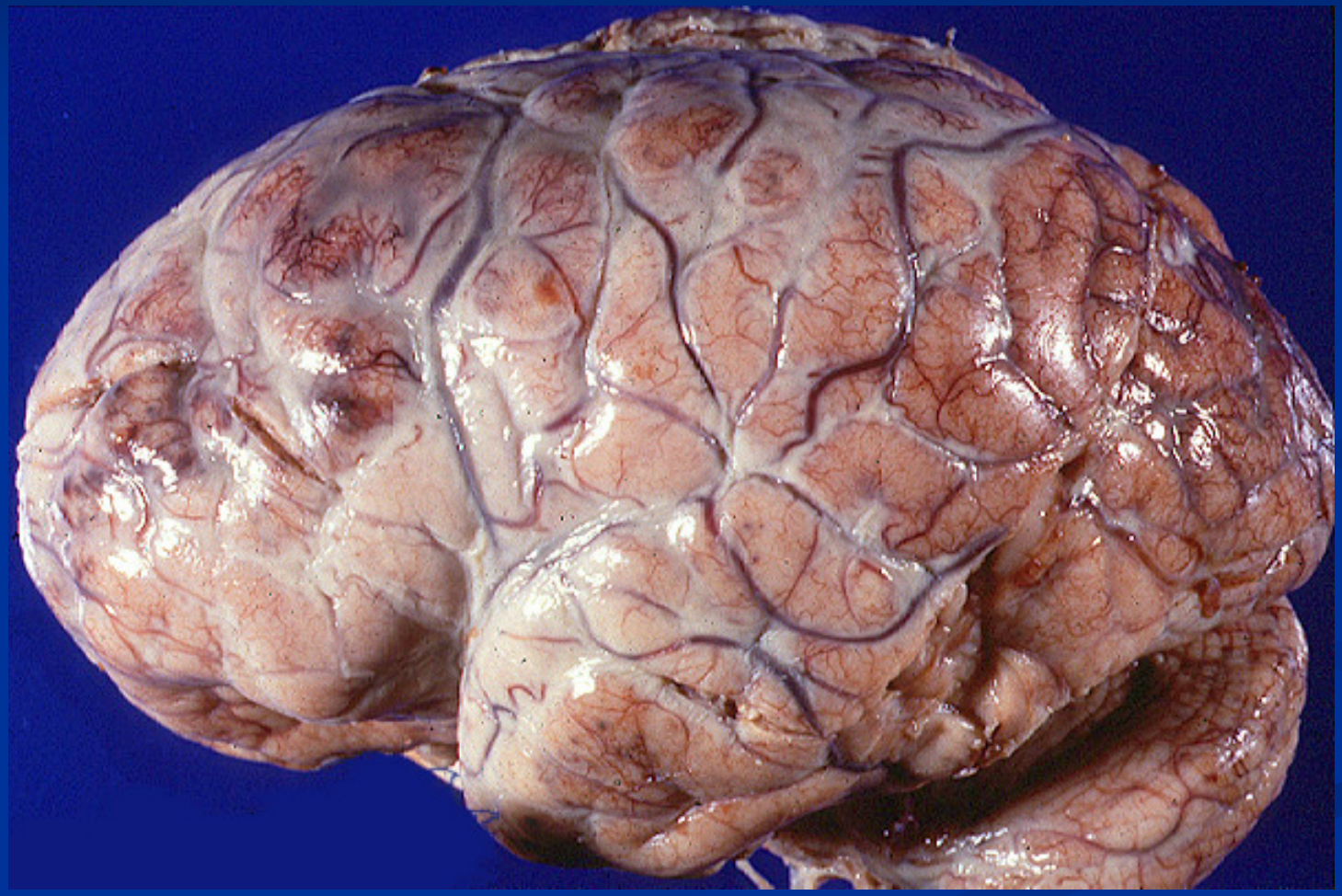
Bacterial Meningitis

- Neonates: E. Coli, group B streptococci
- Infants and children: Hemophilus influenza (before immunization)
- Young adults: Neisseria meningitidis
- Adults: Streptococcus pneumoniae and Listeria monocytogenes

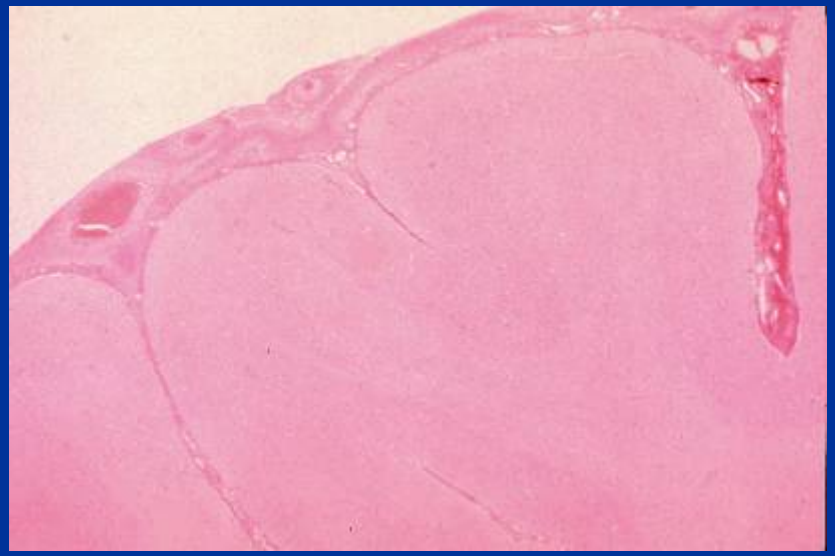
Meningitis: CSF findings

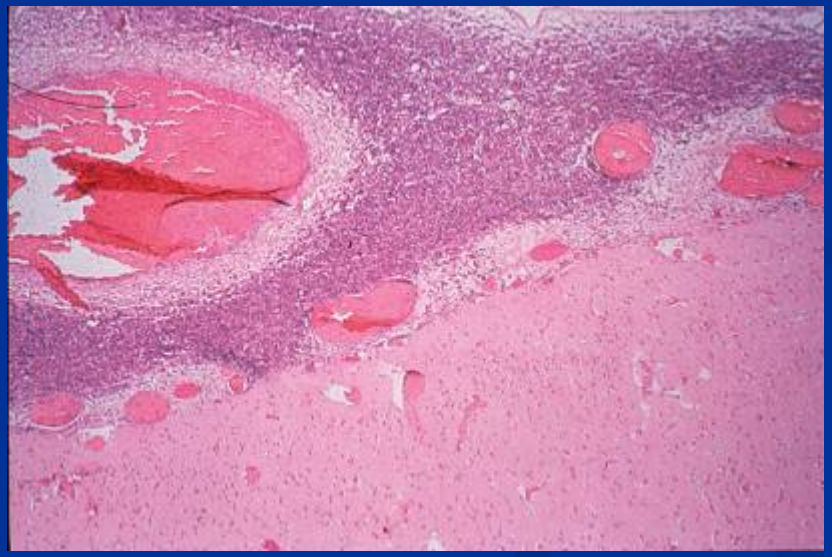
- Increased white blood cells
  - Neutrophils with **bacterial** meningitis
  - Mononuclear cells (lymphocytes and macrophages) with **TB and fungal** infections
  - Lymphocytes with **viral** infection
- Increased protein (mild with viral)
- Reduced glucose with **bacterial** meningitis

PURULENT (BACTERIAL) MENINGITIS

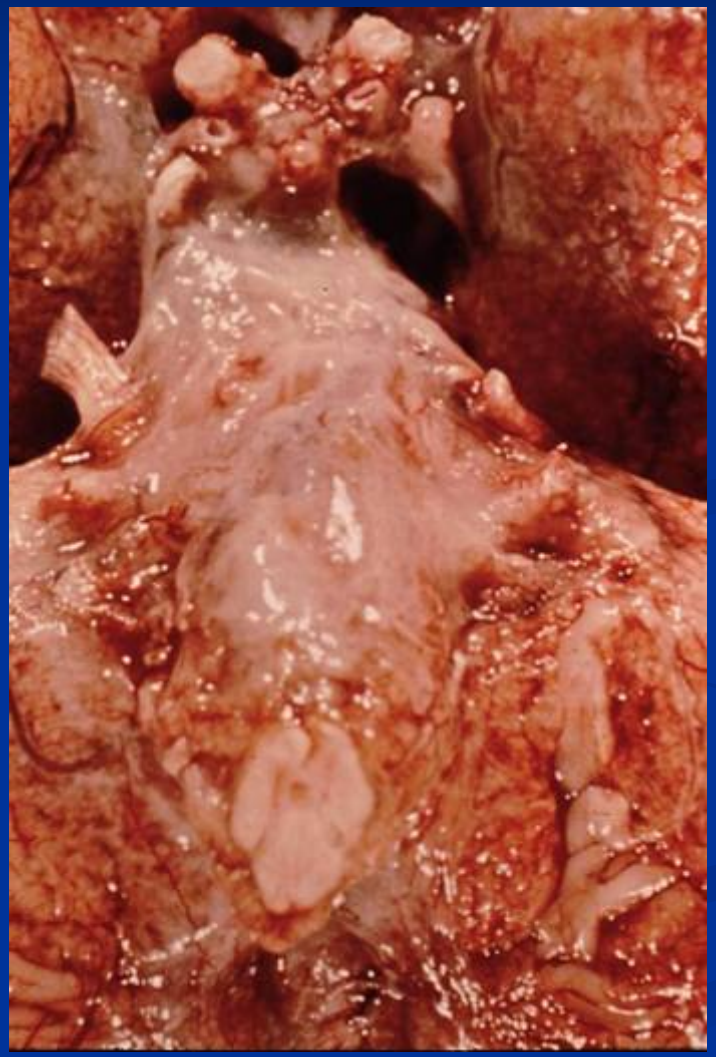


PURULENT MENINGITIS



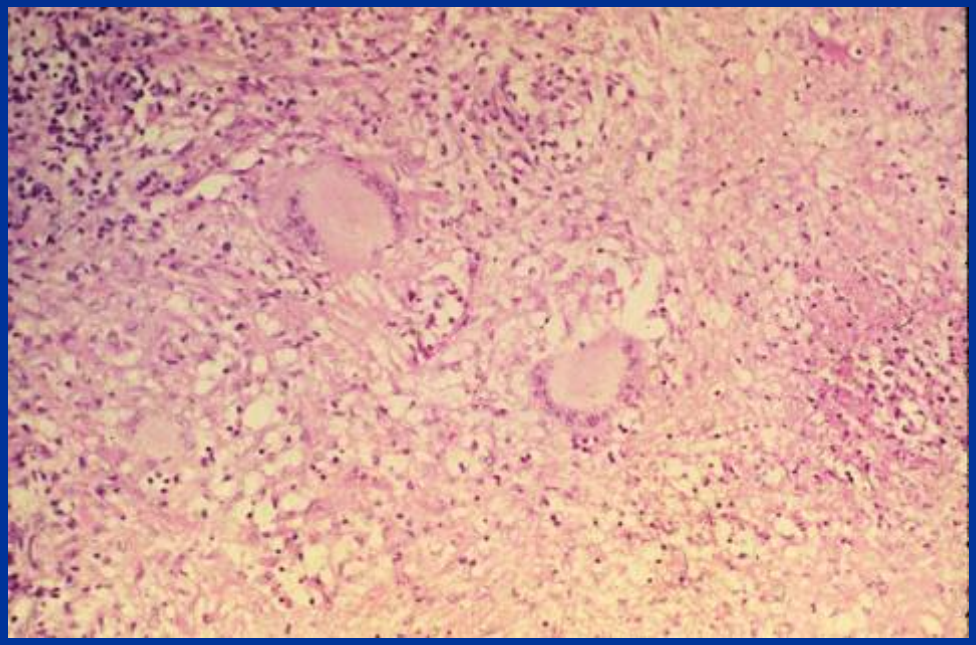


GRANULOMATOUS MENINGITIS:
tuberculosis

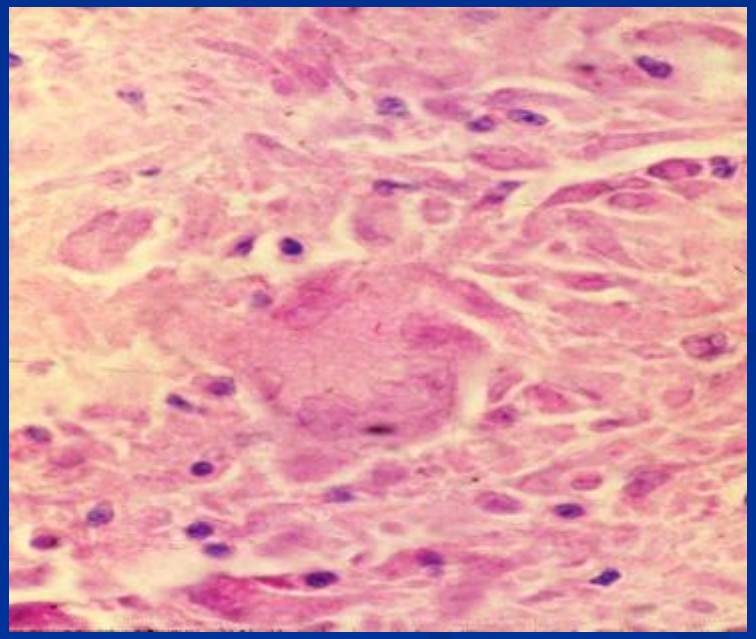


GRANULOMATOUS MENINGITIS

tuberculosis



H&E



Acid Fast

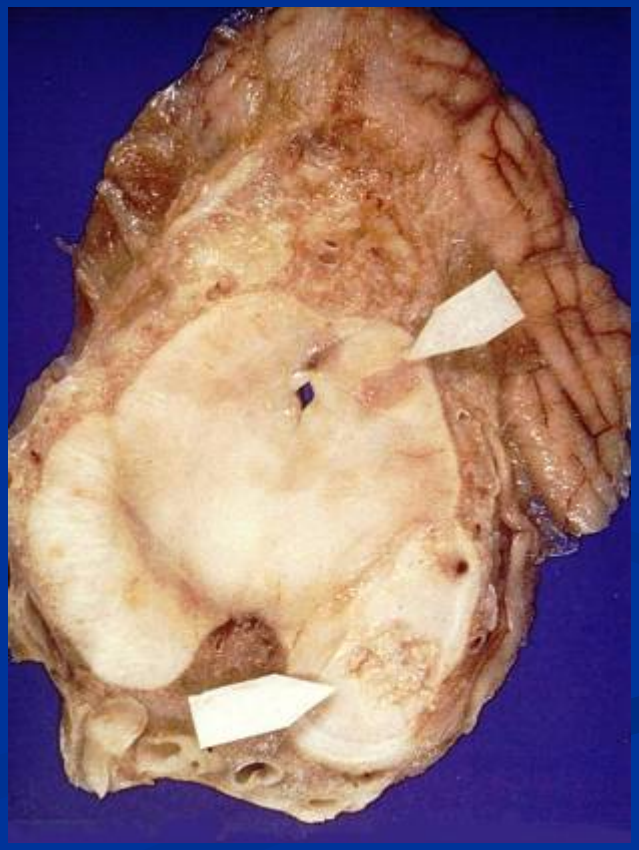
GRANULOMATOUS MENINGITIS
tuberculosis

Sequelae:

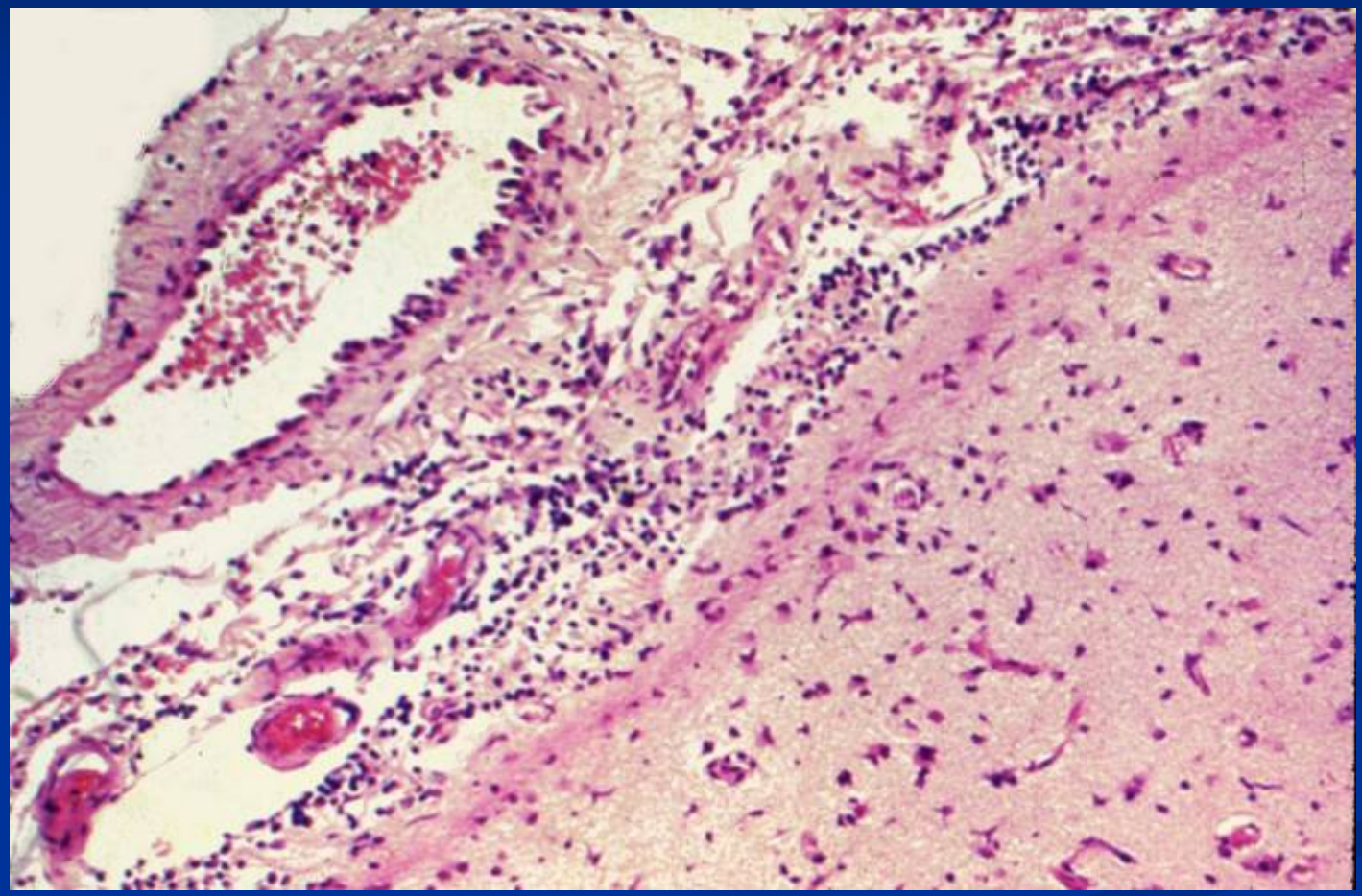
Vasculitis

Small infarcts

Cranial neuropathies



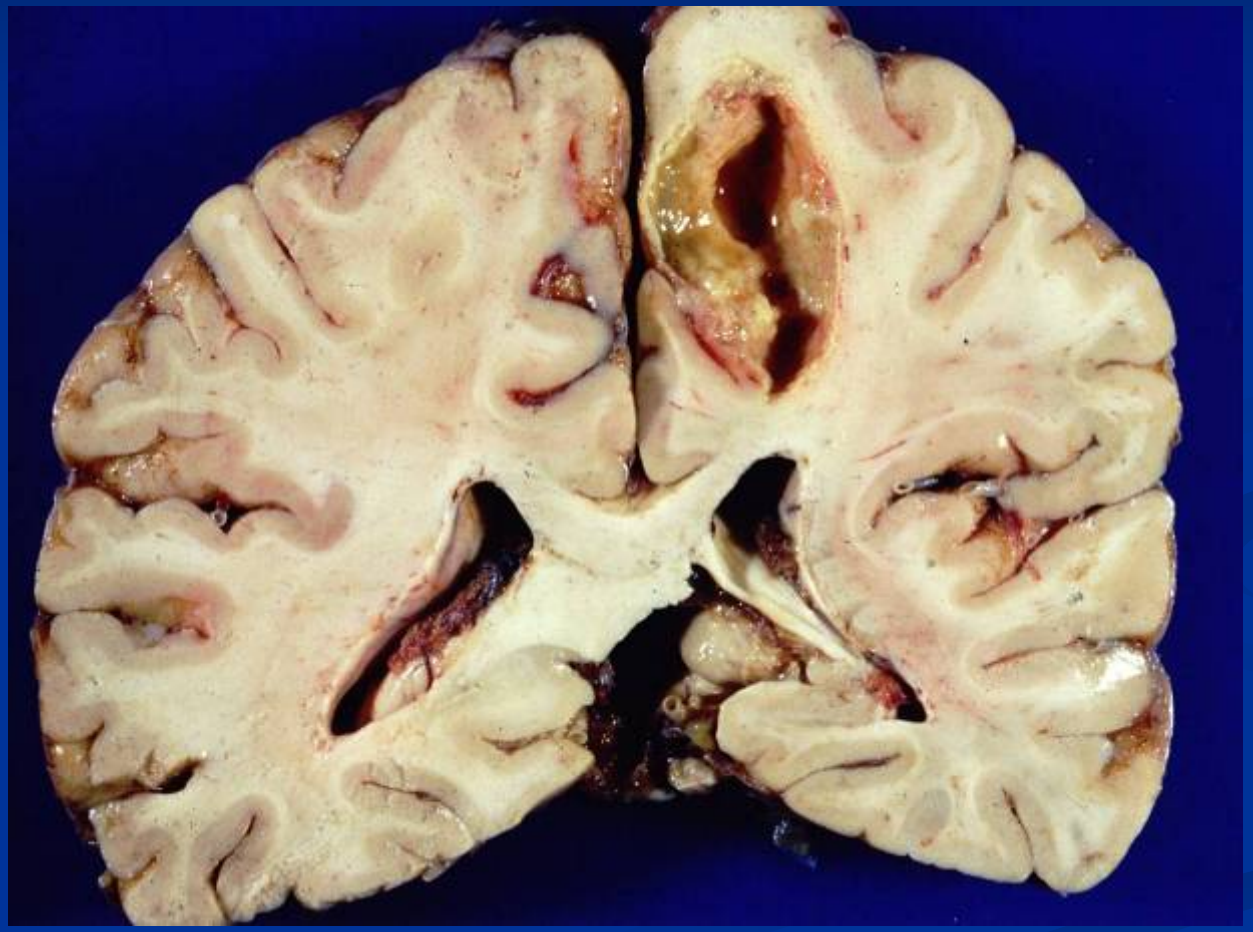
ASEPTIC (VIRAL) MENINGITIS



Cerebral Abscess

- Localized (contained) infection
- Hematogenous spread (heart valves), penetrating wound, paranasal sinuses, middle ear
- Oral flora may be the source of an abscess after dental manipulation
- Organisms are mixed and frequently anaerobic
- Surrounding cerebral edema is common
- CSF is frequently sterile

PURULENT CEREBRAL ABSCESS



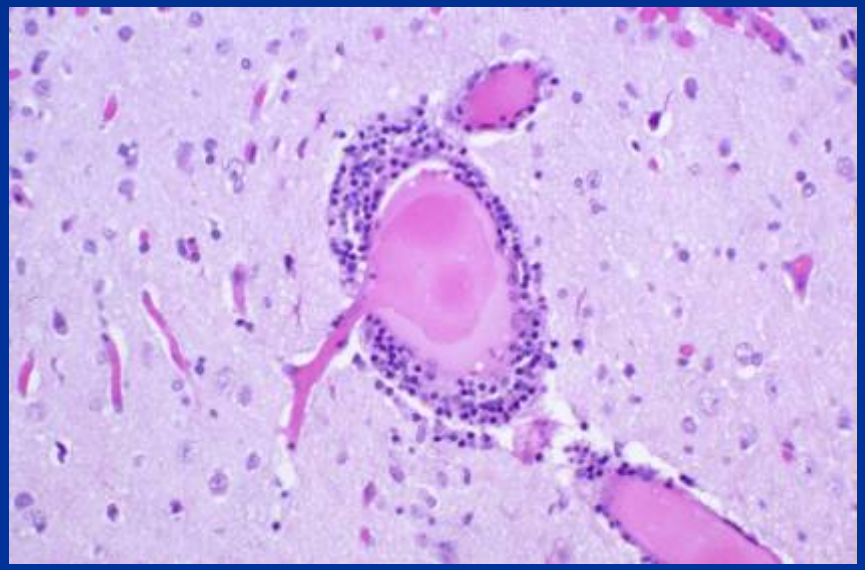
Cerebritis in Immune-compromised Patients

- Fungal Infections
  - Aspergillus
  - Candida
  - Mucor
- Protozoal
  - Toxoplasma
  - Ameba infections can be seen in immunocompromised patients and rarely non-immunocompromised individuals

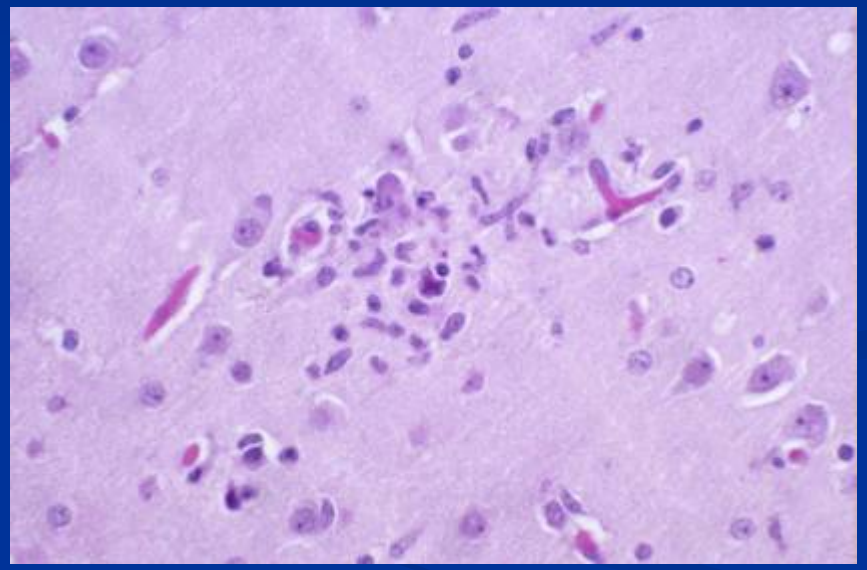
Viral infection

- Route of entry
  - May be blood borne, respiratory or fecal/oral
  - Rabies-peripheral nerve
- Acute viral encephalitis
  - Herpes-activation of latent infection
  - Arbovirus-mosquito borne (West Nile virus)
  - Polio-enteric virus with neuronal tropism
  - Immunocompromised hosts
    - CMV
    - HSV/VZV
    - PML
    - HIV encephalitis (HIVE)

ACUTE (VIRAL) ENCEPHALITIS
microscopic features



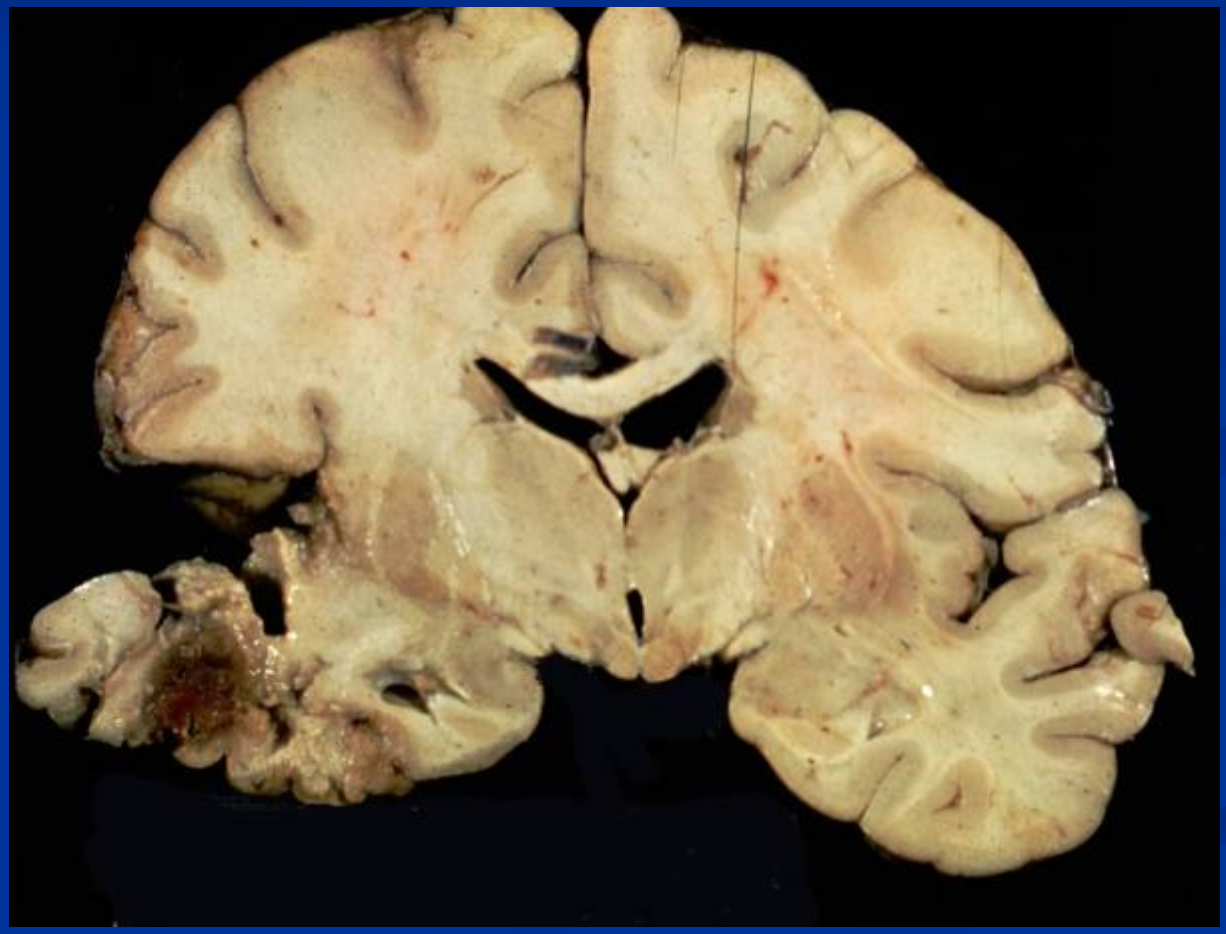
Lymphocytic infiltrates



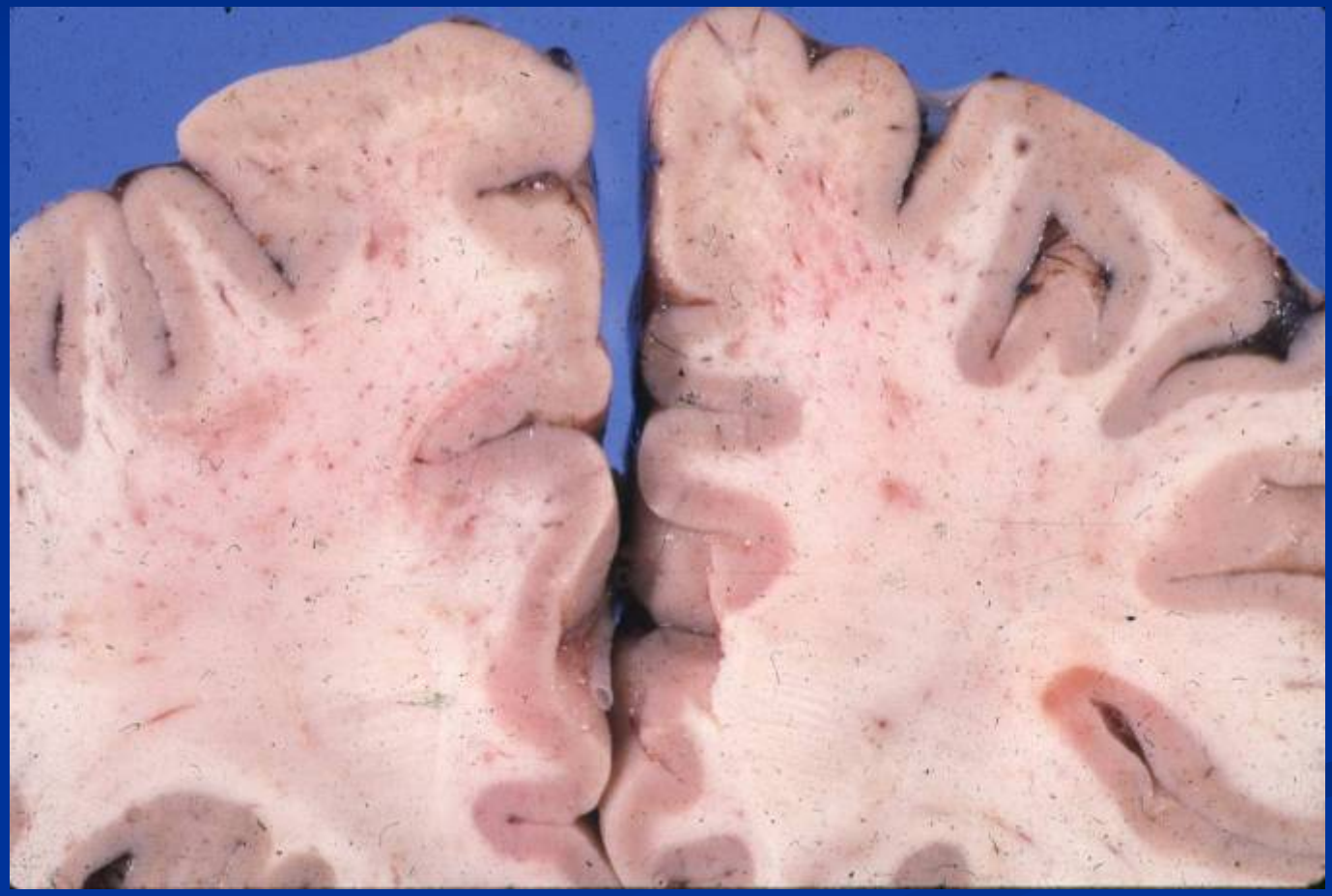
Microglial proliferation with microglial nodules

ACUTE (VIRAL) ENCEPHALITIS

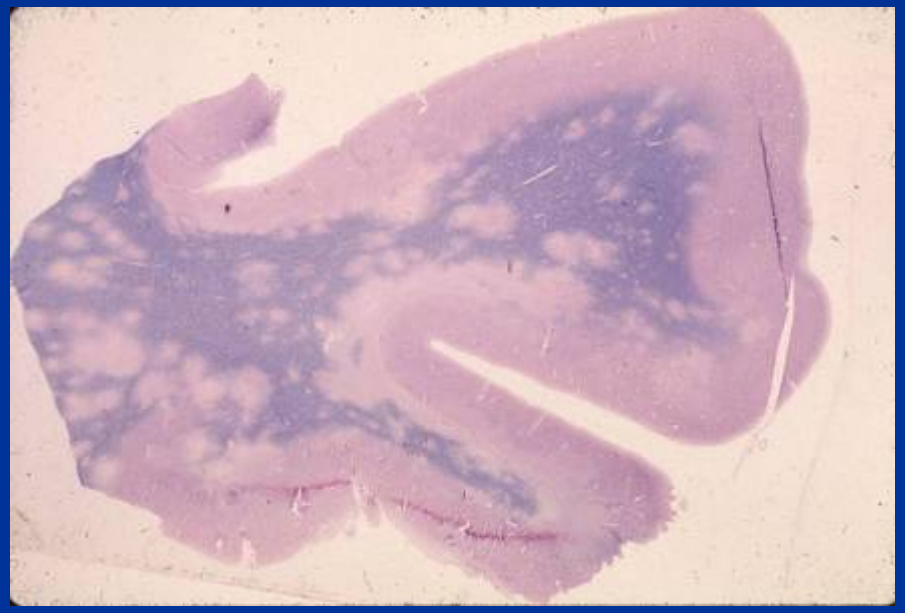
Herpes simplex

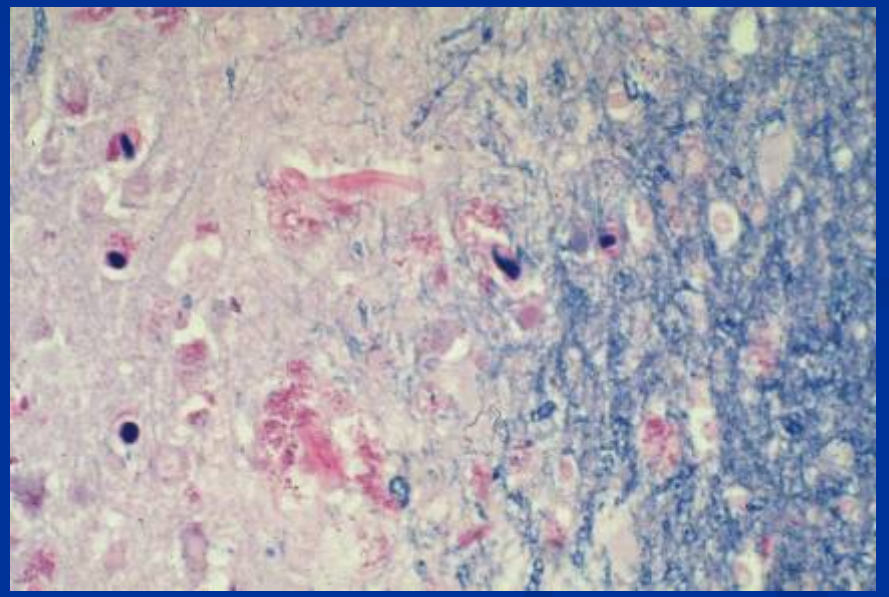


OPPORTUNISTIC VIRAL INFECTIONS:
Progressive multifocal leukoencephalopathy (JC virus)

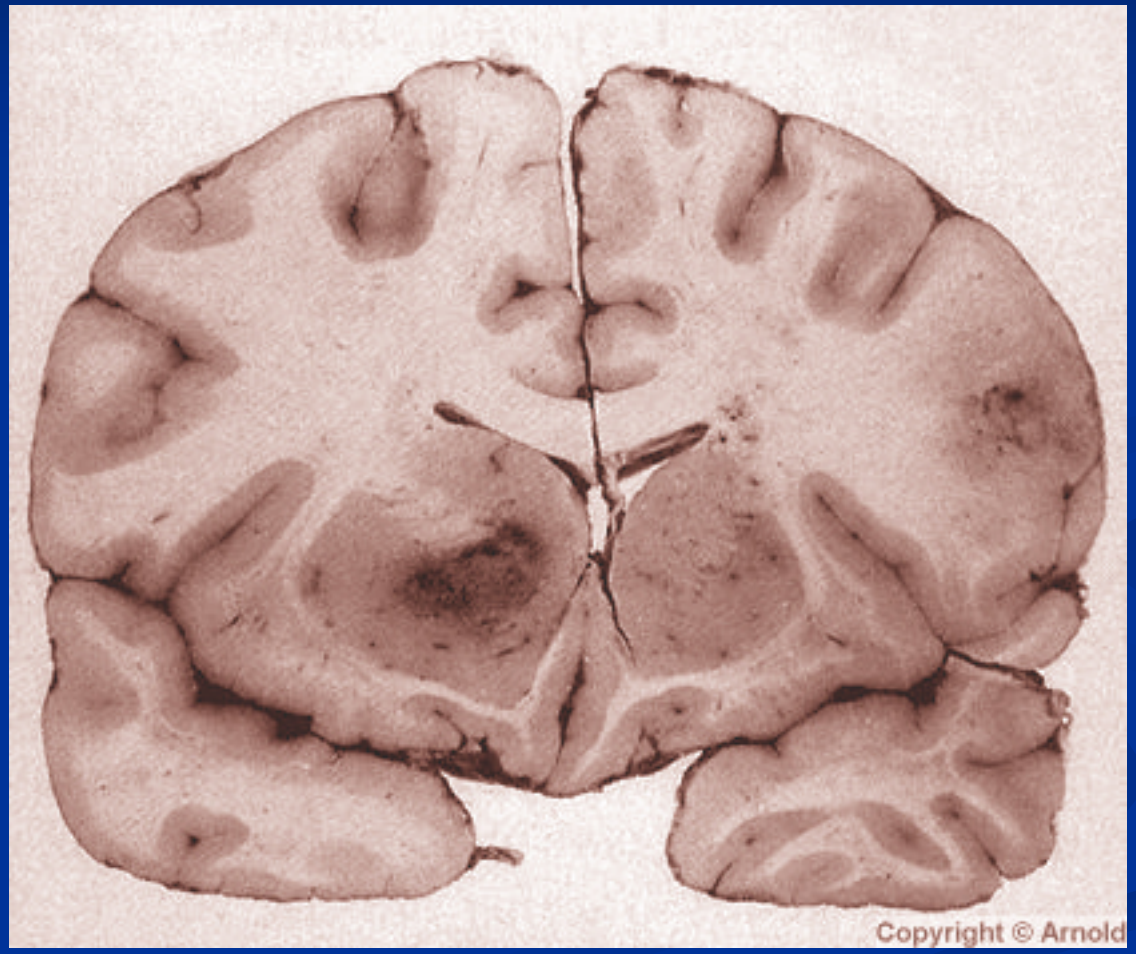


Progressive multifocal leukoencephalopathy

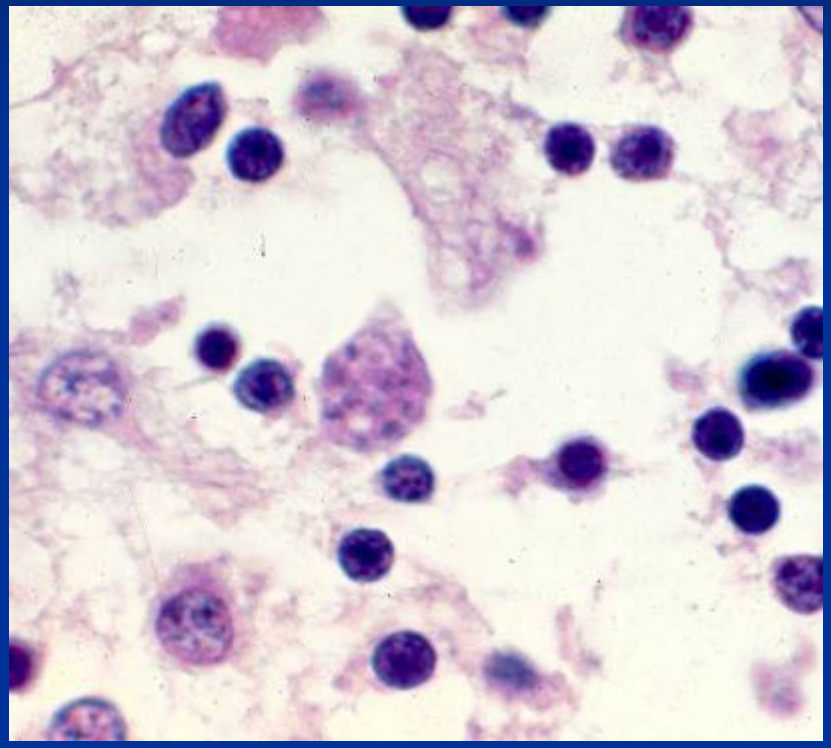


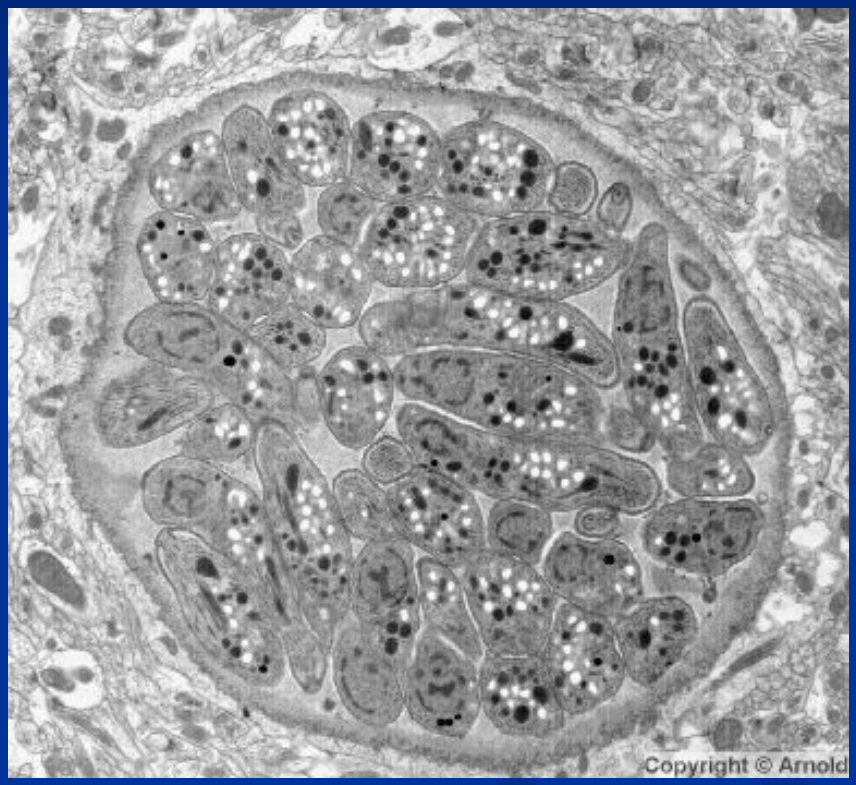


OPPORTUNISTIC INFECTIONS:
Toxoplasmosis



OPPORTUNISTIC INFECTIONS: Toxoplasmosis

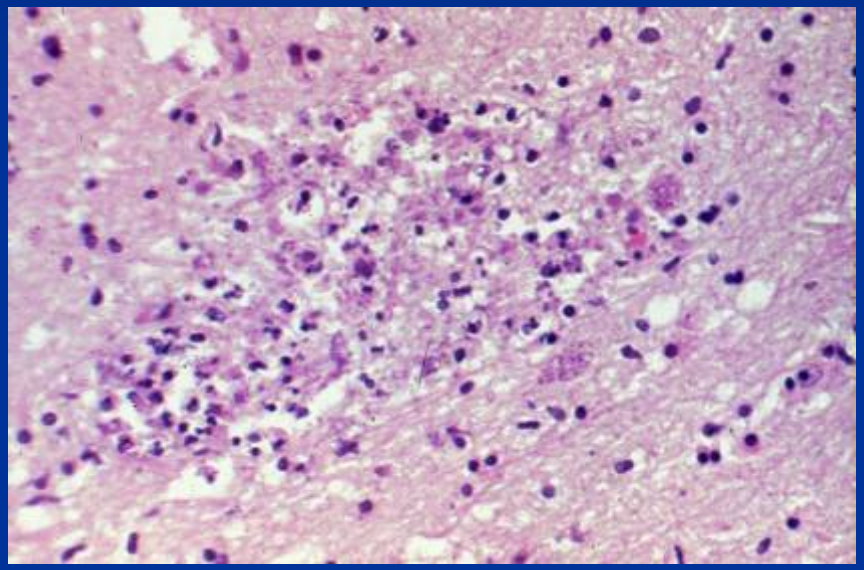




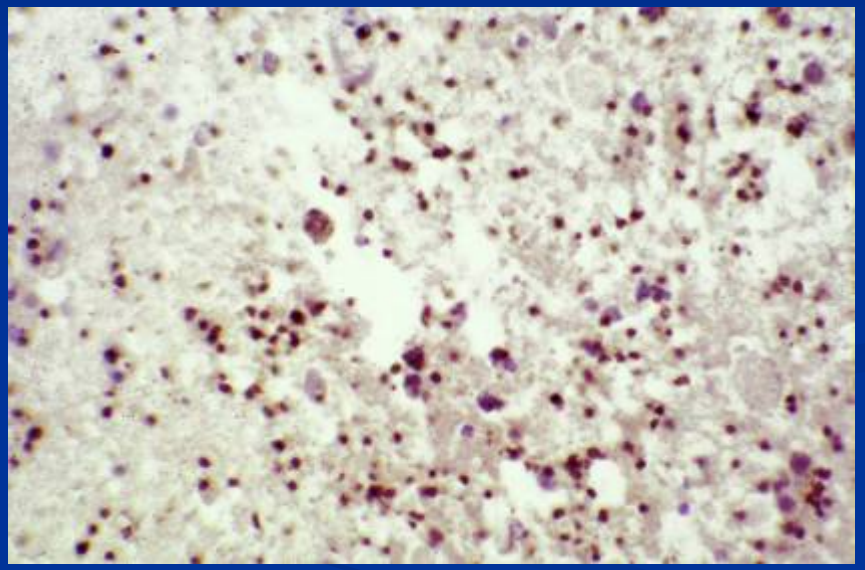
Bradyzoites with cysts

OPPORTUNISTIC INFECTIONS

Toxoplasmosis



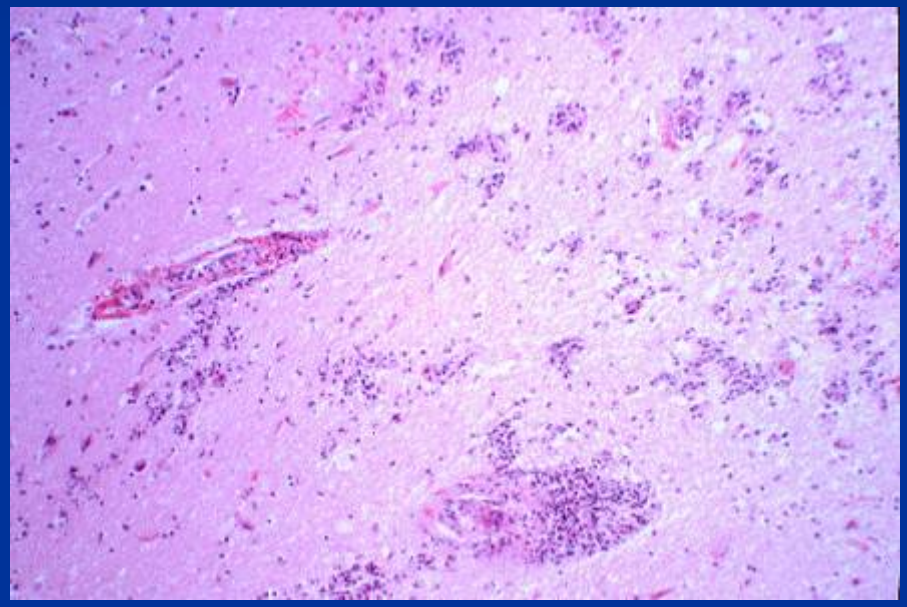
Necrotizing lesion
H&E

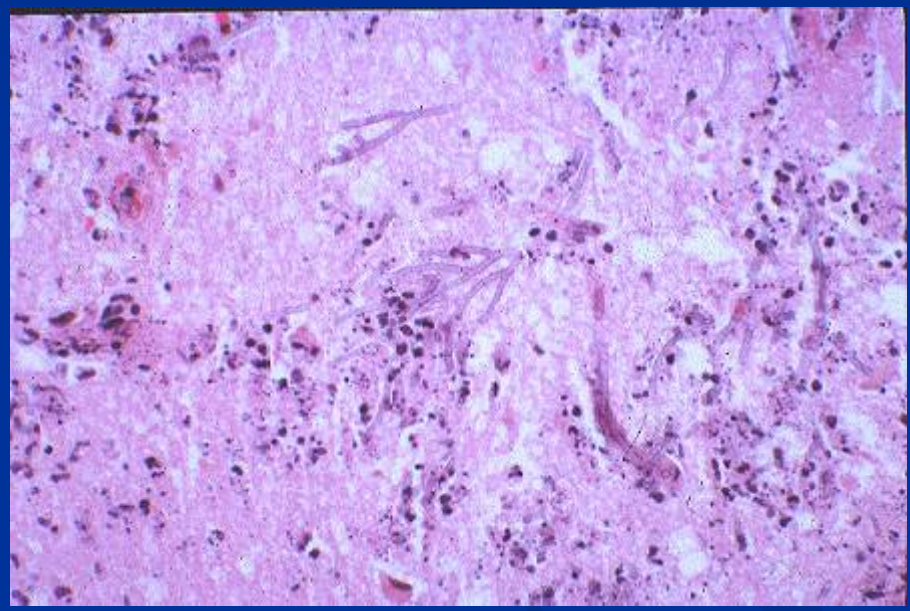


Immunoperoxidase for
Toxo. tachyzoites

OPPORTUNISTIC INFECTIONS

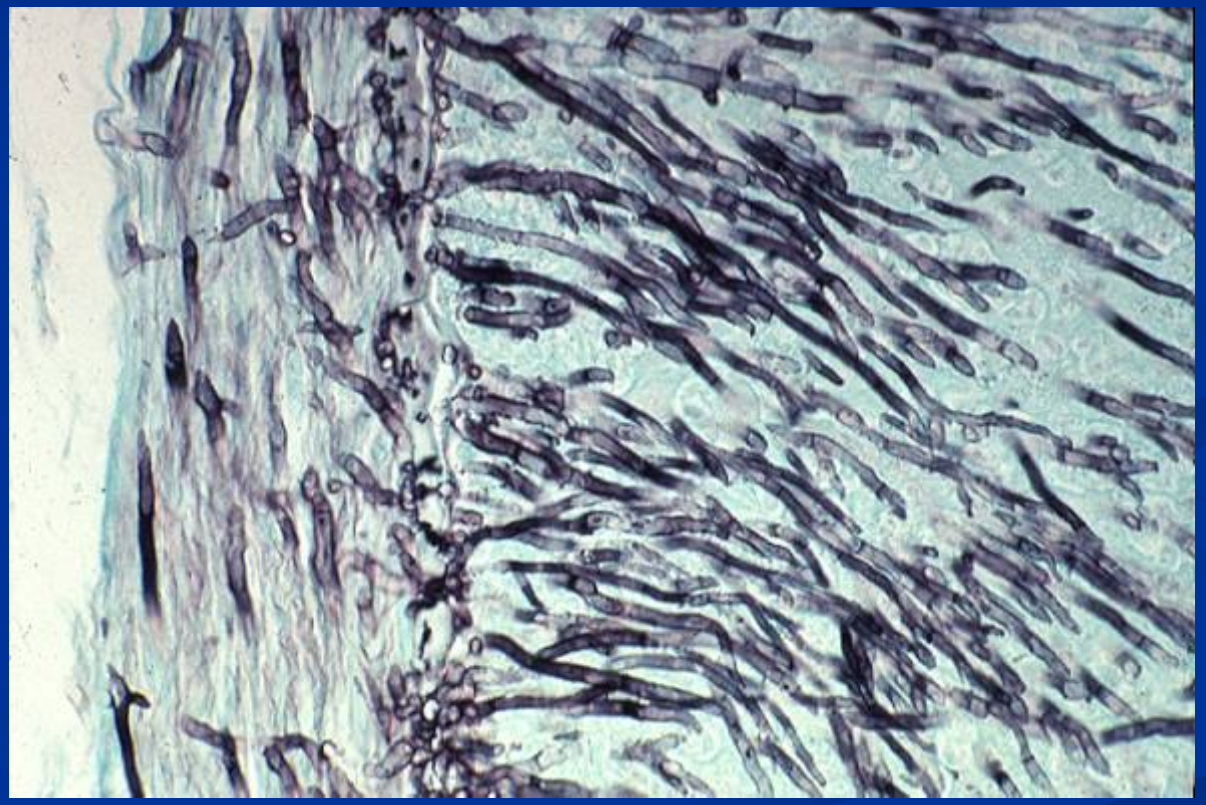
Fungal cerebritis : Aspergillus





OPPORTUNISTIC INFECTIONS

Fungal cerebritis : Aspergillus



Summary: Infections

- Meningitis: Definition, CSF findings
- Abscess: Definition, etiology
- Viral meningitis: Routes of entry (arbo-mosquitos)
- Viral encephalitis: Rabies, HSV, arboviruses
  - Spinal cord: Polio
- Infections in immunocompromised hosts
  - Cerebritis: Fungal (aspergillus, protozoal-toxoplasma)
  - Viral: CMV, VZV, PML, Aids encephalopathy

Primary Tumors of the Central Nervous System

- **Glioma**
  - Astrocytoma
  - Oligodendroglioma
  - Ependymoma
- Neuronal lineage
- Meningioma
- Nerve Sheath Tumors

Primary brain tumors: Cell types

1. **Neuron:** Gangliocytoma, ganglioglioma medulloblastoma
2. **Astrocyte:** Astrocytoma, glioblastoma
3. **Oligodendrocyte:** Oligodendroglioma
4. **Ependymal cell:** Ependymoma
5. **Microglial cell:** Tumors derived from microglial cells have not been described.
6. **Meningeal cell:** Meningiomas are derived from arachnoidal cells and are usually dural-based.

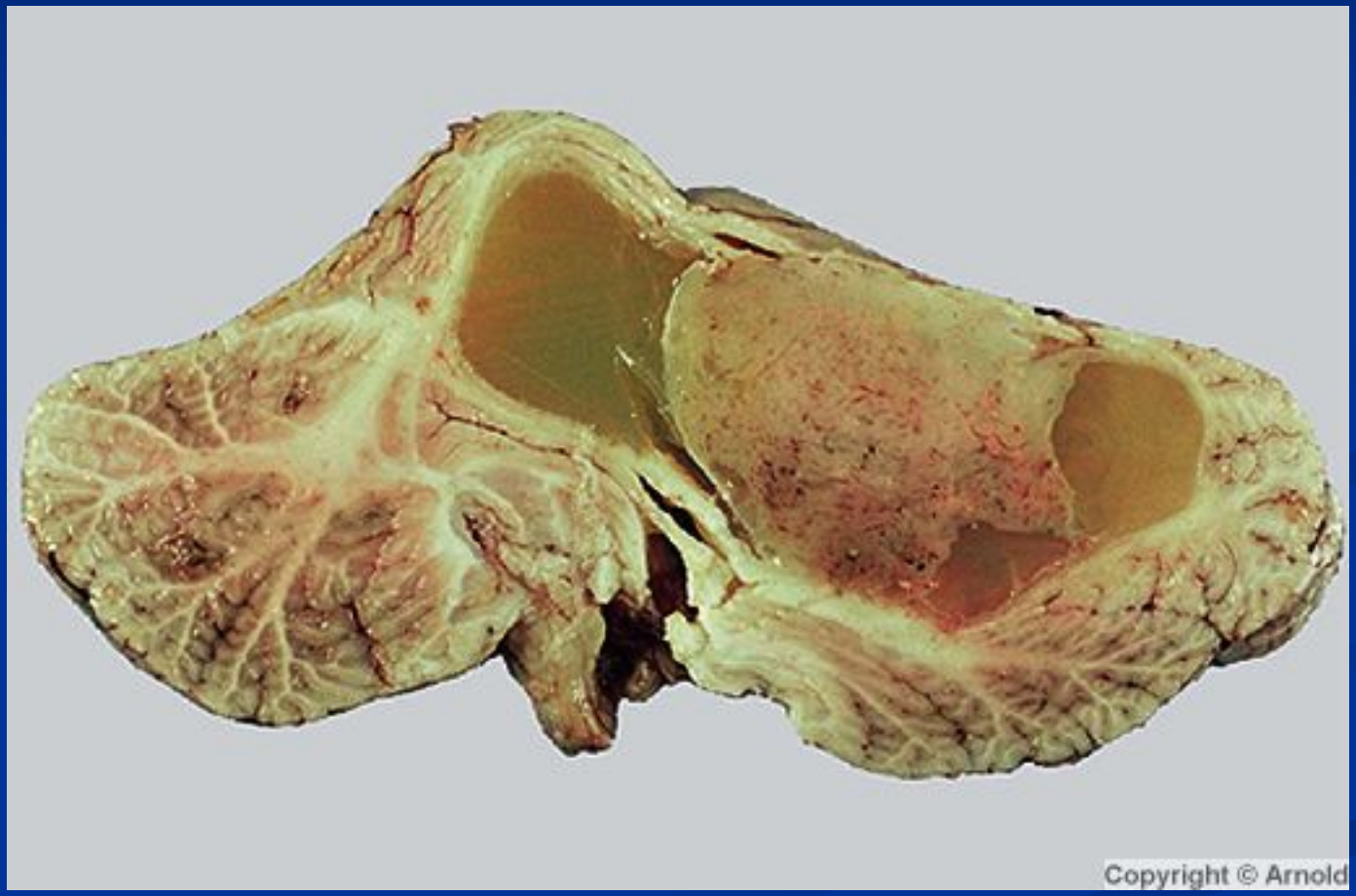
GLIOMAS

- **ASTROCYTOMAS**
- **OLIGODENDROGLIOMAS**
- **EPENDYMOMAS**
- **MIXED GLIOMAS**

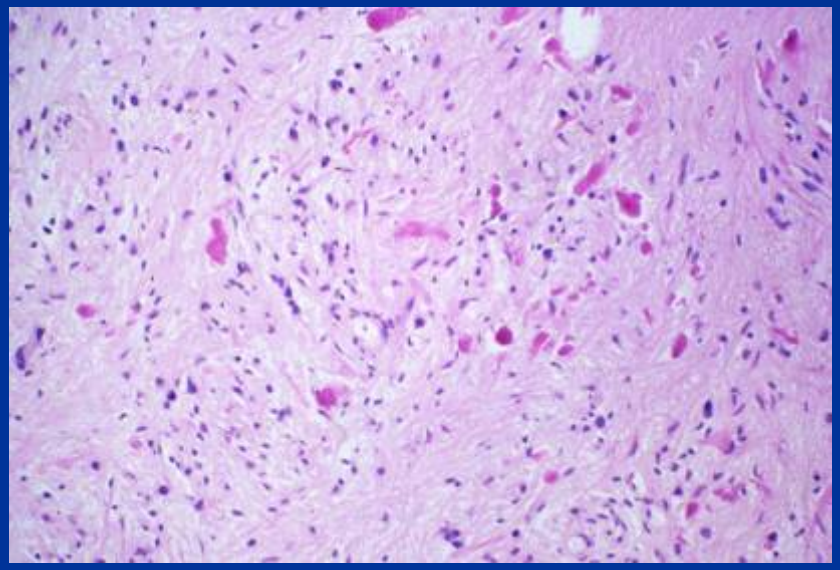
Gliomas

- Diffusely infiltrating (not easily resected)
- Histologic appearance (grade) correlates with overall survival
- May become more malignant (higher grade) over time (especially astrocytomas which become glioblastomas)
- May spread via CSF
- Rarely (never) metastasize

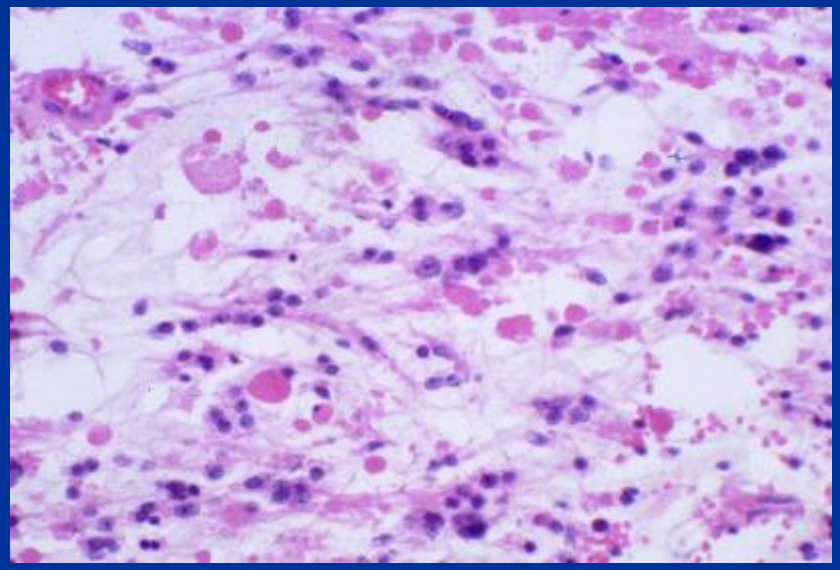
JUVENILE PILOCYTIC ASTROCYTOMA



JUVENILE PILOCYTIC ASTROCYTOMA

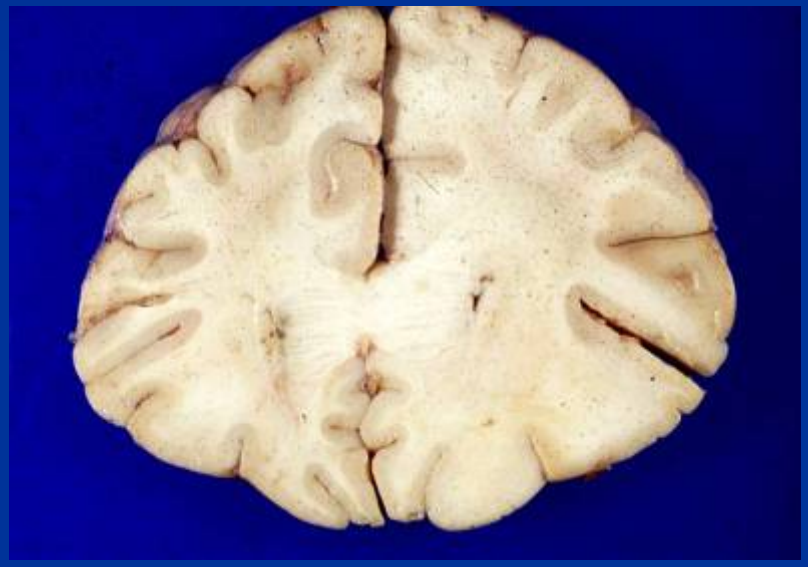


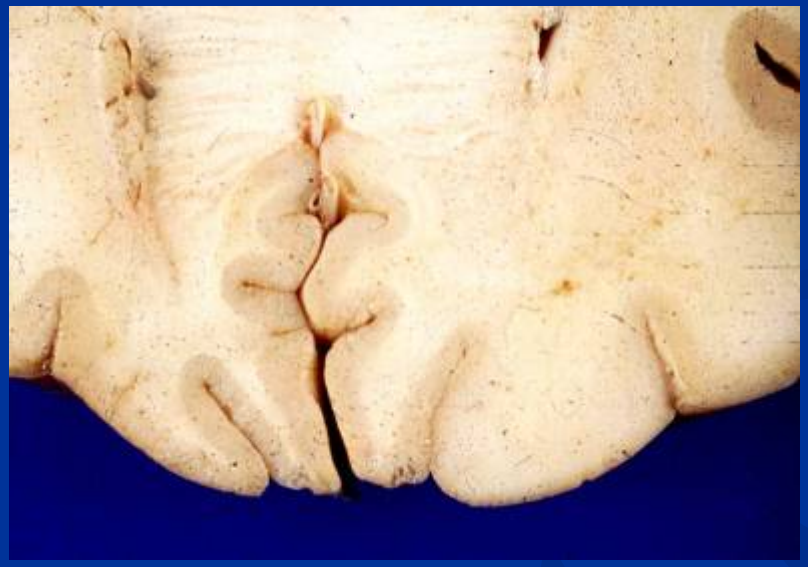
Rosenthal fibers



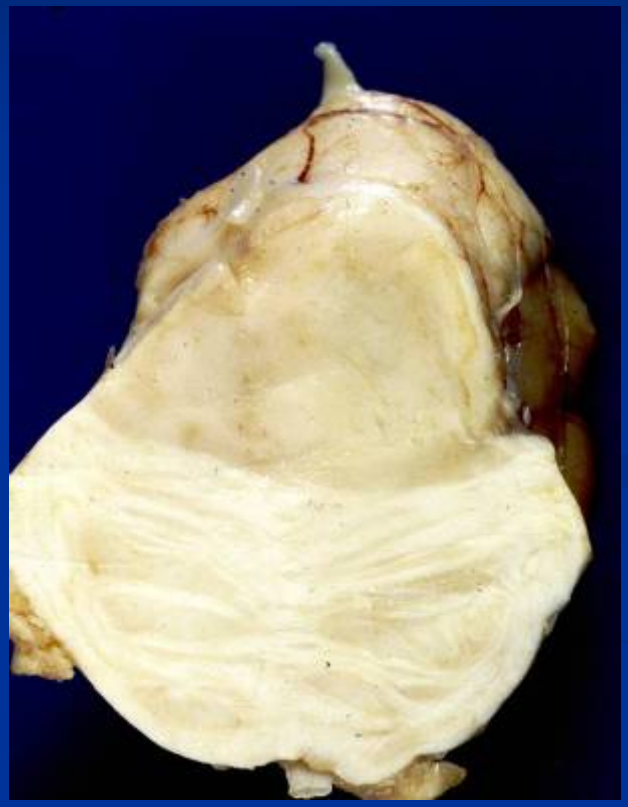
Eosinophilic granular bodies

ASTROCYTOMA

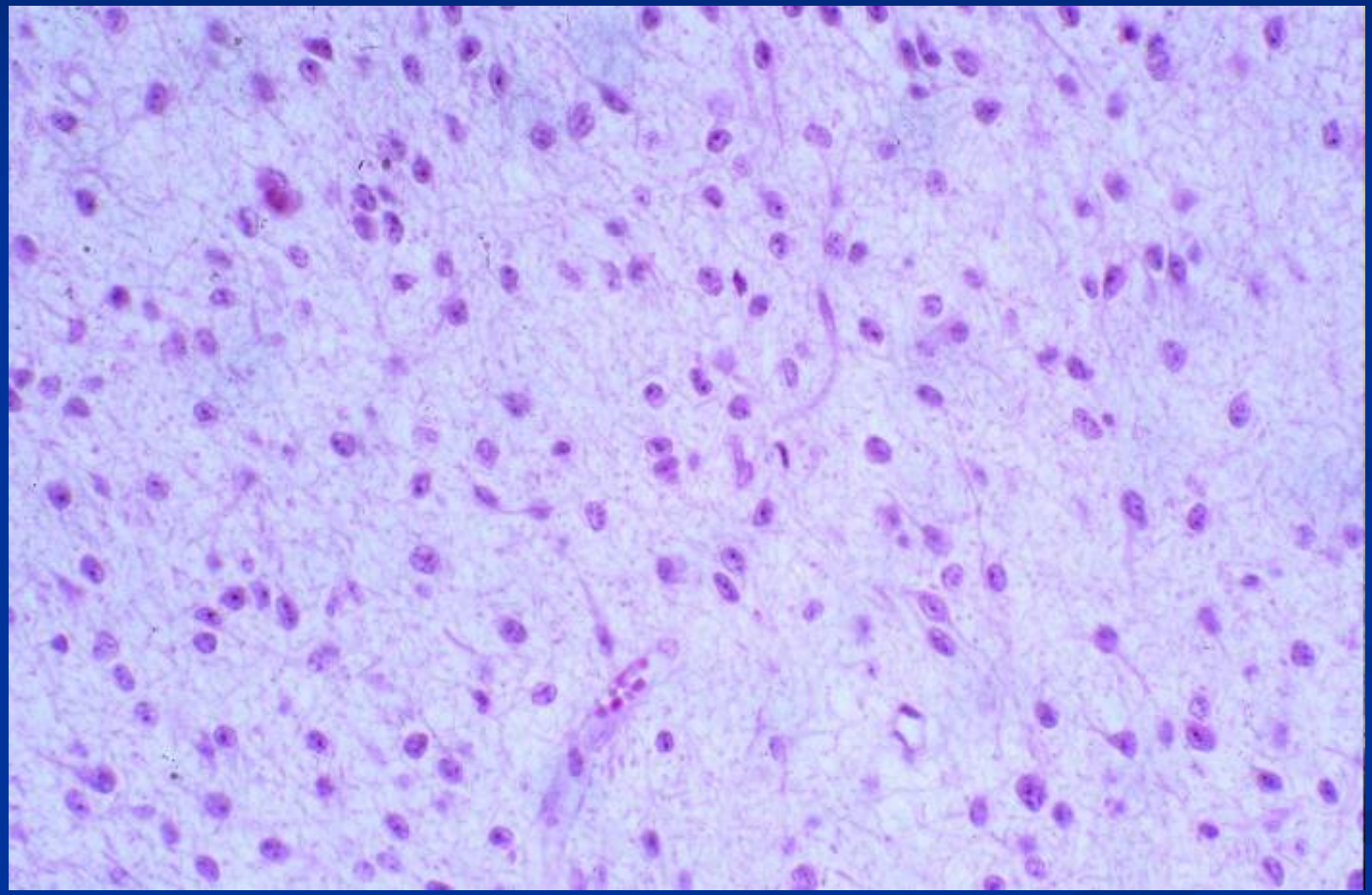




ASTROCYTOMA

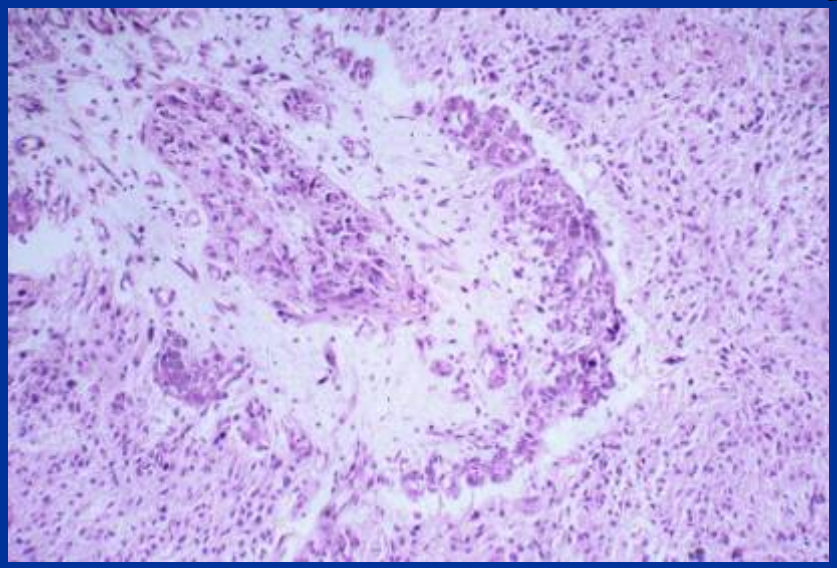


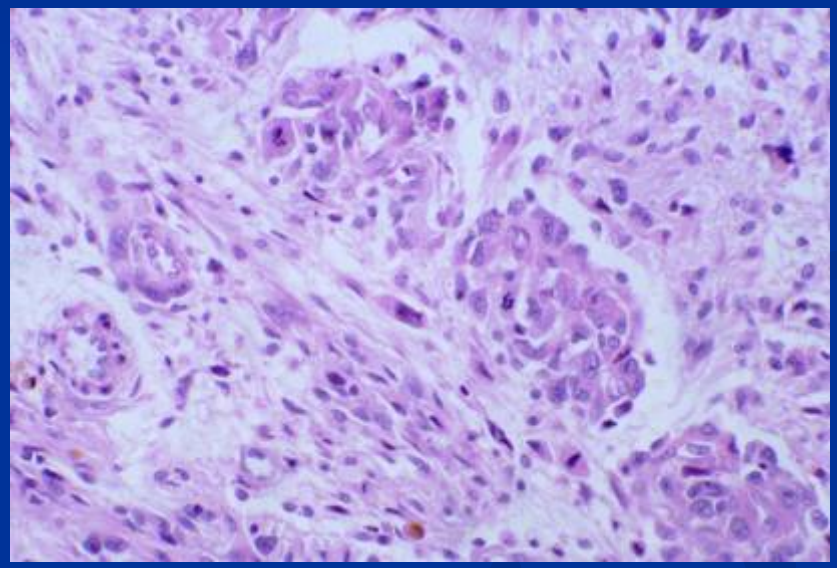
ASTROCYTOMA



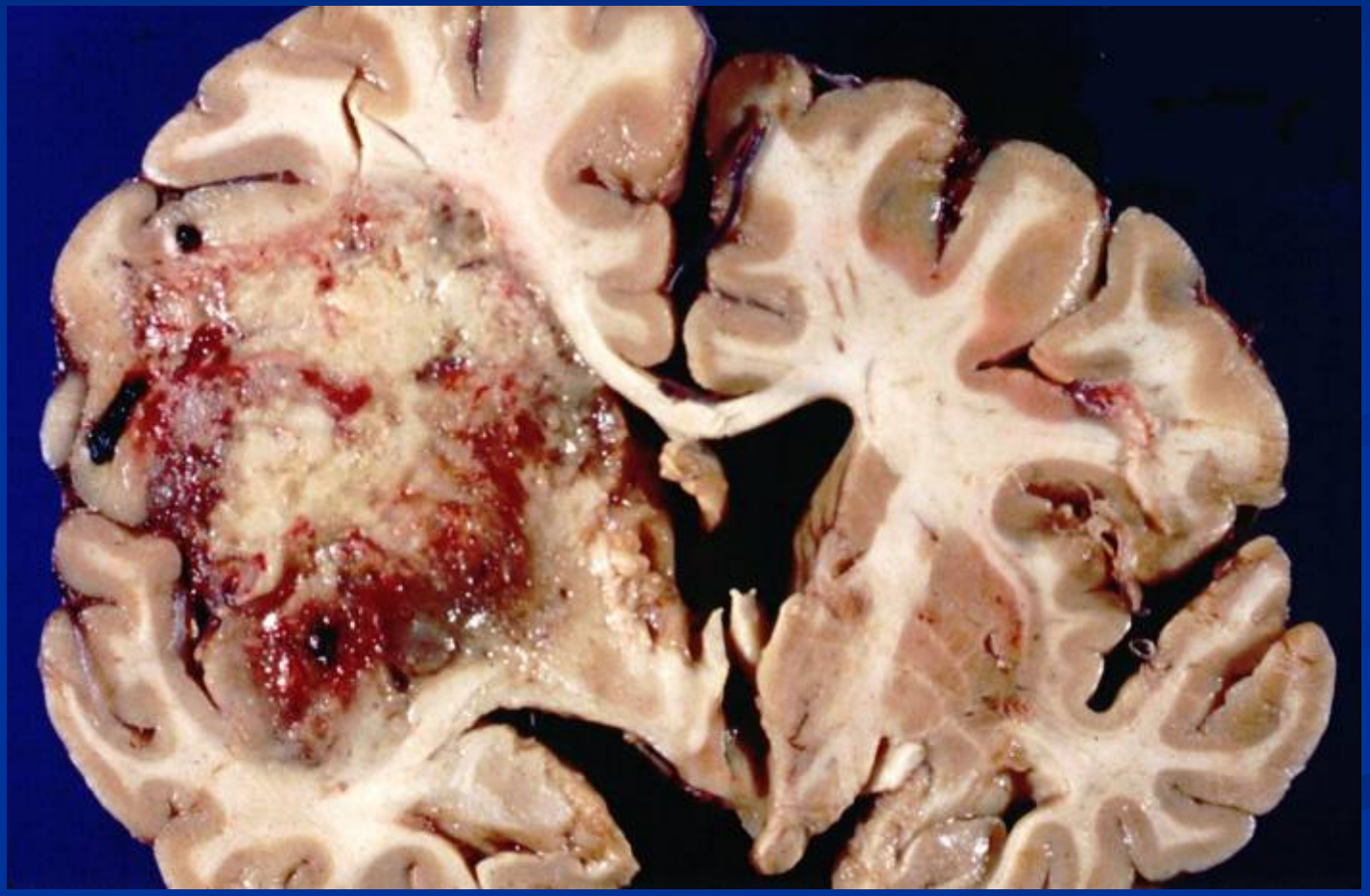
ASTROCYTOMA
FEATURES OF ANAPLASIA

vascular proliferation

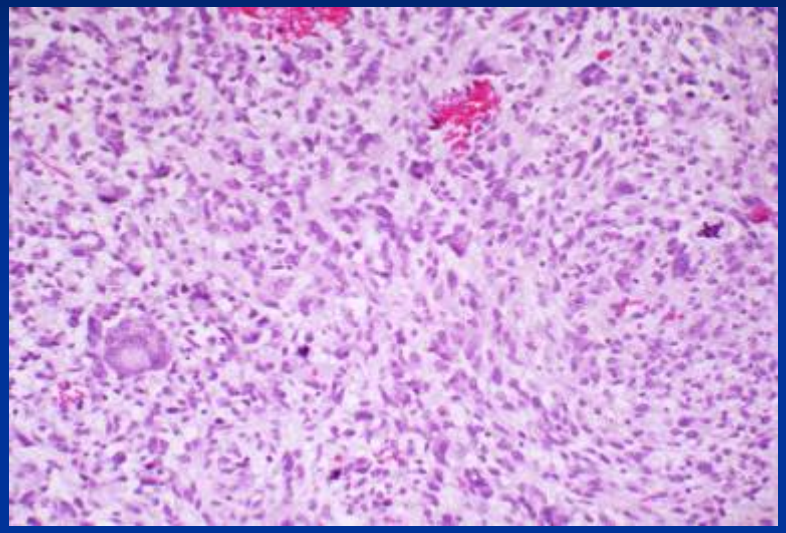


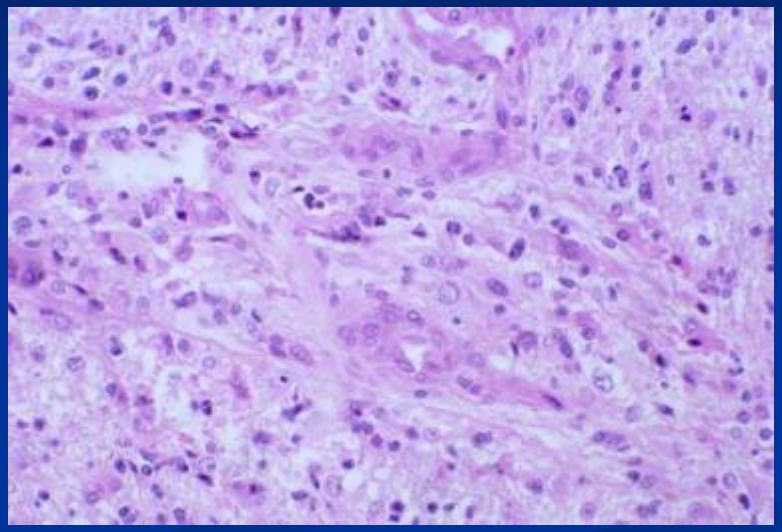


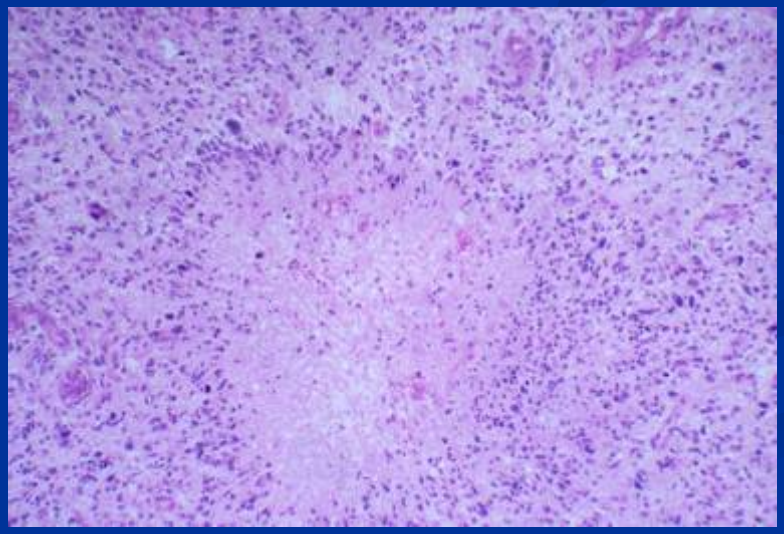
GLIOBLASTOMA MULTIFORME



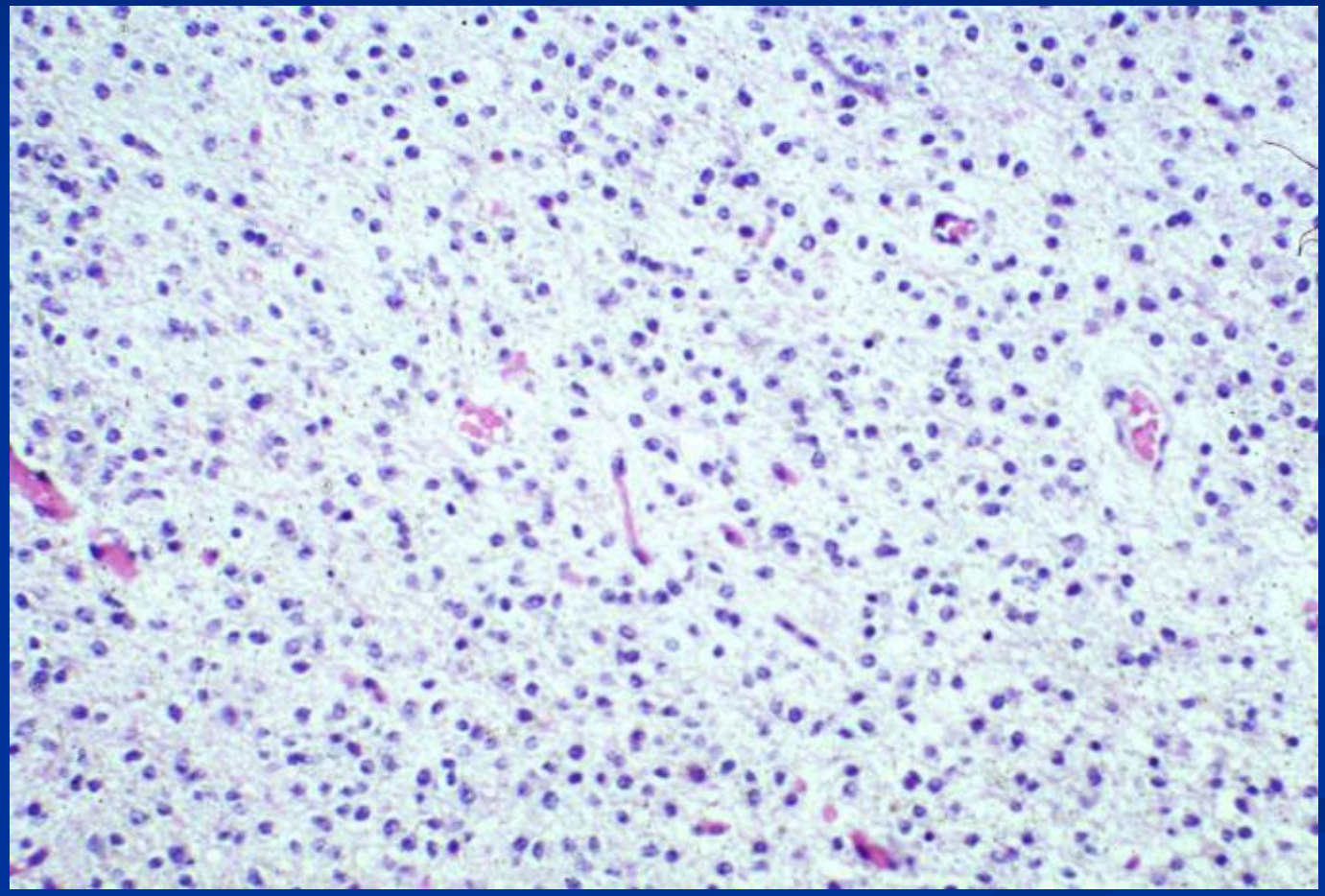
GLIOBLASTOMA MULTIFORME



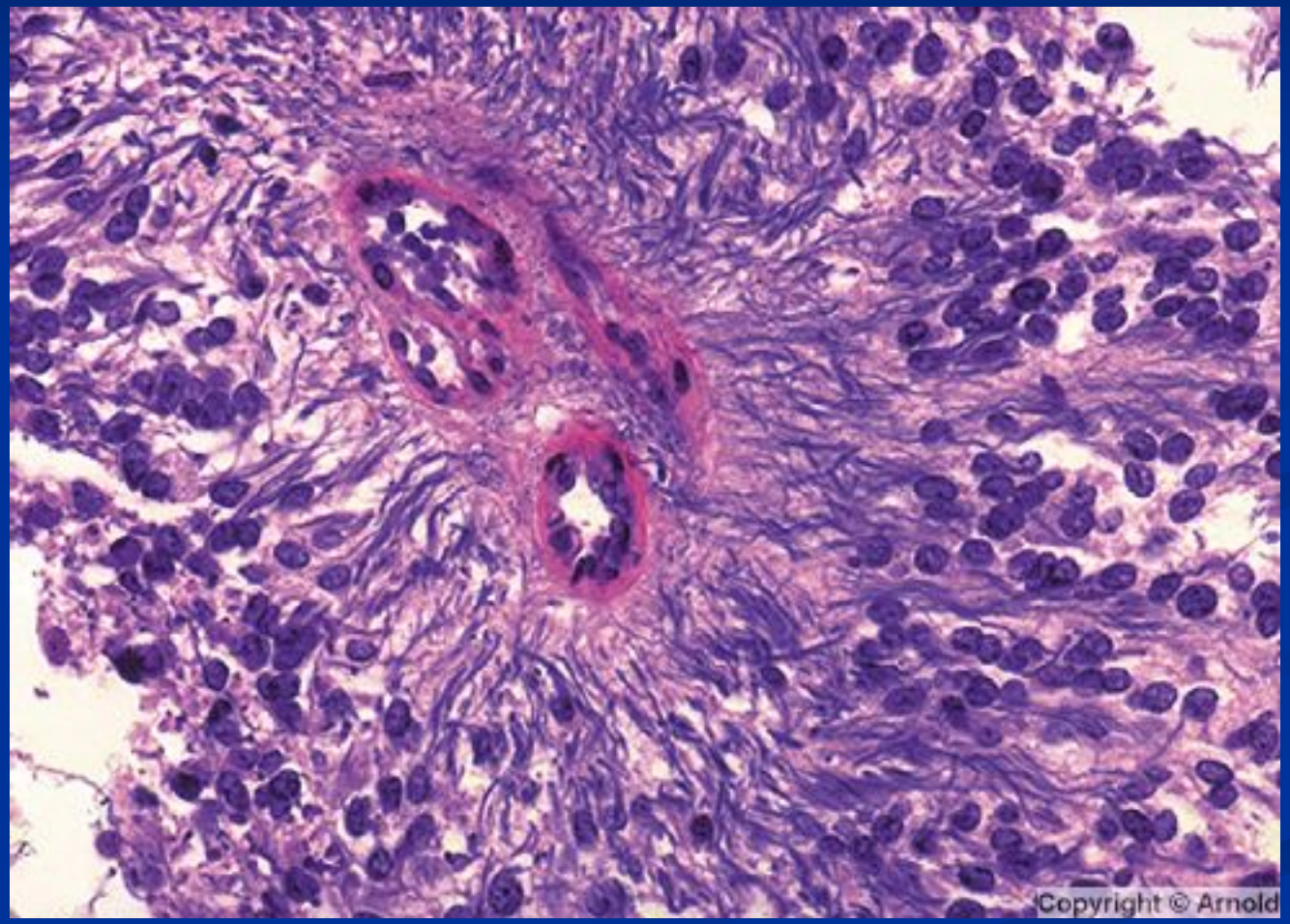




OLIGODENDROGLIOMA



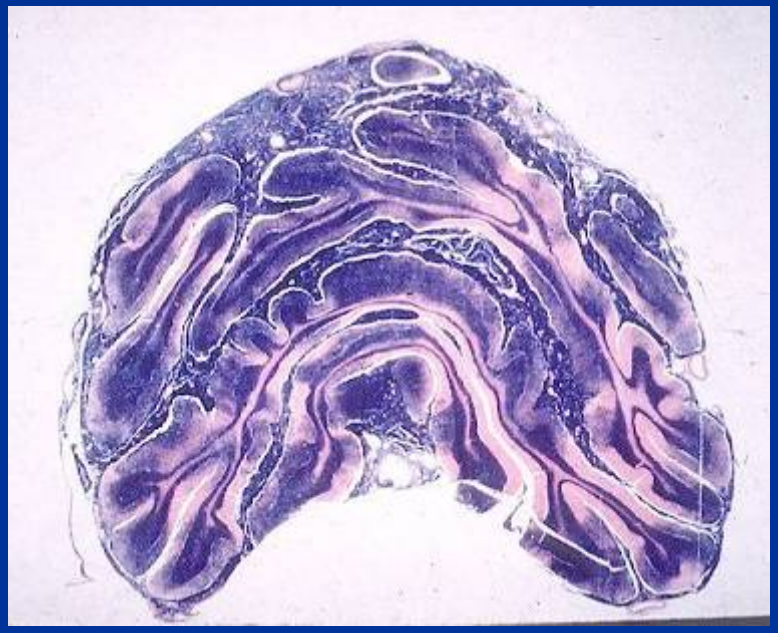
EPENDYMOMA

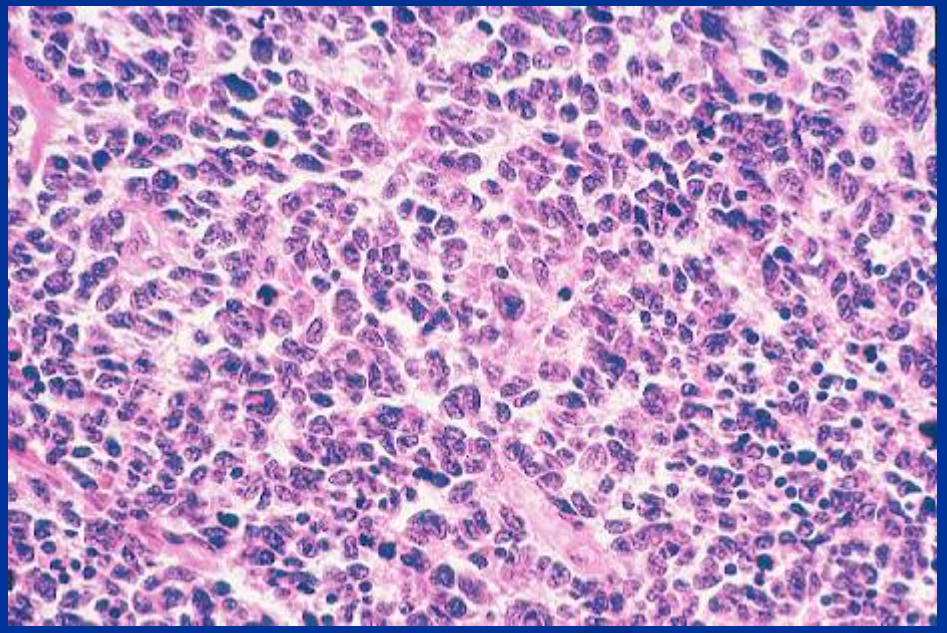


Non-glial tumors

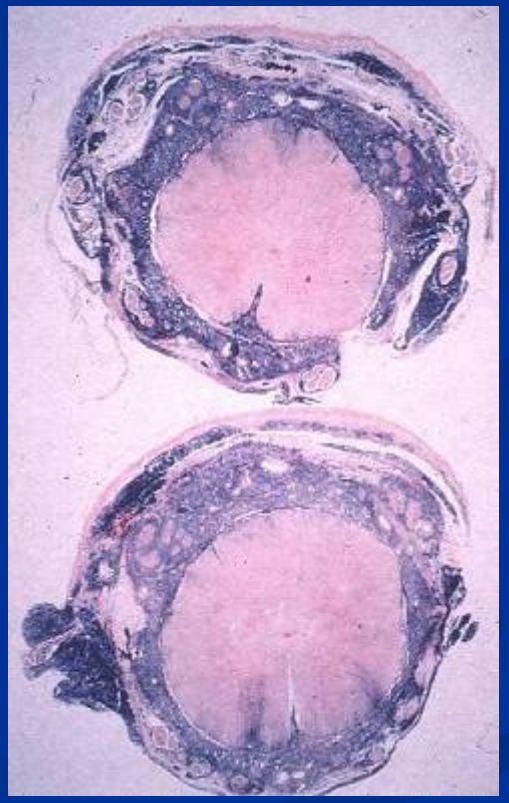
- Medulloblastoma: Malignant cerebellar tumor of childhood
- Meningioma: Benign, superficial, well-circumscribed tumor derived from arachnoidal cells
- Nerve sheath tumors: Schwannoma and neurofibroma, well-circumscribed, encapsulated tumors involving cranial nerves, spinal nerves and other peripheral nerves

MEDULLOBLASTOMA

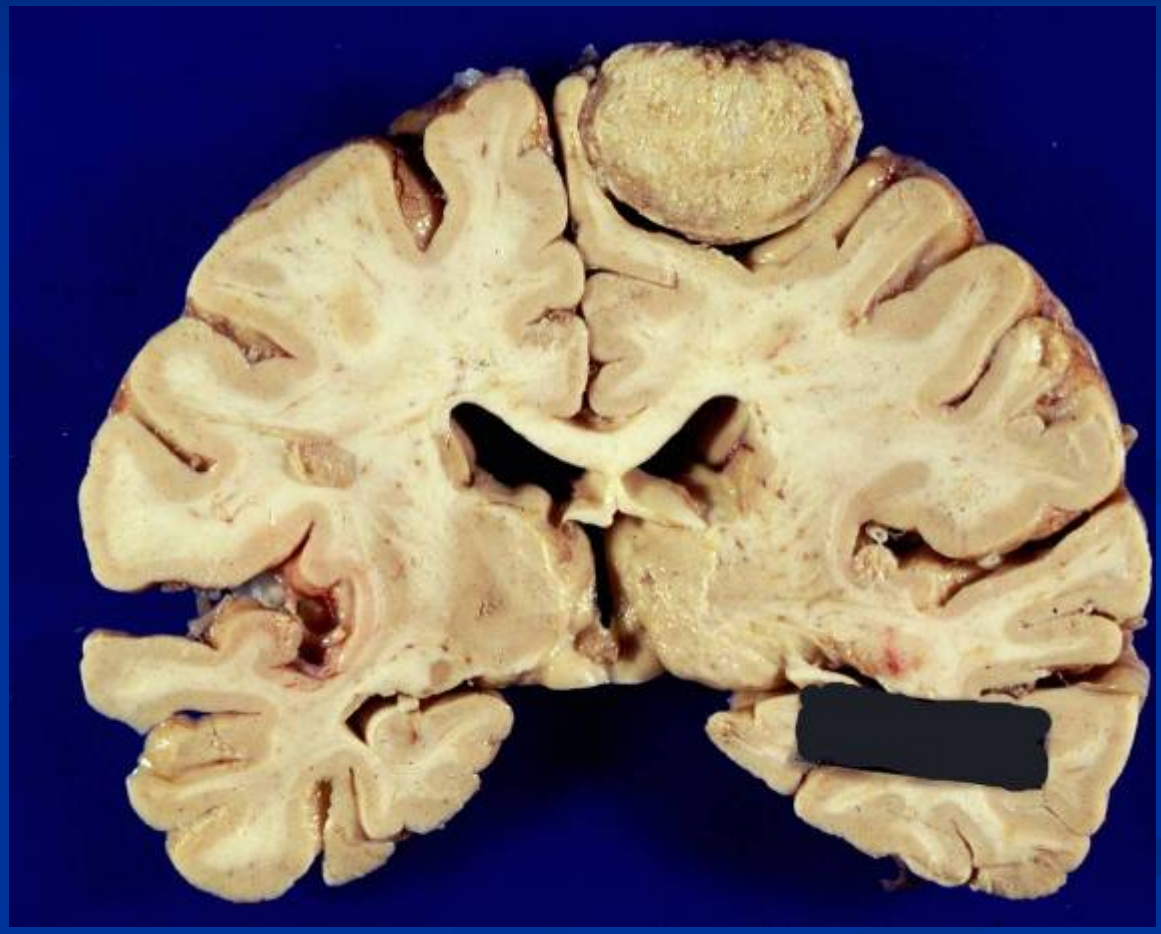




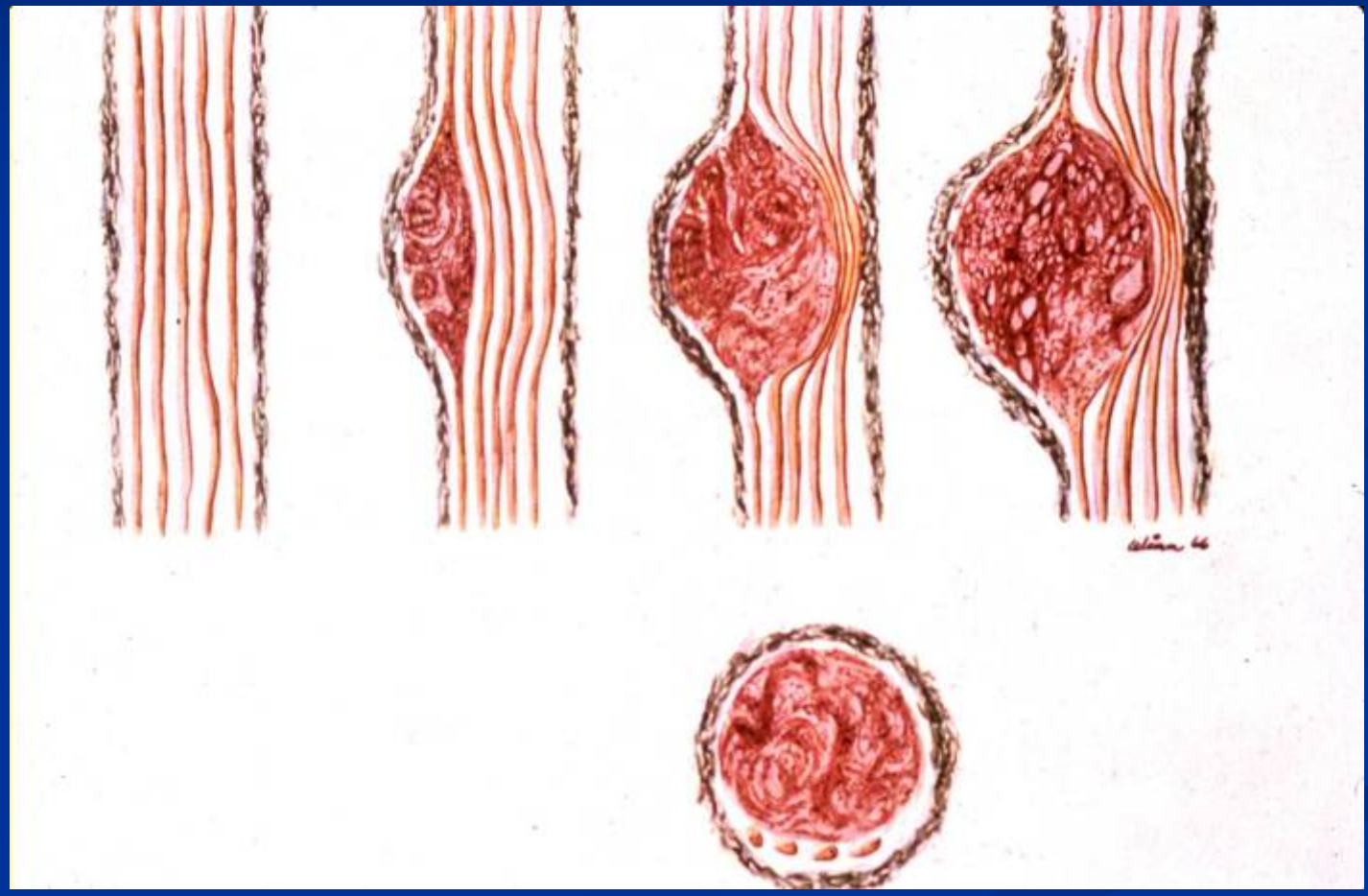
MEDULLOBLASTOMA



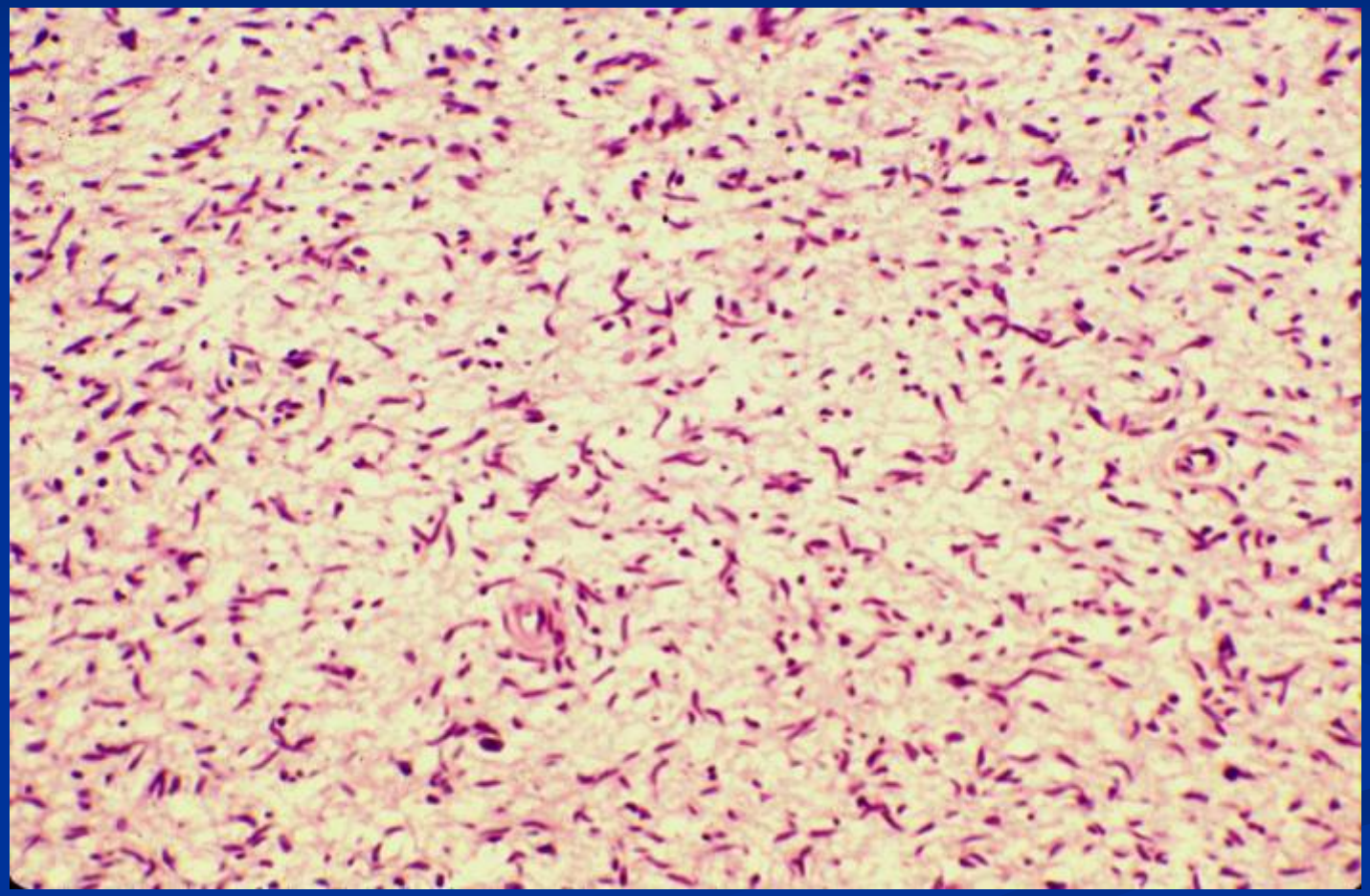
MENINGIOMA



SCHWANNOMA



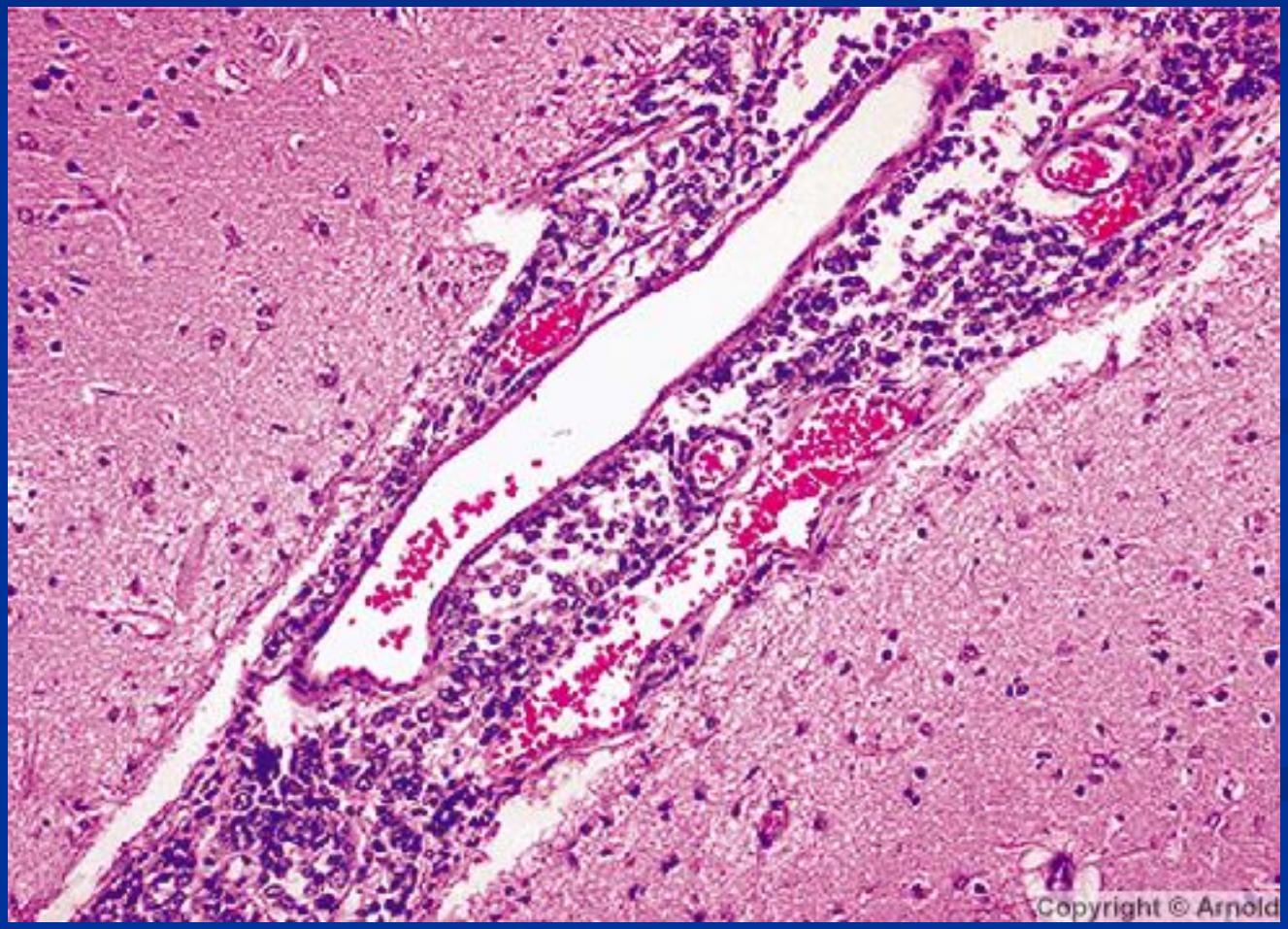
NEUROFIBROMA



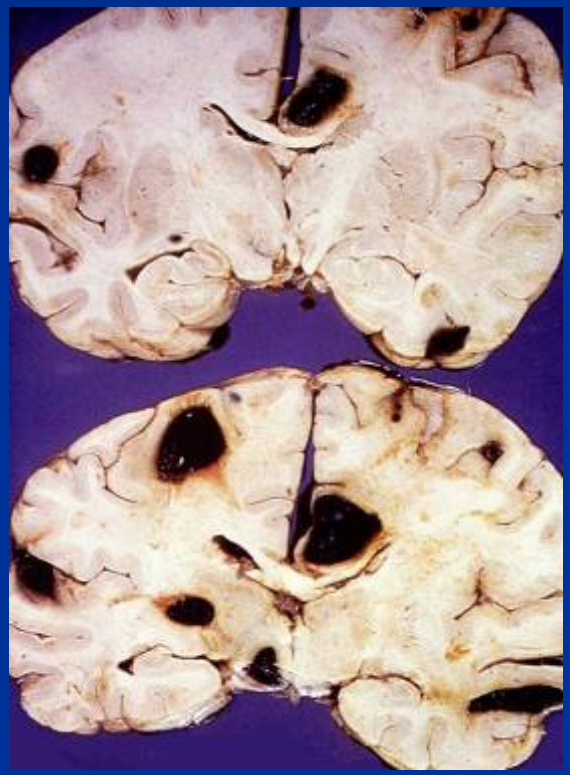
Secondary Involvement of the Central Nervous System

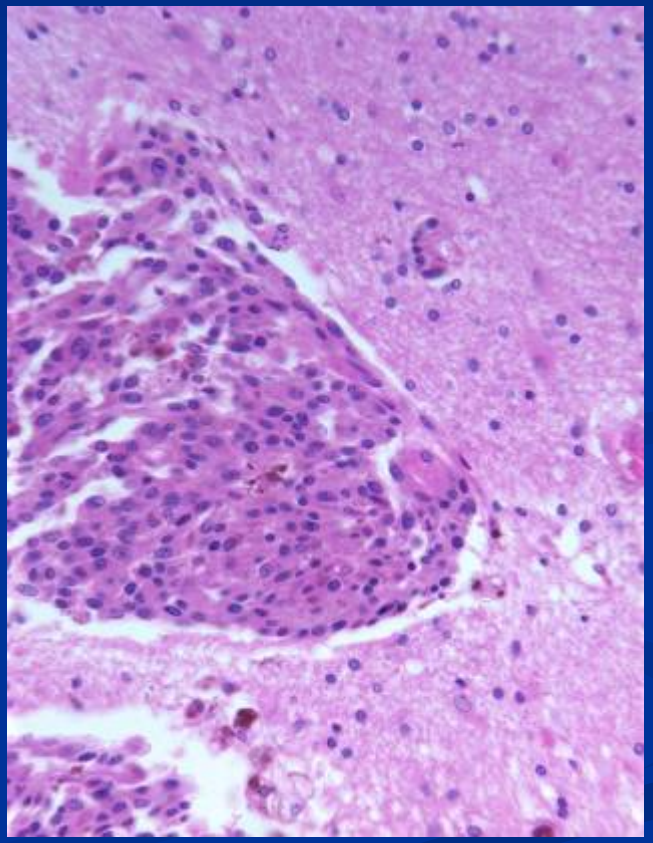
- Metastatic tumor
  - Melanoma
  - Renal cell
  - Lung
- Contiguous involvement (pituitary adenoma and craniopharyngioma)

METASTATIC TUMORS
leptomeningeal carcinomatosis

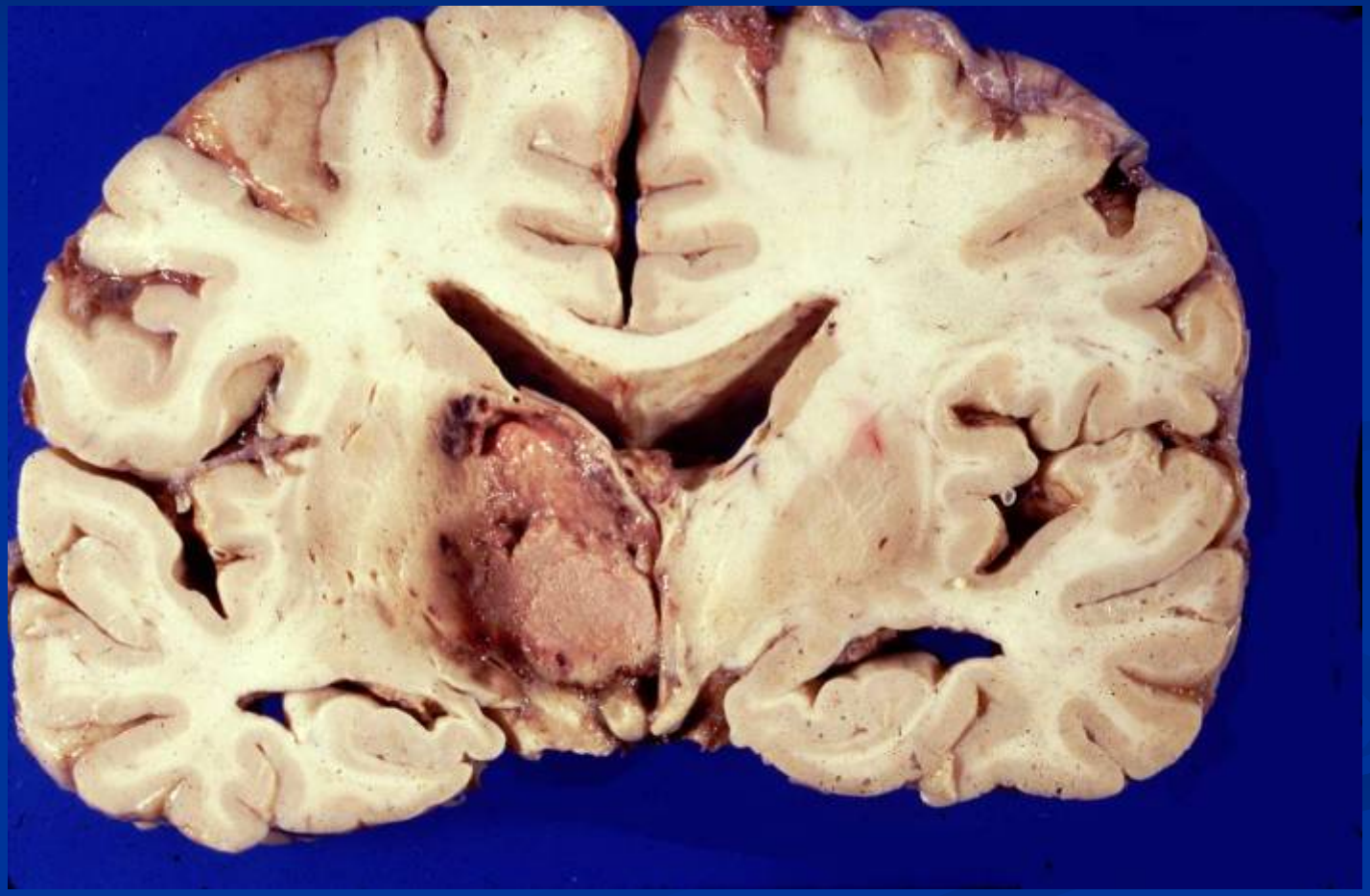


METASTATIC MELANOMA





PRIMARY CNS LYMPHOMA

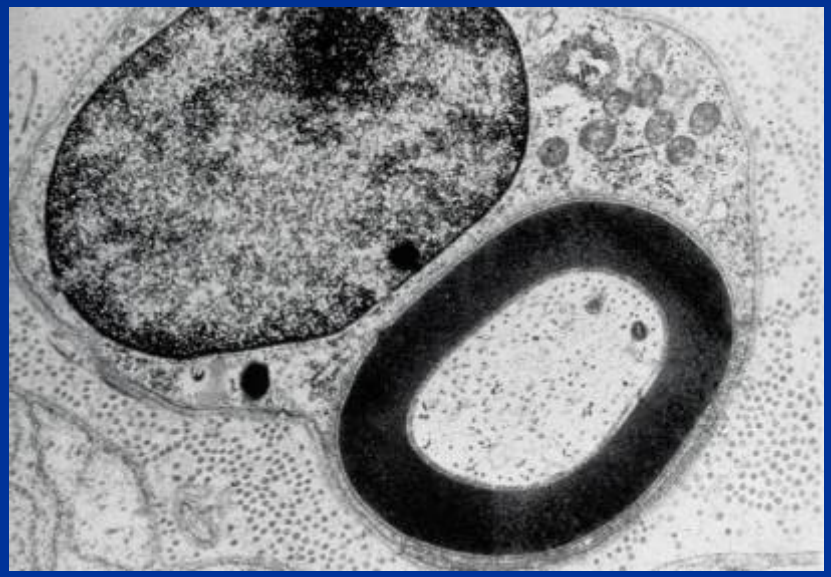


Summary: Brain tumors

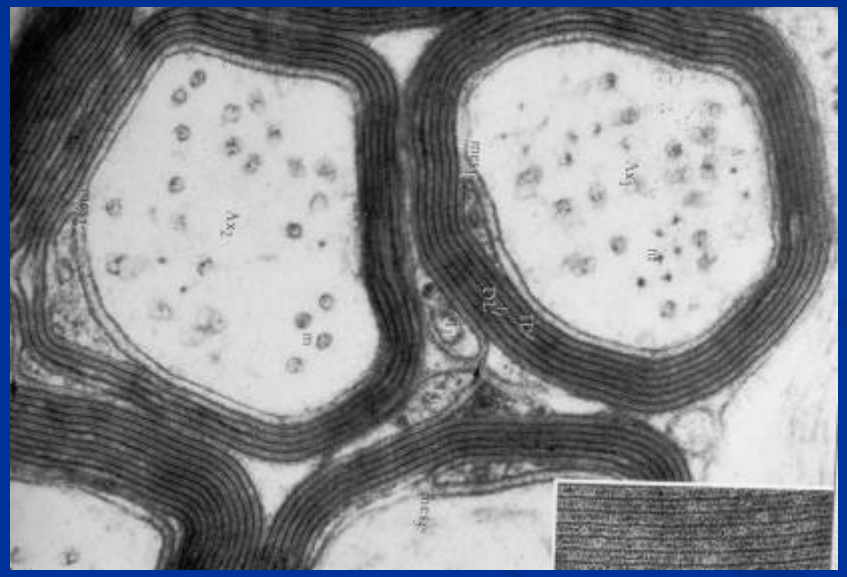
- Primary brain tumors: glia (low grade vs. high grade), neurons, meninges
- Nerve sheath tumors: schwannoma and neurofibroma
- Secondary brain tumors: Metastatic (lung-males, breast-females, melanoma, renal cell carcinoma)
- Tumors arising outside the CNS with CNS symptoms: pituitary adenoma, craniopharyngioma

DISEASES OF MYELIN AND PERIPHERAL NERVE

MYELIN

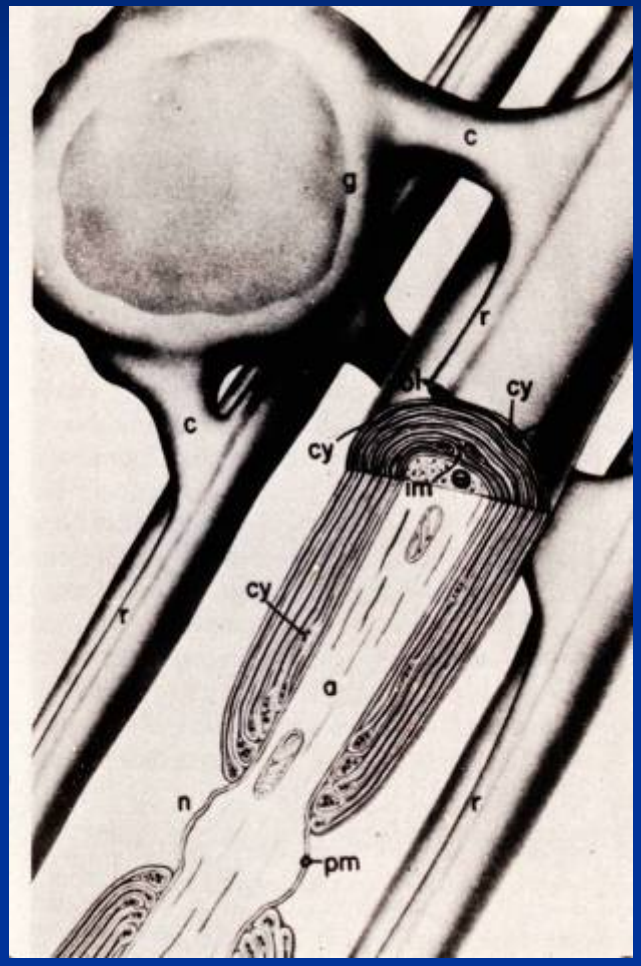


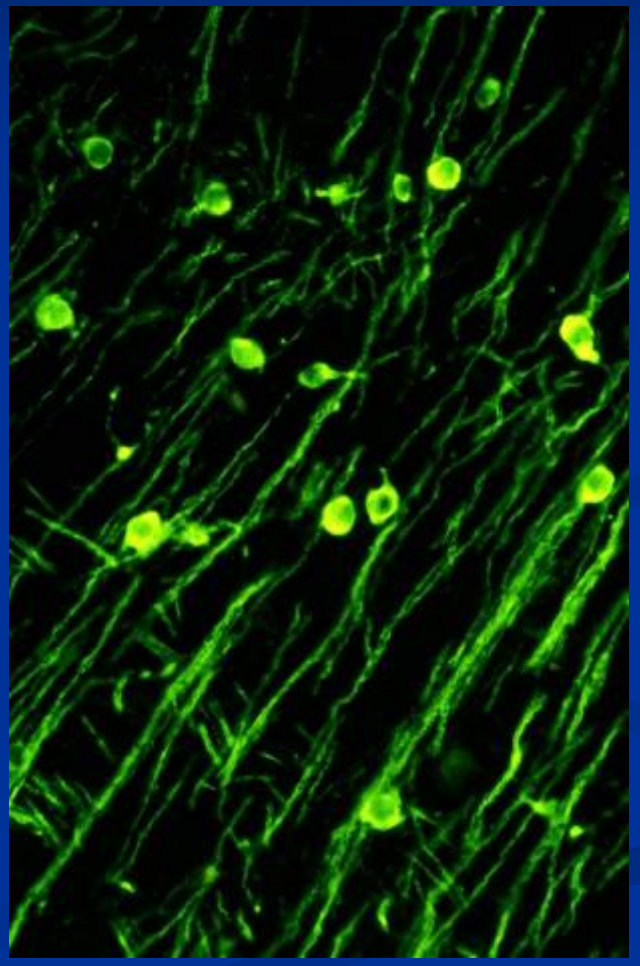
PNS MYELIN



CNS
MYELIN

CNS MYELIN
oligodendrocytes





DISEASES OF MYELIN

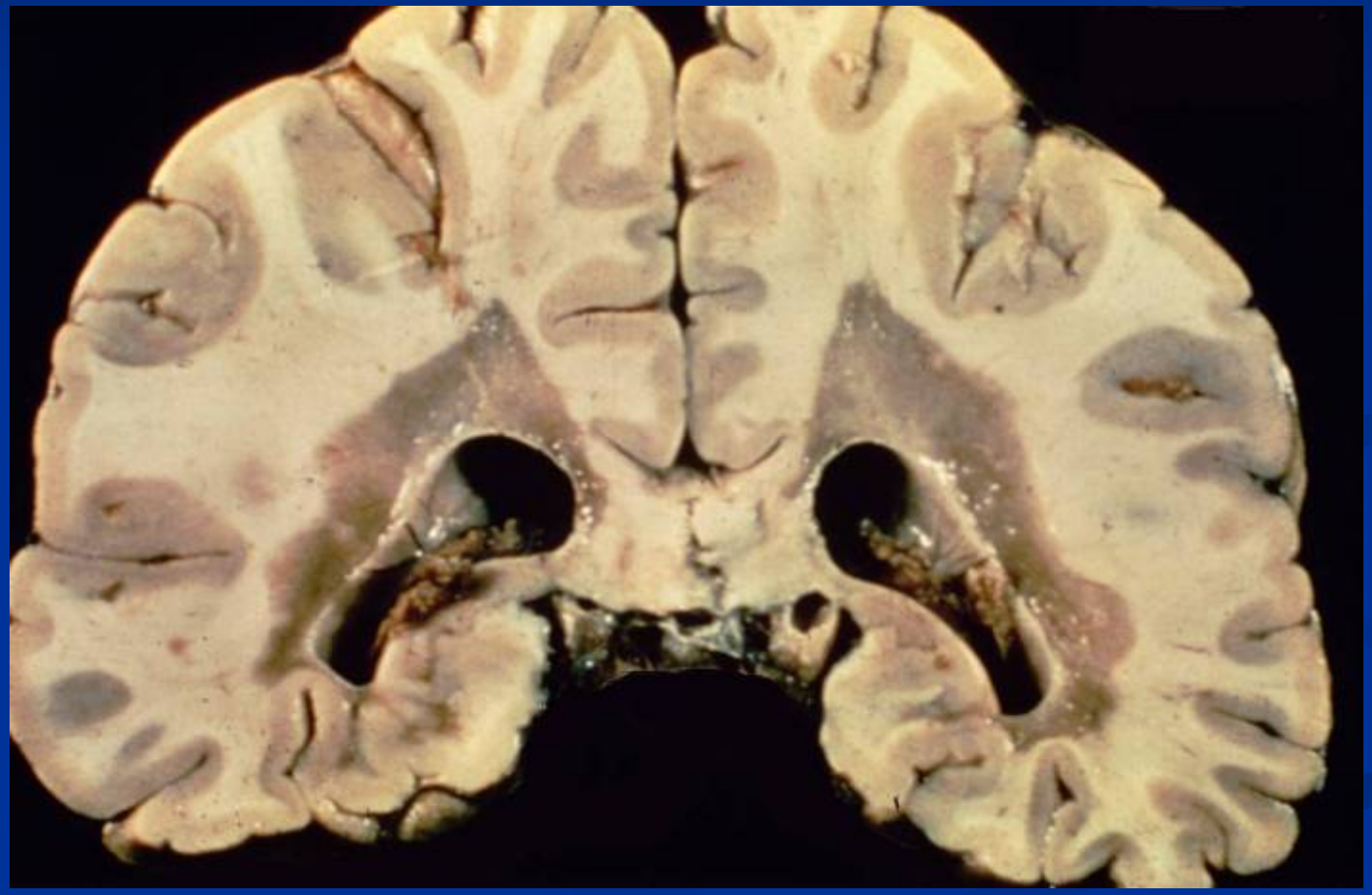
- DEMYELINATING DISEASES:
- Acquired disorders of myelin, such as multiple sclerosis.

- DYSMYELINATING DISEASES:
- Genetic disorders of myelin and its turnover, such as leukodystrophies

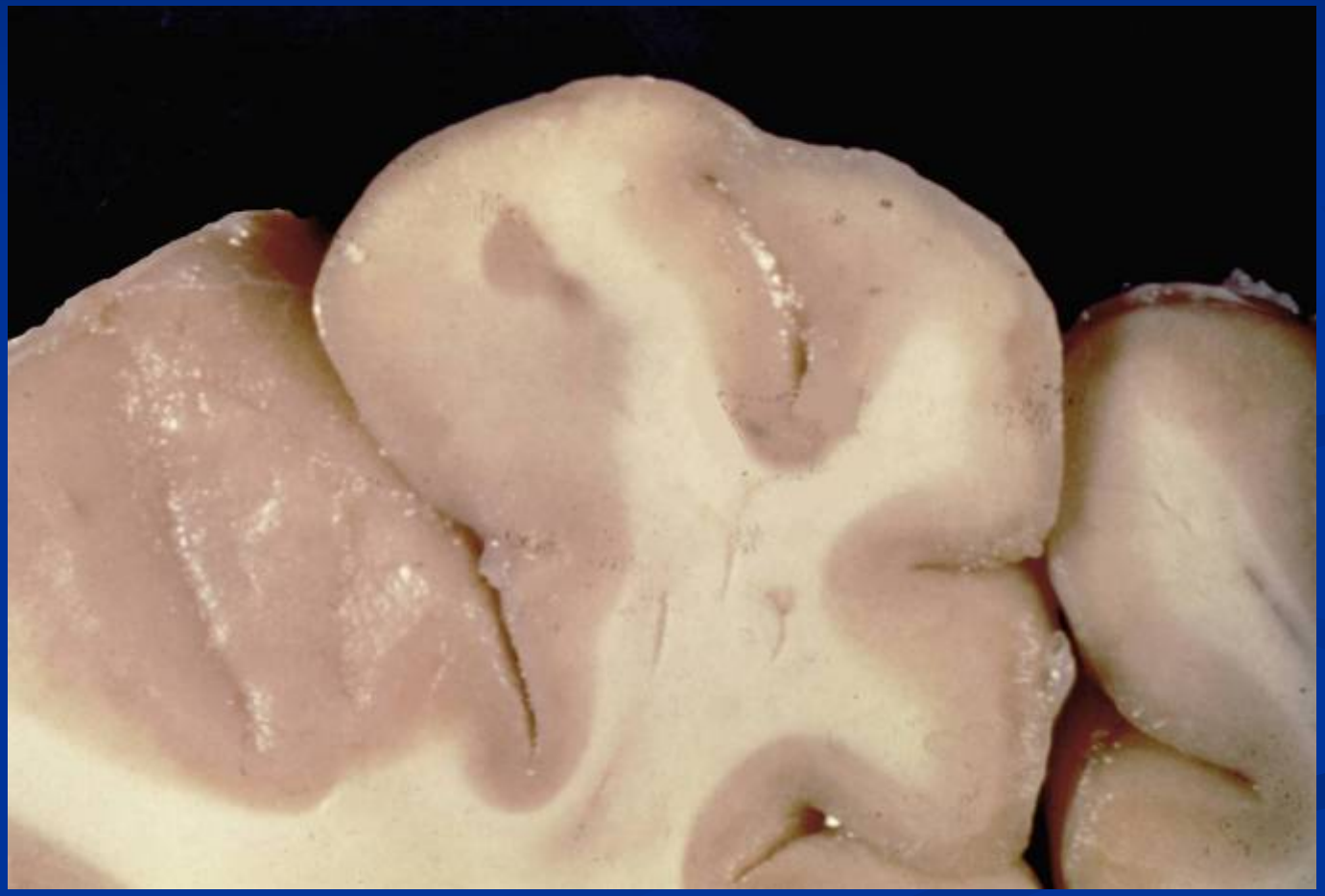
MULTIPLE SCLEROSIS

- Multiple sclerosis is the most common disease of CNS myelin; prevalence of 1:1000.
  - Central nervous system myelin is selectively destroyed (axons are relatively preserved)
  - Onset is frequently in 30 and 40 year old age groups.
  - The disease is typically progressive with relapsing and remitting accumulations of focal neurologic deficits.
  - The etiology is thought to be autoimmune in nature

MULTIPLE SCLEROSIS PLAQUES

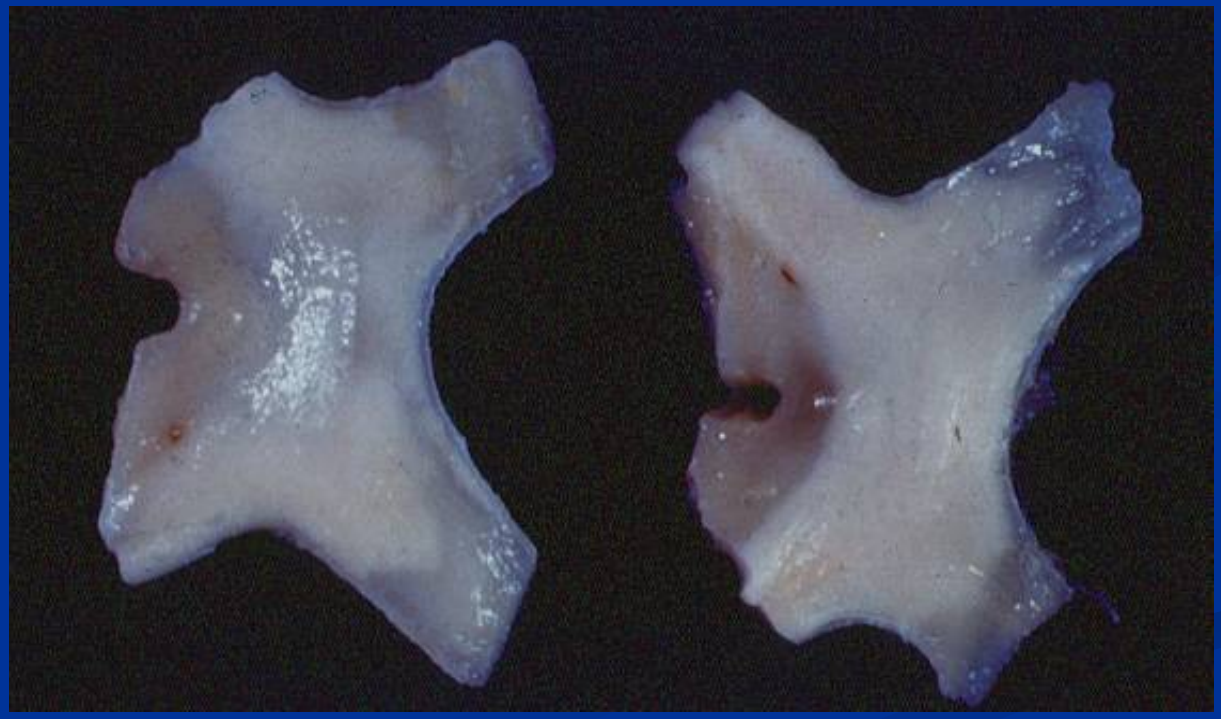


MULTIPLE SCLEROSIS PLAQUE

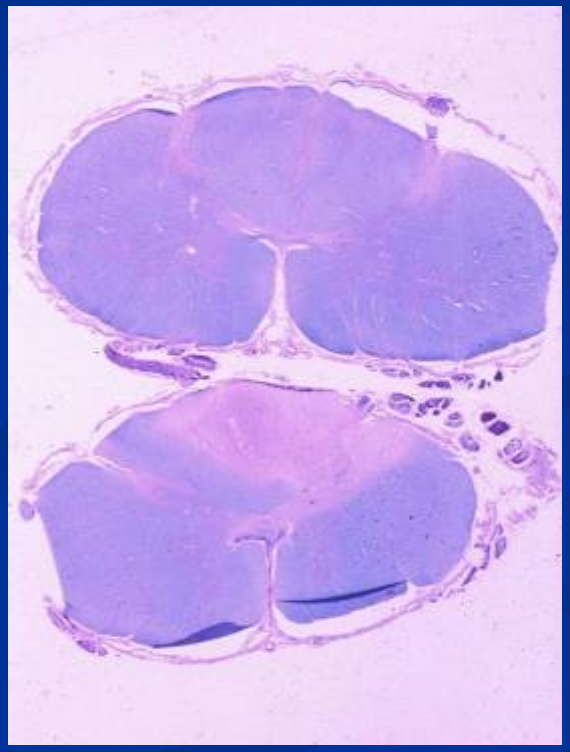


MULTIPLE SCLEROSIS PLAQUES

optic chiasm

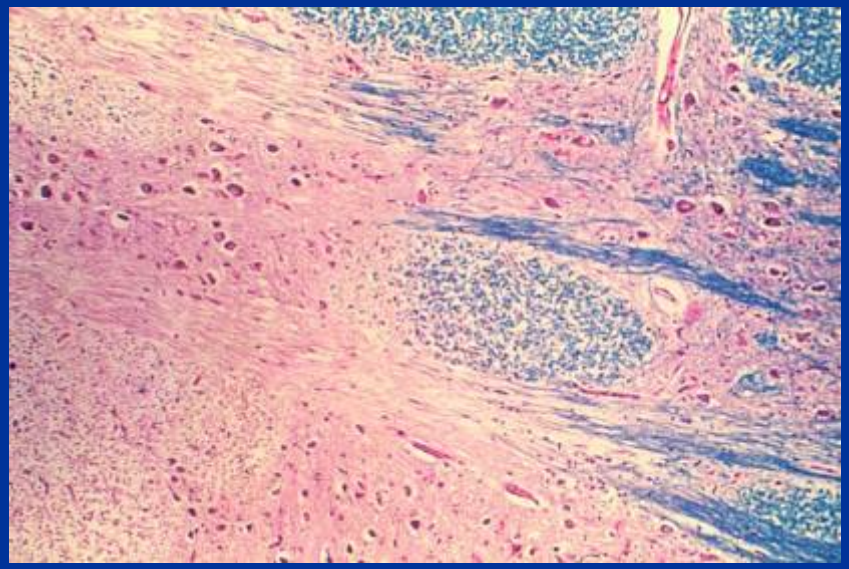


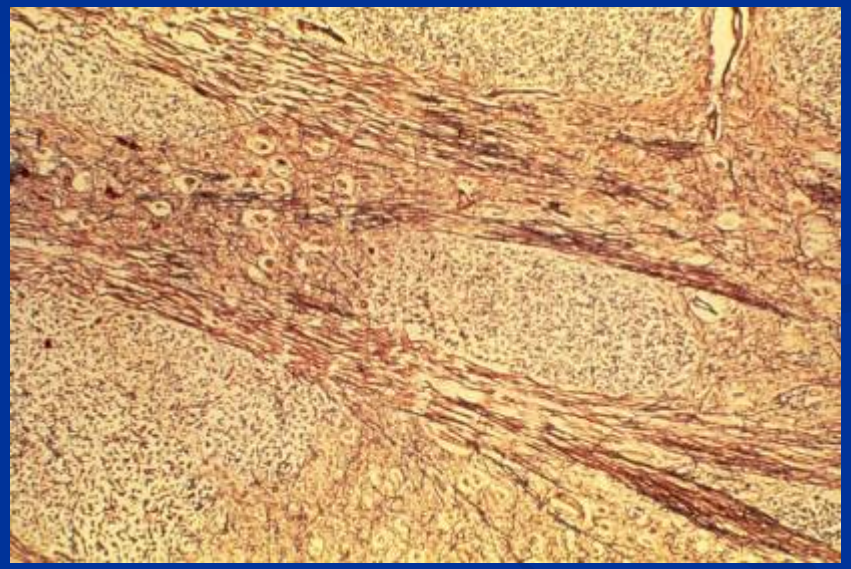
MULTIPLE SCLEROSIS PLAQUES



PONTINE MS PLAQUE

adjacent sections for myelin and axons

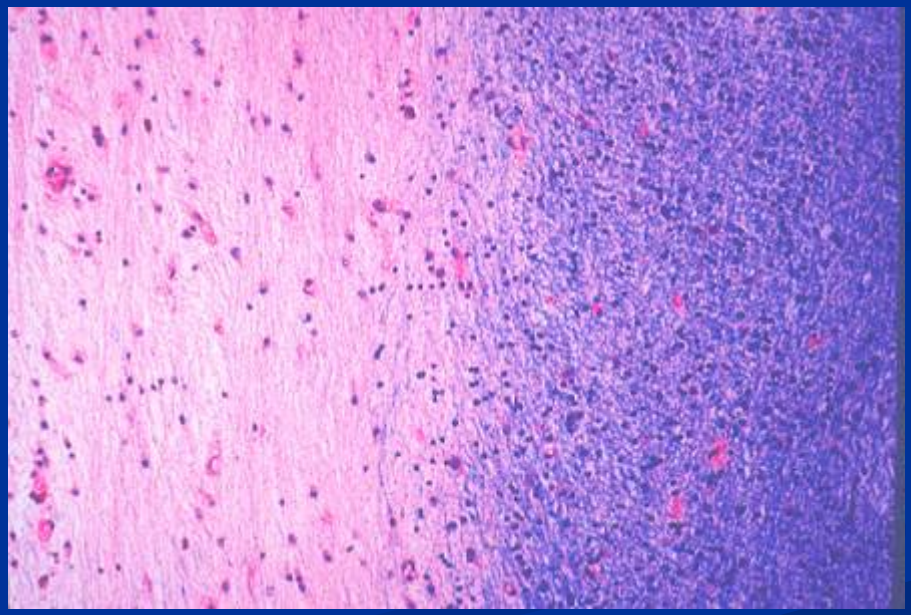




- Luxol fast-blue-PAS

Bielschowsky

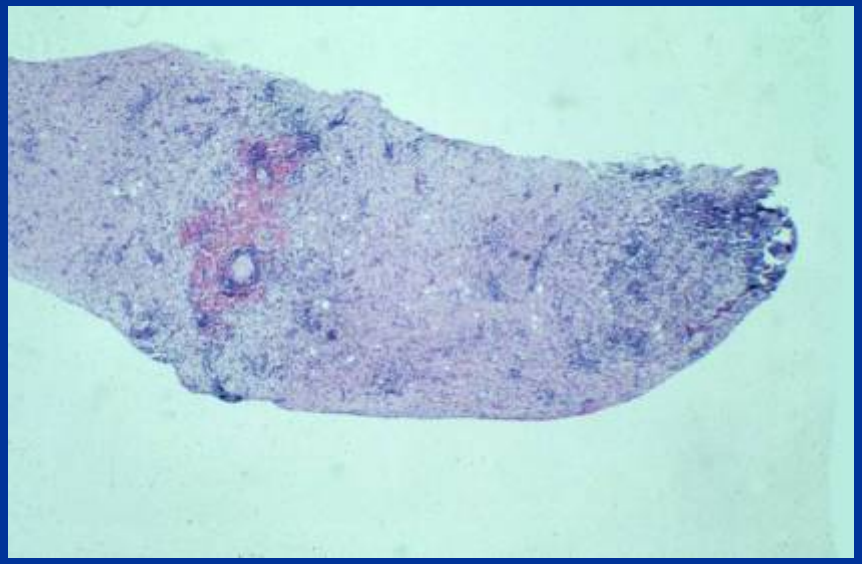
MULTIPLE SCLEROSIS PLAQUE
sharp circumscription



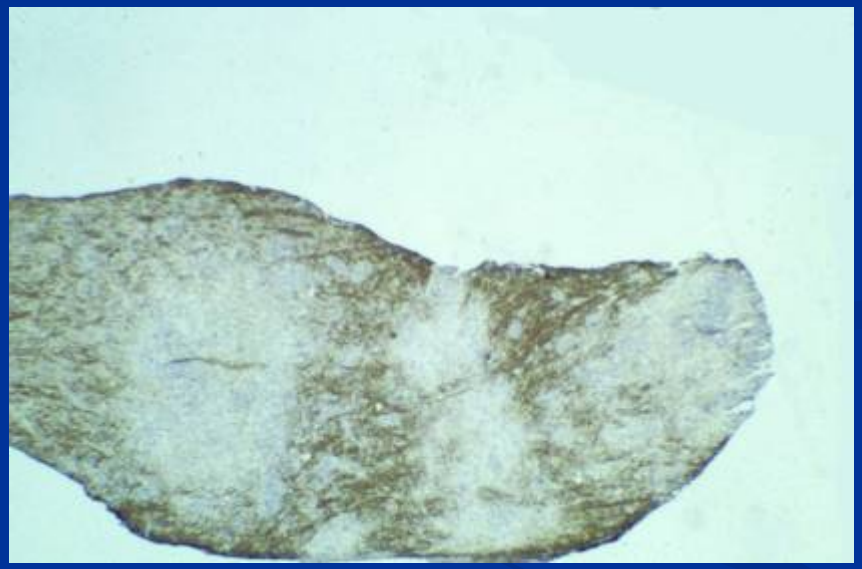
ACUTE DISSEMINATED ENCEPHALOMYELITIS

- Post- or parainfectious encephalomyelitis:
  - following a viral infection
- Postvaccinial encephalomyelitis:
  - Pasteur rabies and smallpox vaccination
  - Akin to EAE (experimental allergic enceph.)
- ADE is an acute, monophasic illness
- Pathology:
  - Perivenous lymphocytic infiltrates with demyelination
- Autoimmune mechanism

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

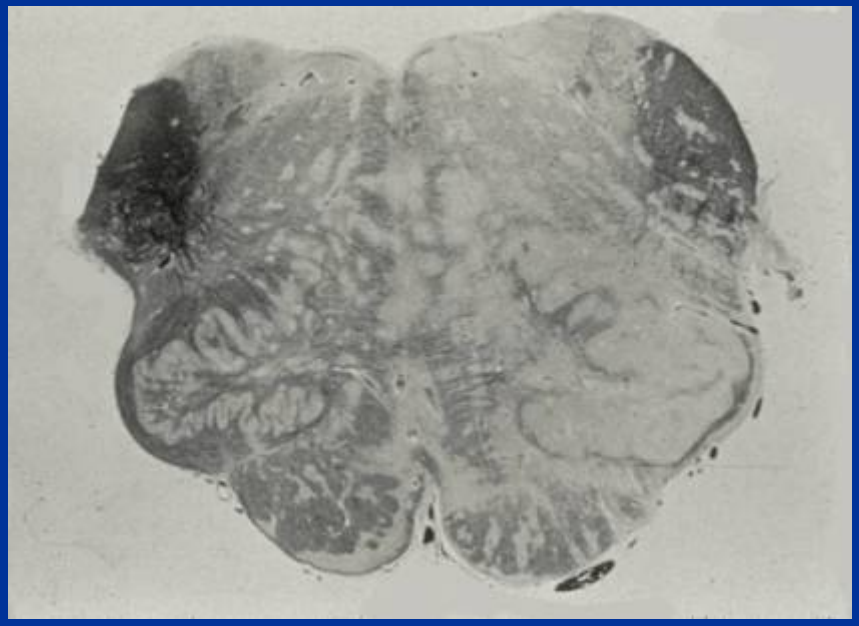


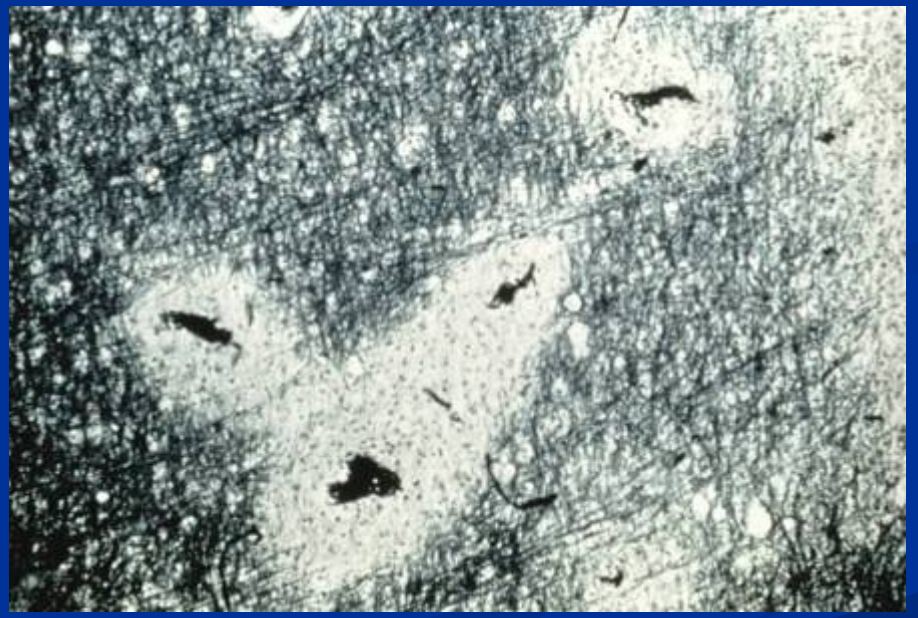
H & E



Myelin basic protein IHC

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)





Myasthenia Gravis

- An autoimmune neuromuscular disease that results from autoantibodies at the neuromuscular junction.
  - Characterized by variable weakness of voluntary muscles (eye muscles may be weak)
  - Worsens with activity (and late in the day)
- May be associated with other autoimmune disorders such as thyroid disease, rheumatoid arthritis and SLE
- Often associated with a thymoma, removal of the thymoma may be curative.

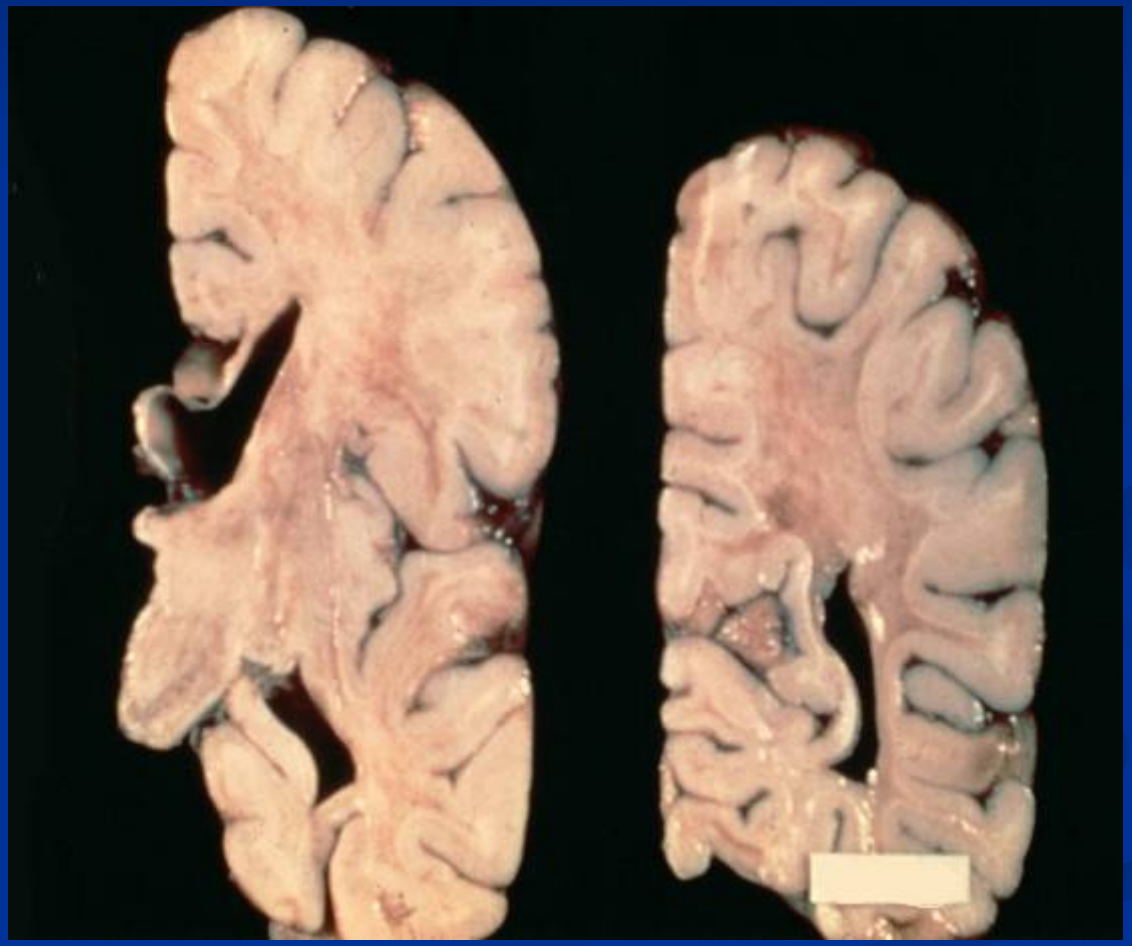
LEUKODYSTROPHIES

- CLINICAL: A variety of inherited diseases with variable age of onset (usually in childhood) and rate of progression, which typically result in diffuse severe dysfunction.
- PATHOGENESIS: Recessive mutations in proteins related to myelin structure or metabolism
- The peripheral nervous system also may be involved in a number of forms

PATHOLOGY OF LEUKODYSTROPHIES

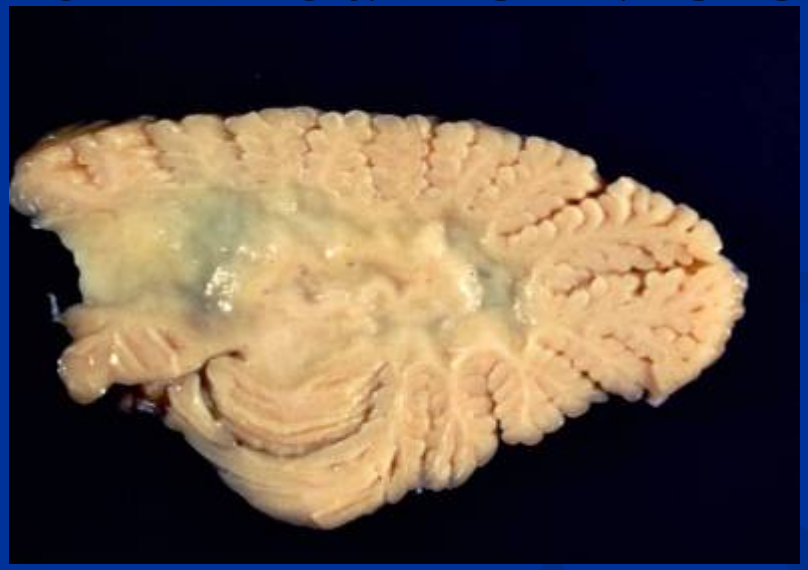
- Demyelination in large confluent foci within the cerebral hemispheres and other sites
- GENERAL:
  1. Loss of myelin and oligodendroglia
  2. Relative preservation of axons
- DISEASE SPECIFIC:
  1. Globoid cells (Krabbe's disease)
  2. Metachromatic material in macrophages and neurons (metachromatic leukodystrophy, aryl sulfatase deficient)
  3. Adrenal atrophy and cytosomal inclusions (ALD, peroxisomal abnormality)

METACHROMATIC LEUKODYSTROPHY



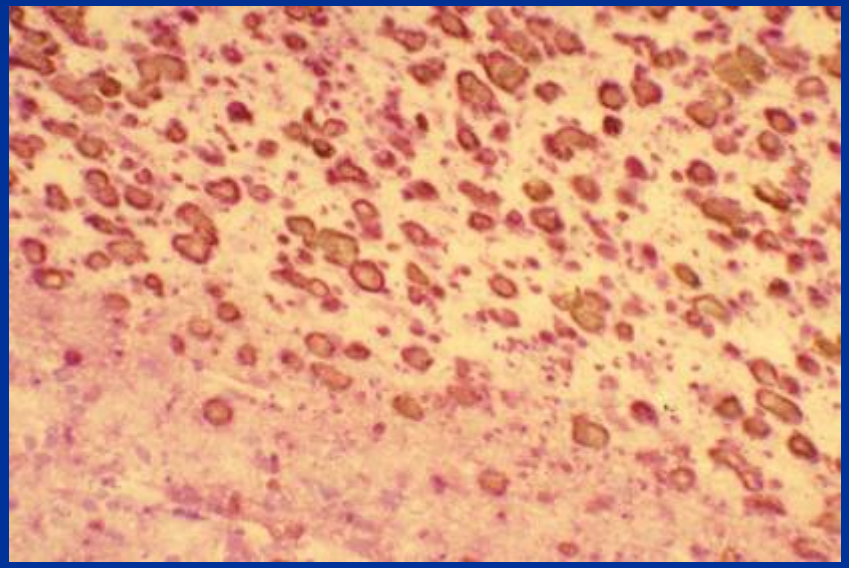
METACHROMATIC LEUKODYSTROPHY

sparing of subcortical arcuate fibers

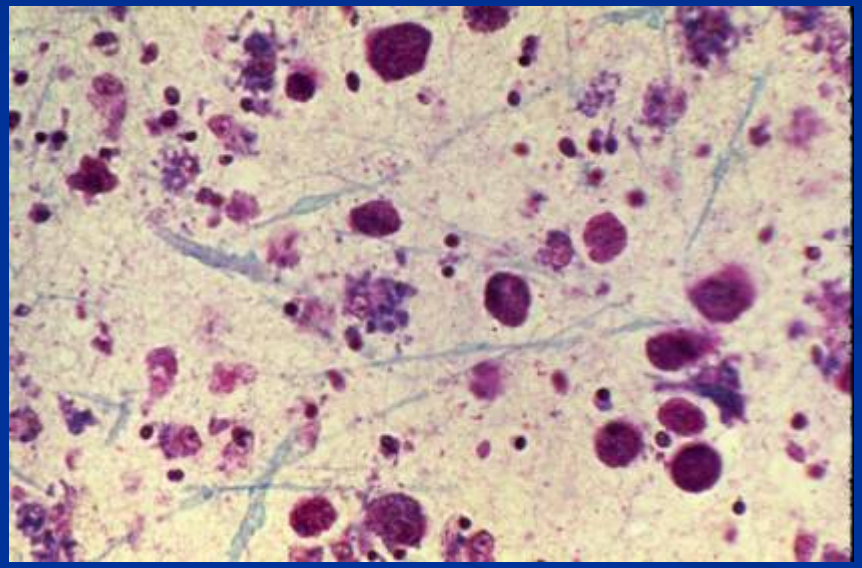


METACHROMATIC LEUKODYSTROPHY

(aryl sulfatase deficiency)

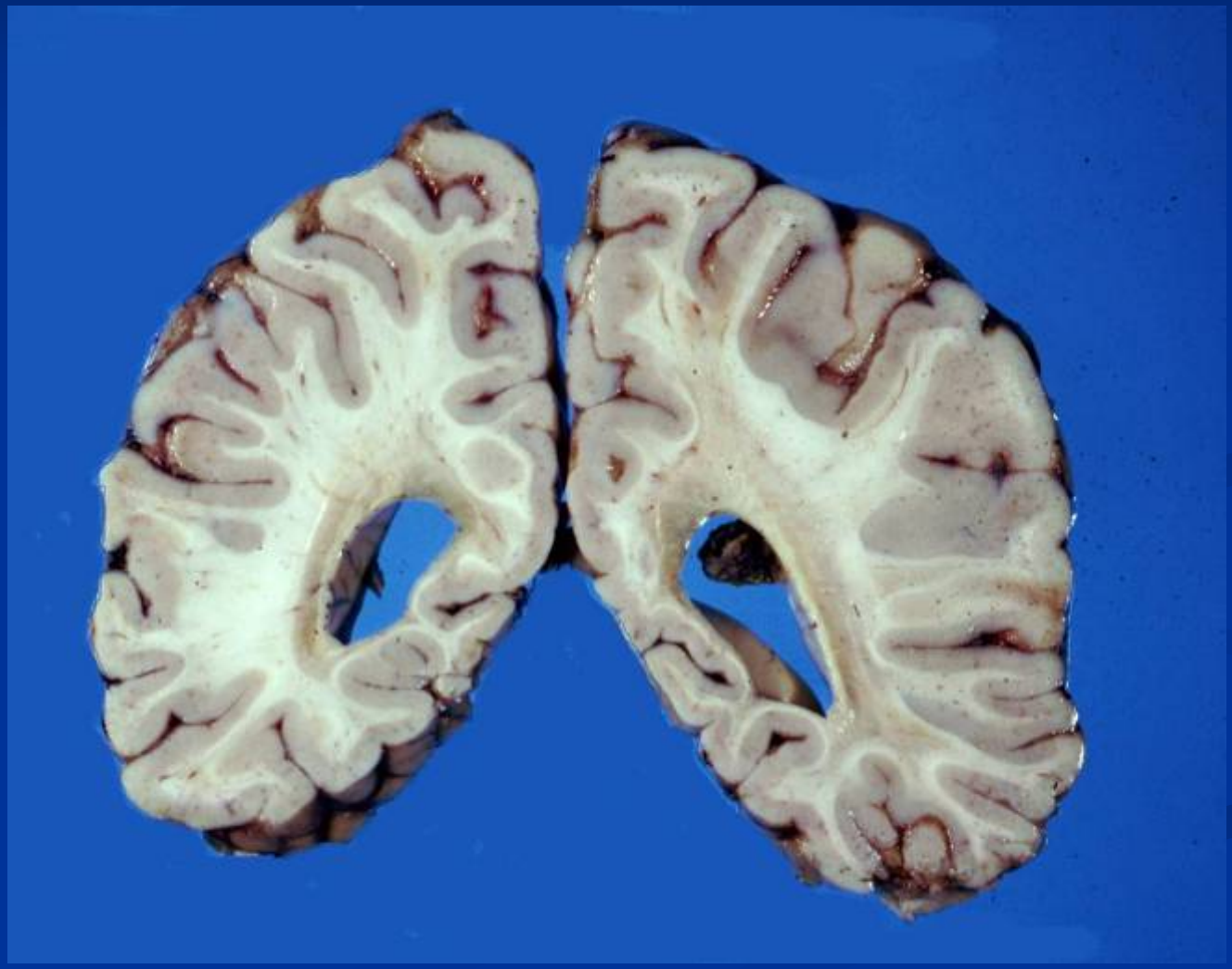


Acidified cresyl violet metachromasia



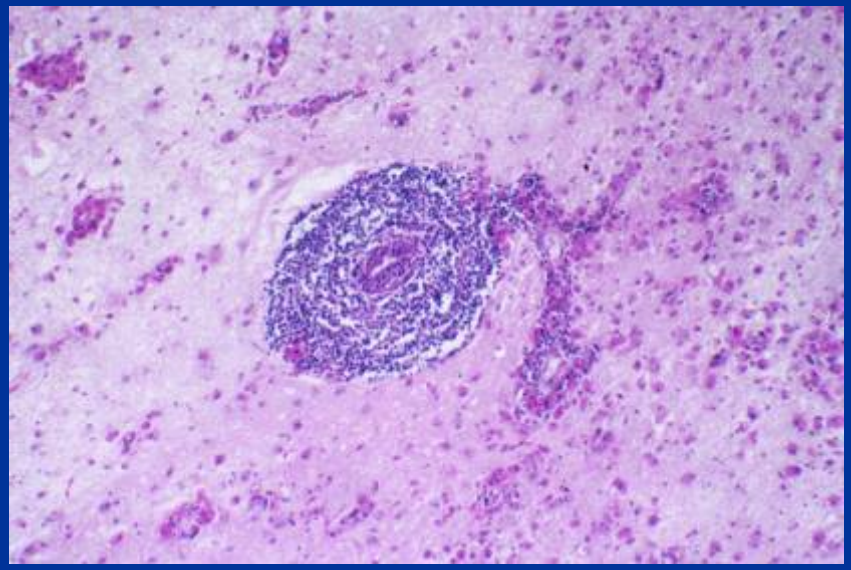
LFB-PAS

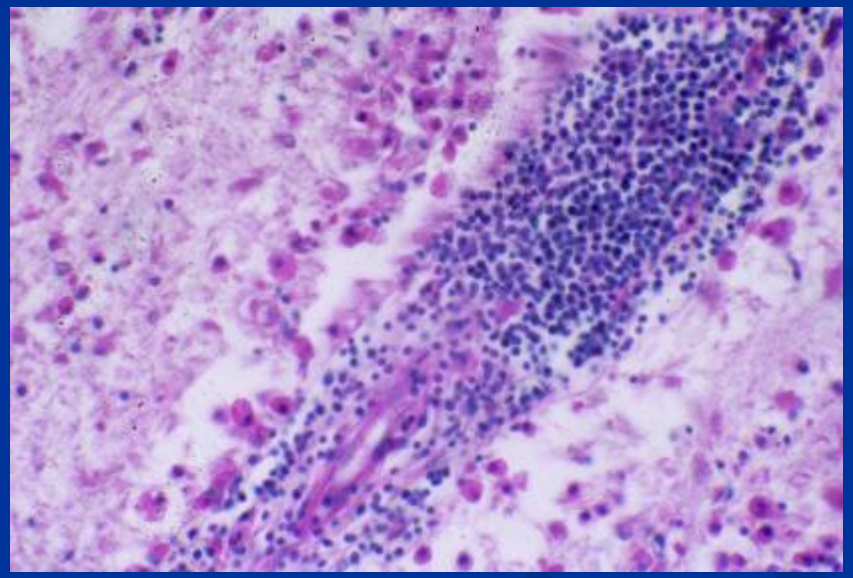
ADRENOLEUKODYSTROPHY



ADRENOLEUKODYSTROPHY

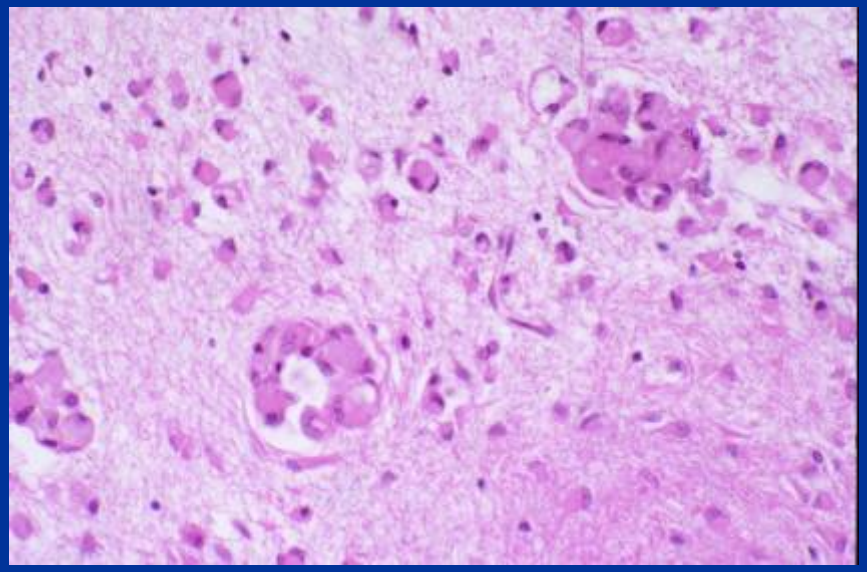
lymphocytic infiltrates

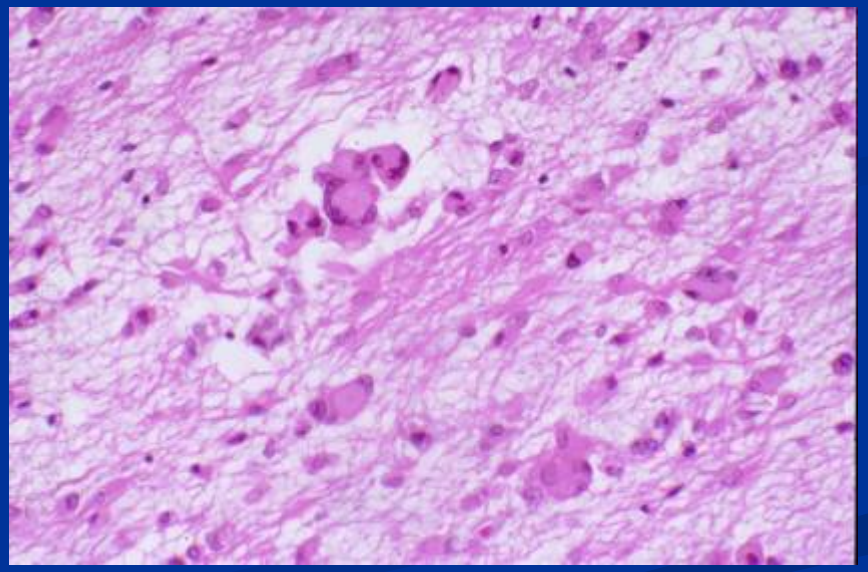




KRABBE'S DISEASE (GLOBOID CELL LEUKODYSTROPHY)

cerebroside-β-galactosidase deficiency



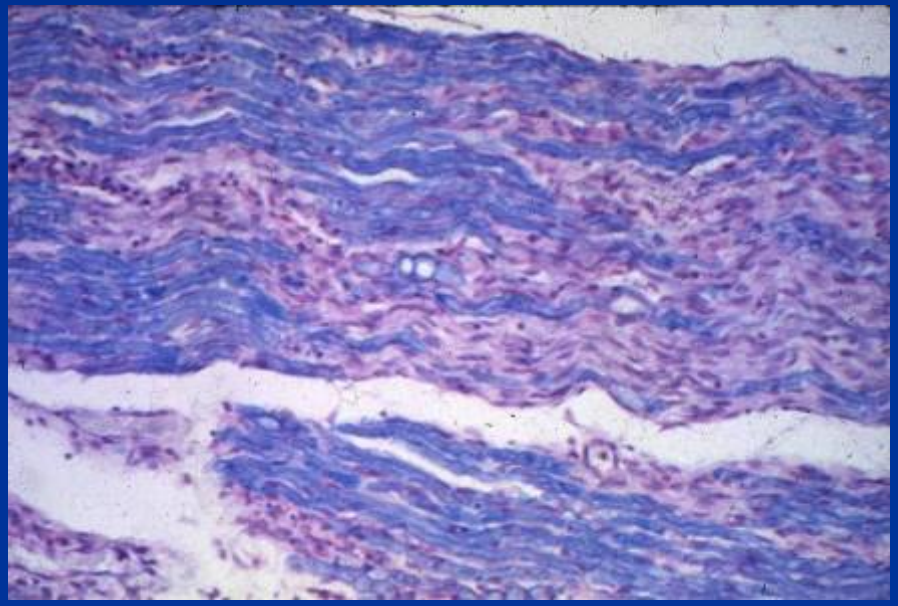


DISEASES OF PERIPHERAL NERVE

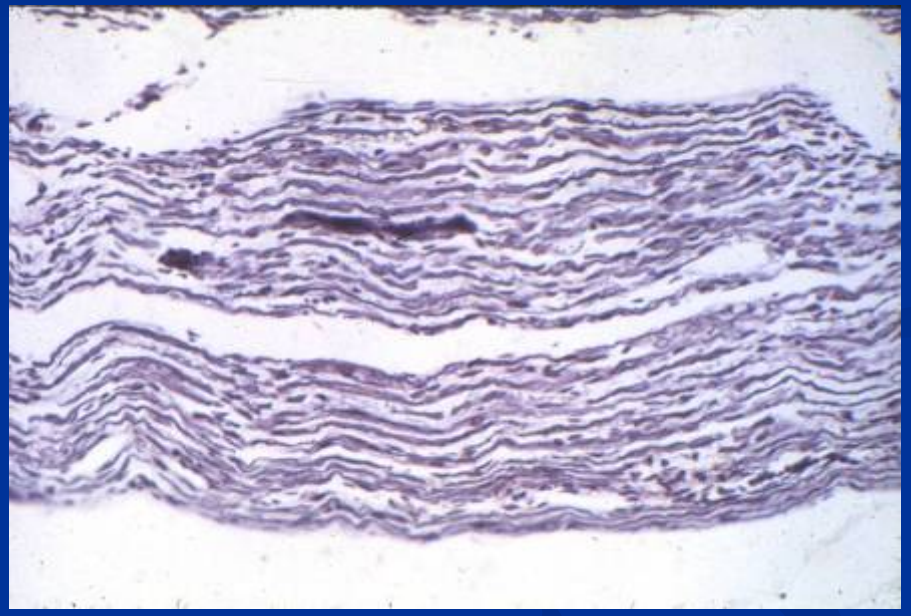
CLASSIFICATION BY PATHOLOGY

- Demyelinating neuropathies
  - Guillain-Barre-Landry syndrome
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Axonal neuropathies: most neuropathies are axonal but pathology often is nonspecific
  - Examples include hypertrophic neuropathies, herpes zoster, HIV, alcoholic and diabetic neuropathies

DEMYELINATING NEUROPATHY
GUILLAIN-BARRE-LANDRY

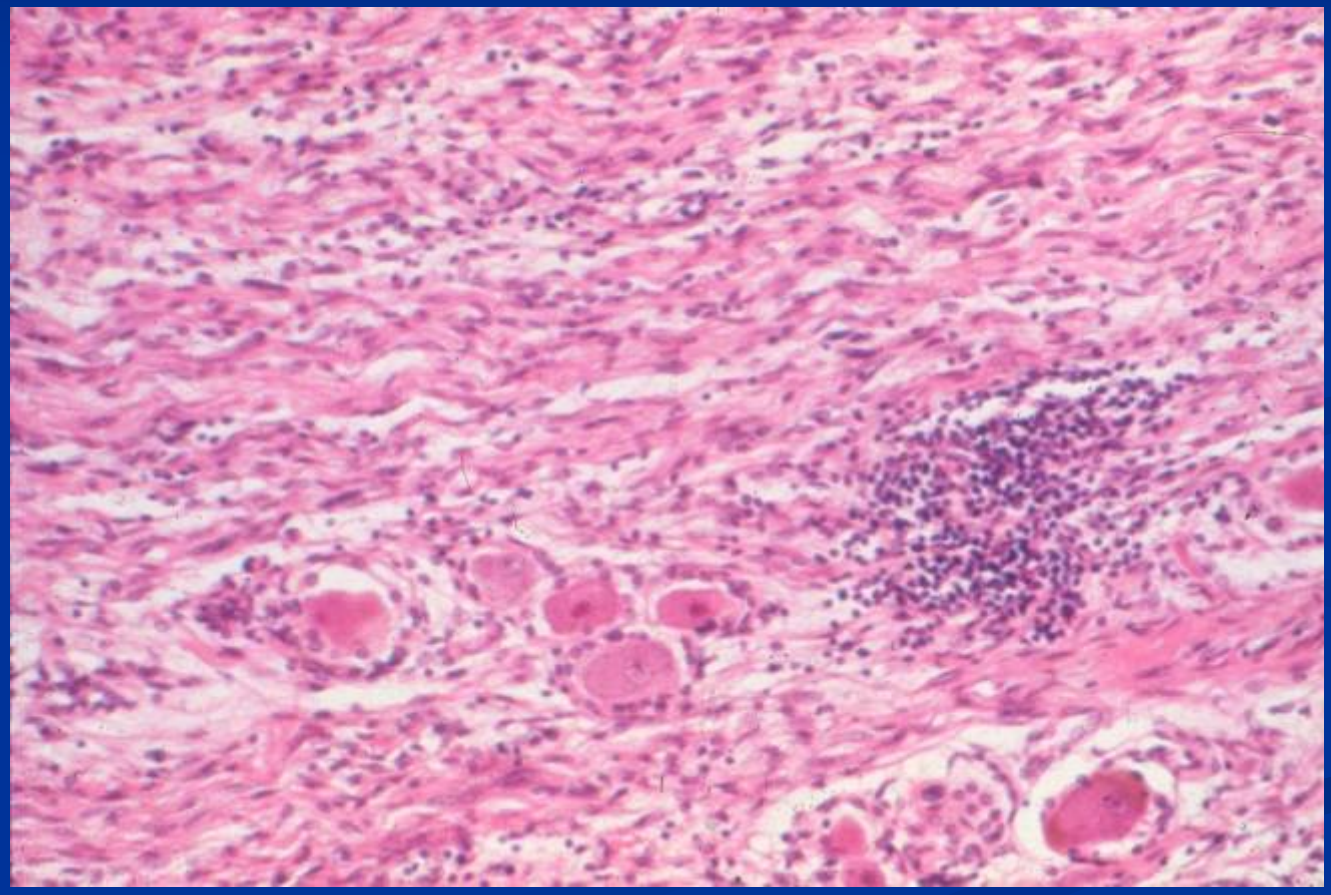


LFB-PAS



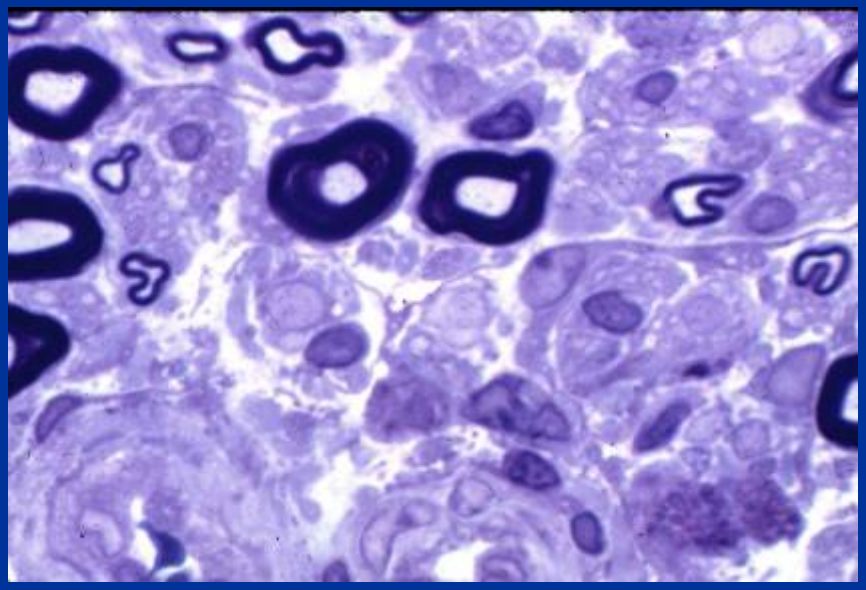
Silver stain

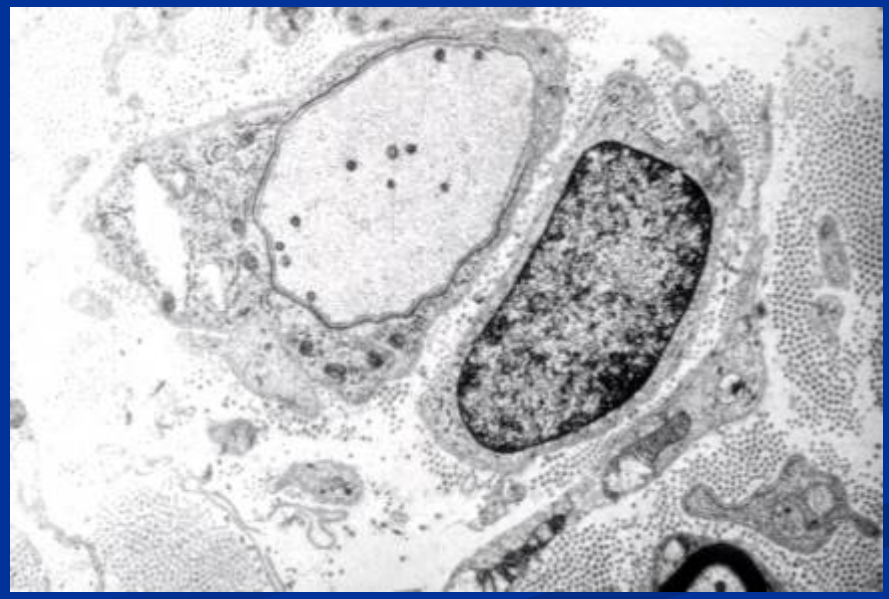
DEMYELINATING NEUROPATHY
GUILLAIN-BARRE-LANDRY
inflammatory demyelination



DEMYELINATING NEUROPATHY GUILLAIN-BARRE-LANDRY

evidence of remyelination





Summary: Demyelinating/Dysmyelinating diseases

- Demyelinating disease: most common is MS, acute disseminated encephalomyelitis (rare, follows viral infection, vaccination)
- Leukodystrophies: Genetic diseases (many enzyme abnormalities are defined) resulting in myelin loss, occur early in life.
- Peripheral nerve demyelination: Guillain-Barre Syndrome, autoimmune, potential for remyelination with complete recovery

Neurodegenerative diseases

Dementia:

Alzheimer's disease, Pick's disease

Movement Disorders:

Parkinson's disease, Huntington's disease, Multiple Systems Atrophy

Motor Disease:

ALS, Werdnig-Hoffman, Poliomyelitis

Prion disease

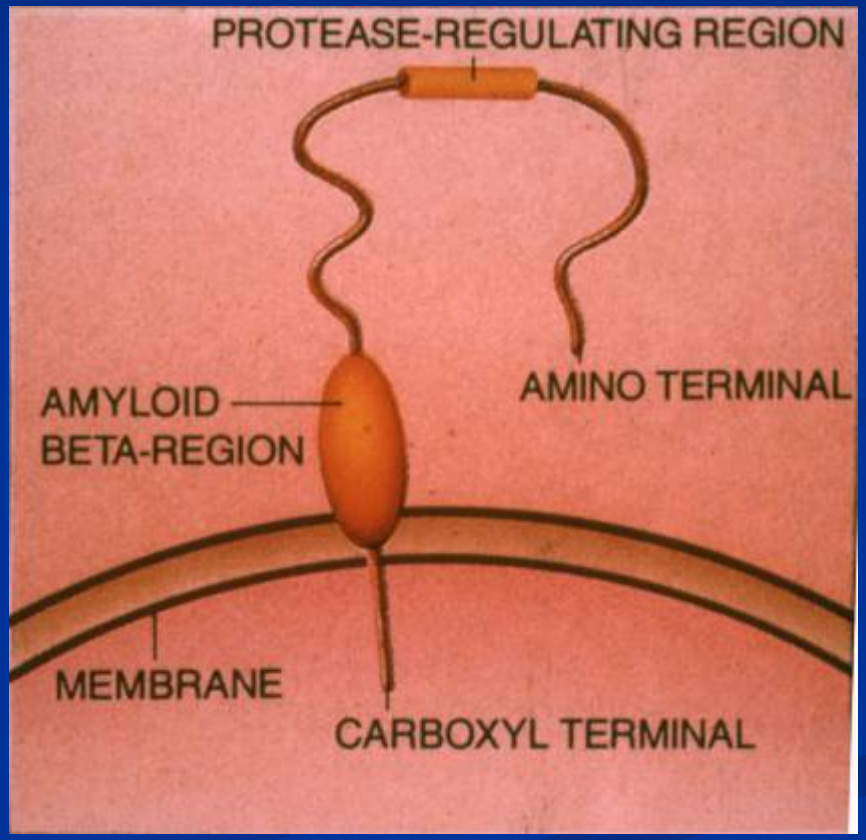
Alzheimer's disease: Clinical features

- Clinical features of dementia
  - **Impairment of recent memory**
  - Aphasia (naming), apraxia (motor), agnosia (object), executive functioning
  - Impaired level of function
  - Progressive over time
  - 47% of people over 85 years of age are affected

Alzheimer's disease: Pathogenesis

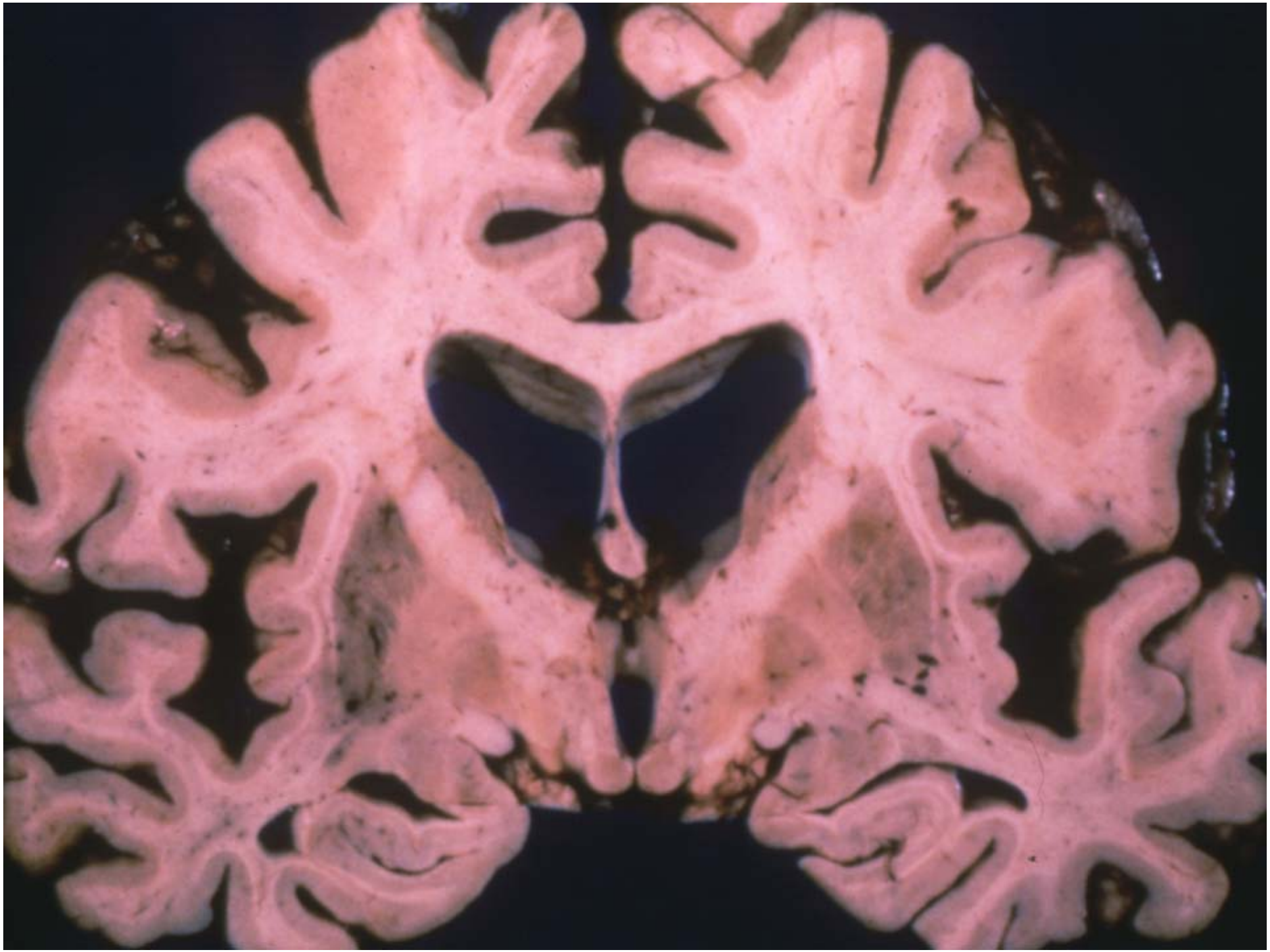
- The amyloid hypothesis:

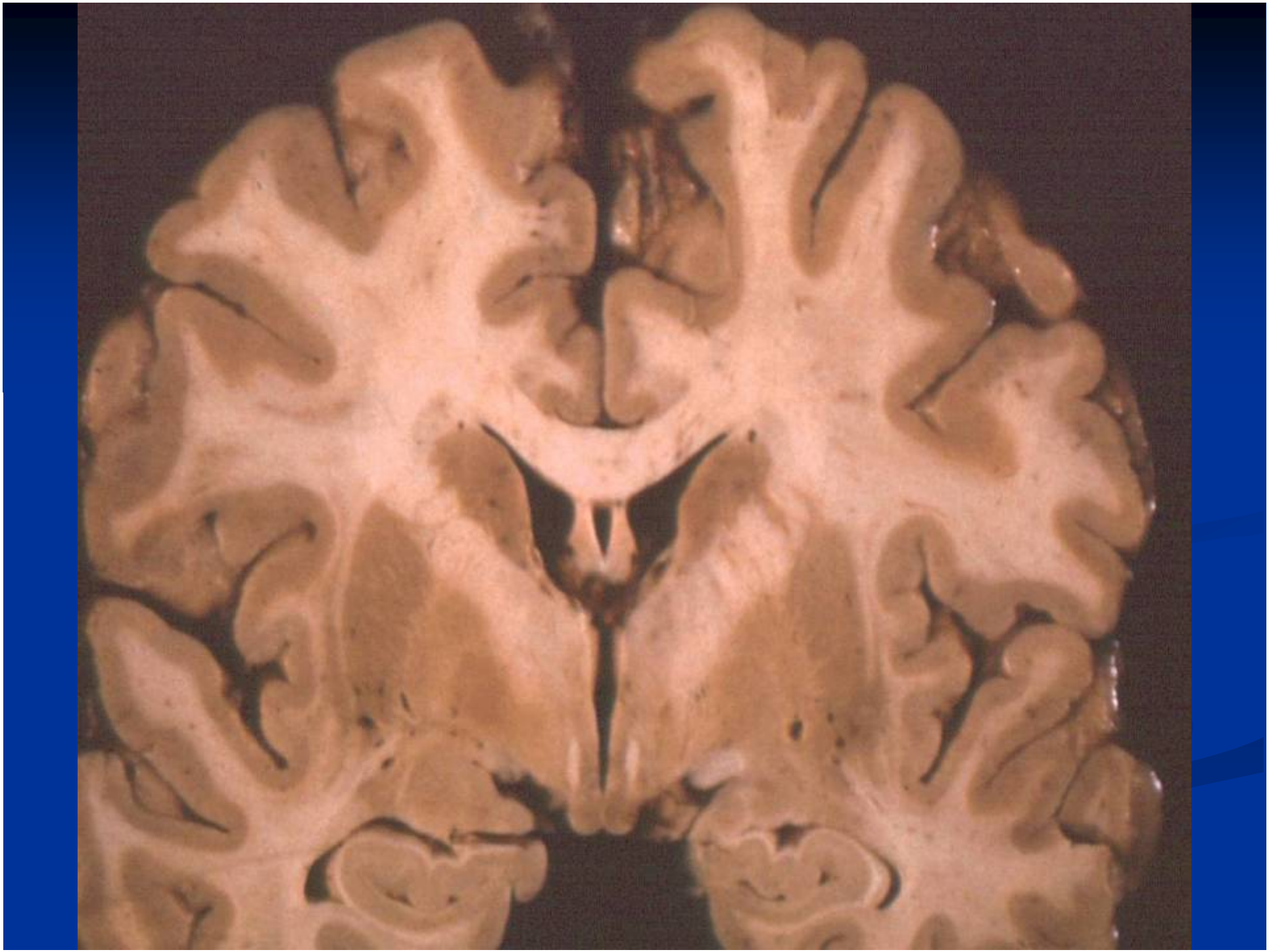
Abnormal APP processing leads to deposits of insoluble B-pleated amyloid protein

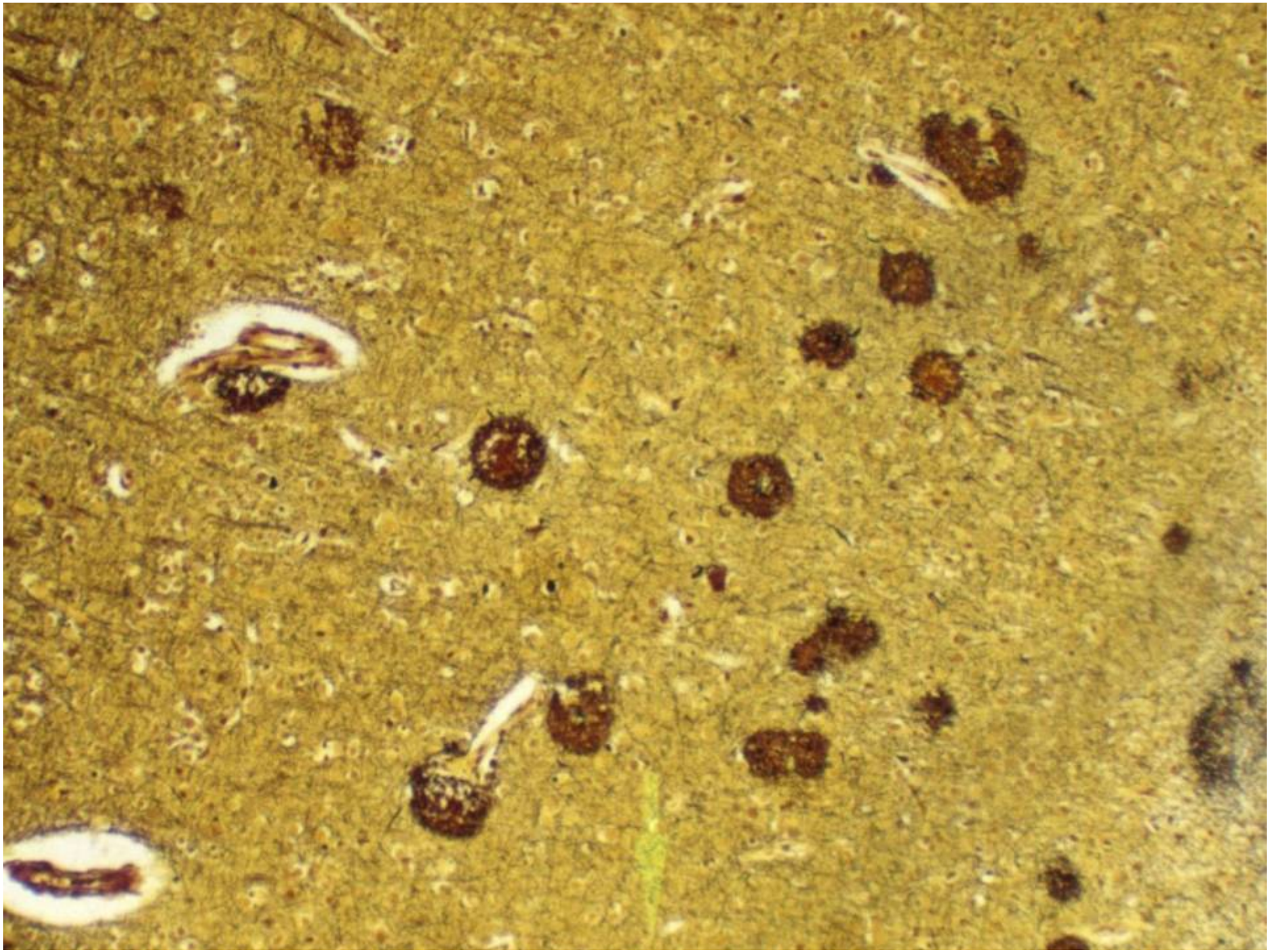


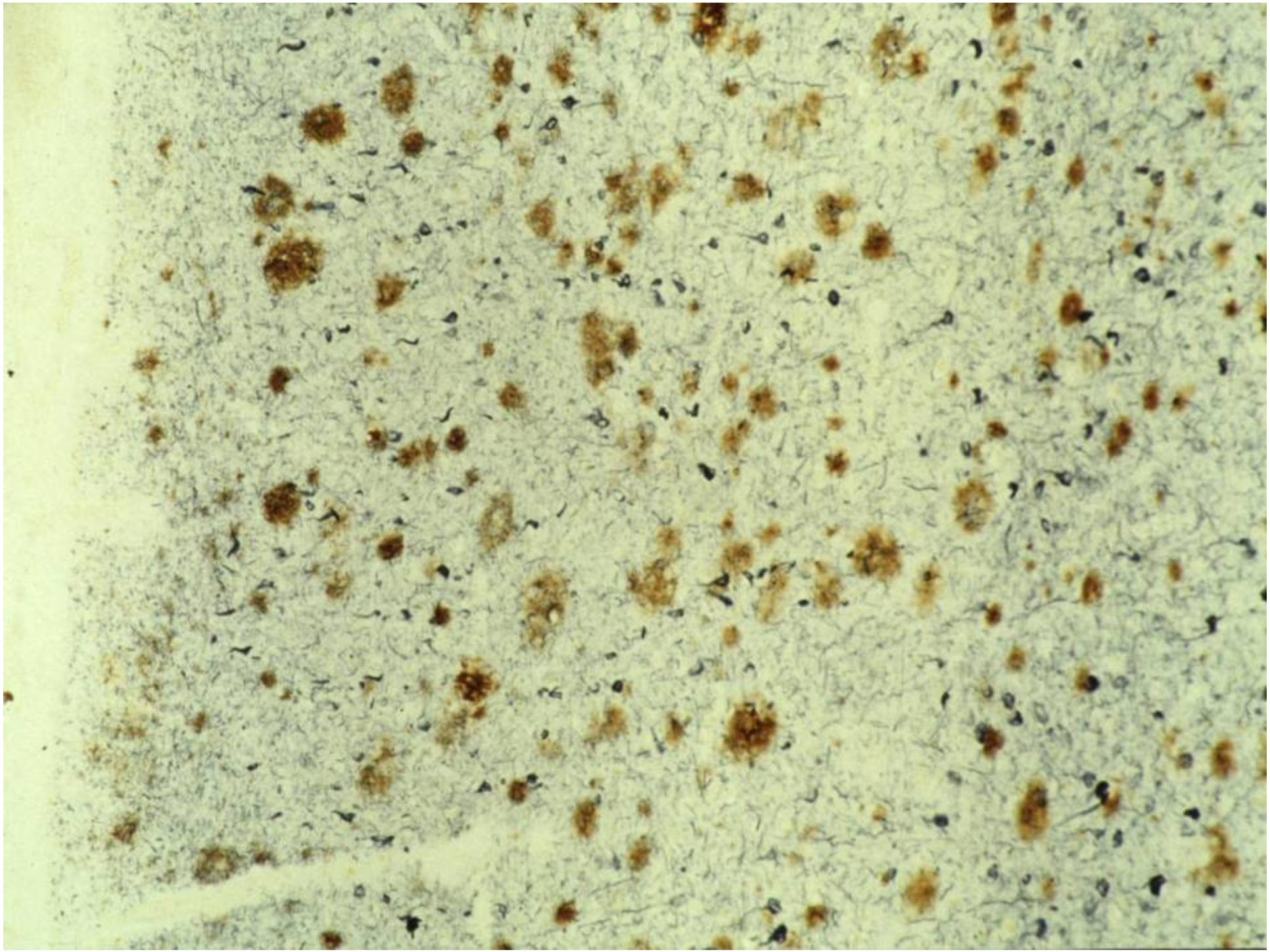
Alzheimer's disease: Gross and microscopic features

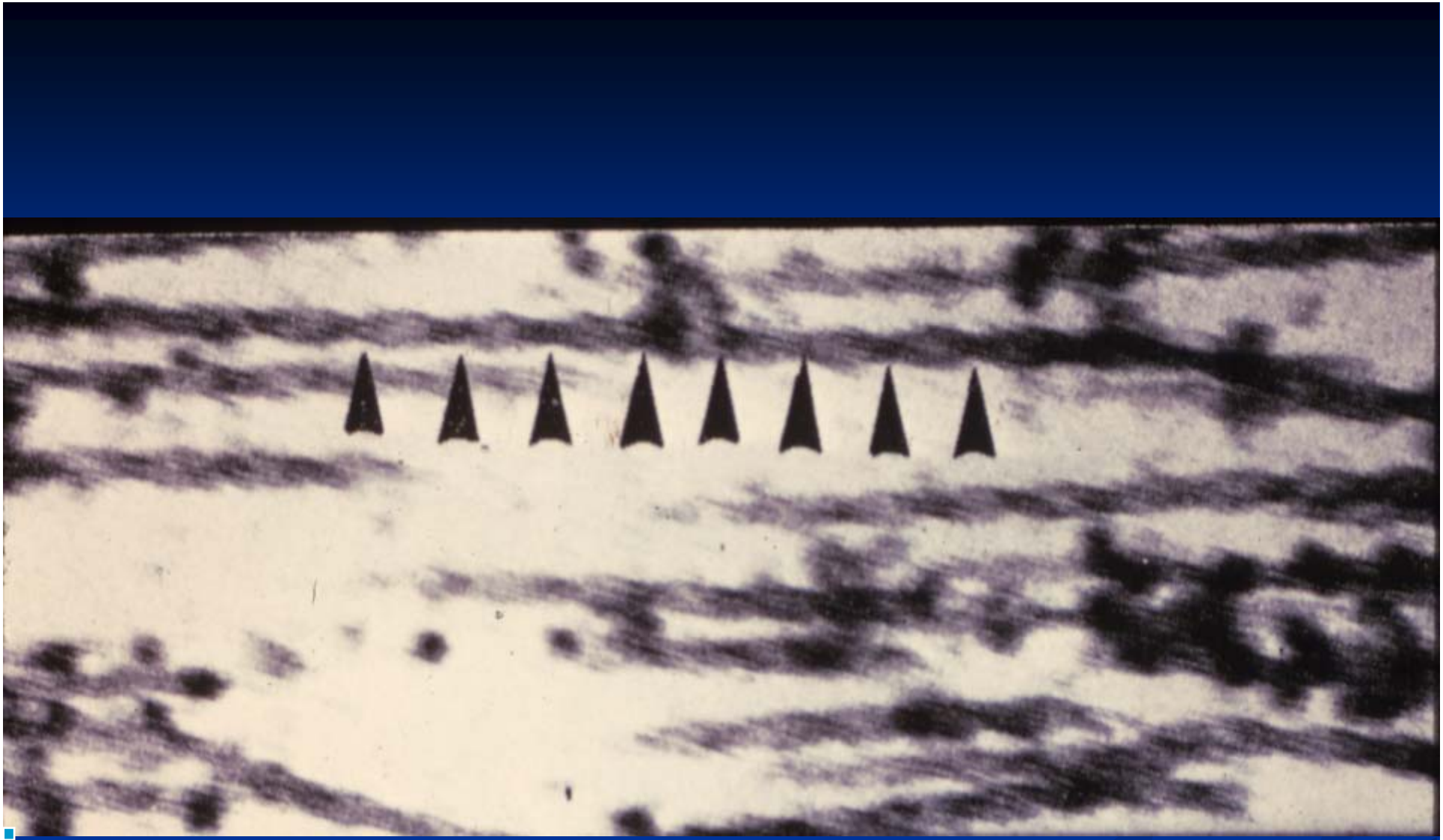
- **Gross brain atrophy: neuronal loss**
- **Neuritic (senile) plaques** containing **B-amyloid**
- **Neurofibrillary tangles** composed of phosphorylated microtubule associated **tau protein**
- **Cerebral amyloidosis**











Other Dementias

- Dementia with Lewy bodies
  - Second most common neurodegenerative cause of dementia
  - Lewy bodies and neurodegeneration affect brainstem and cortex
- Pick's disease and other frontal temporal dementias
  - Classification depends on histologic examination and is complicated

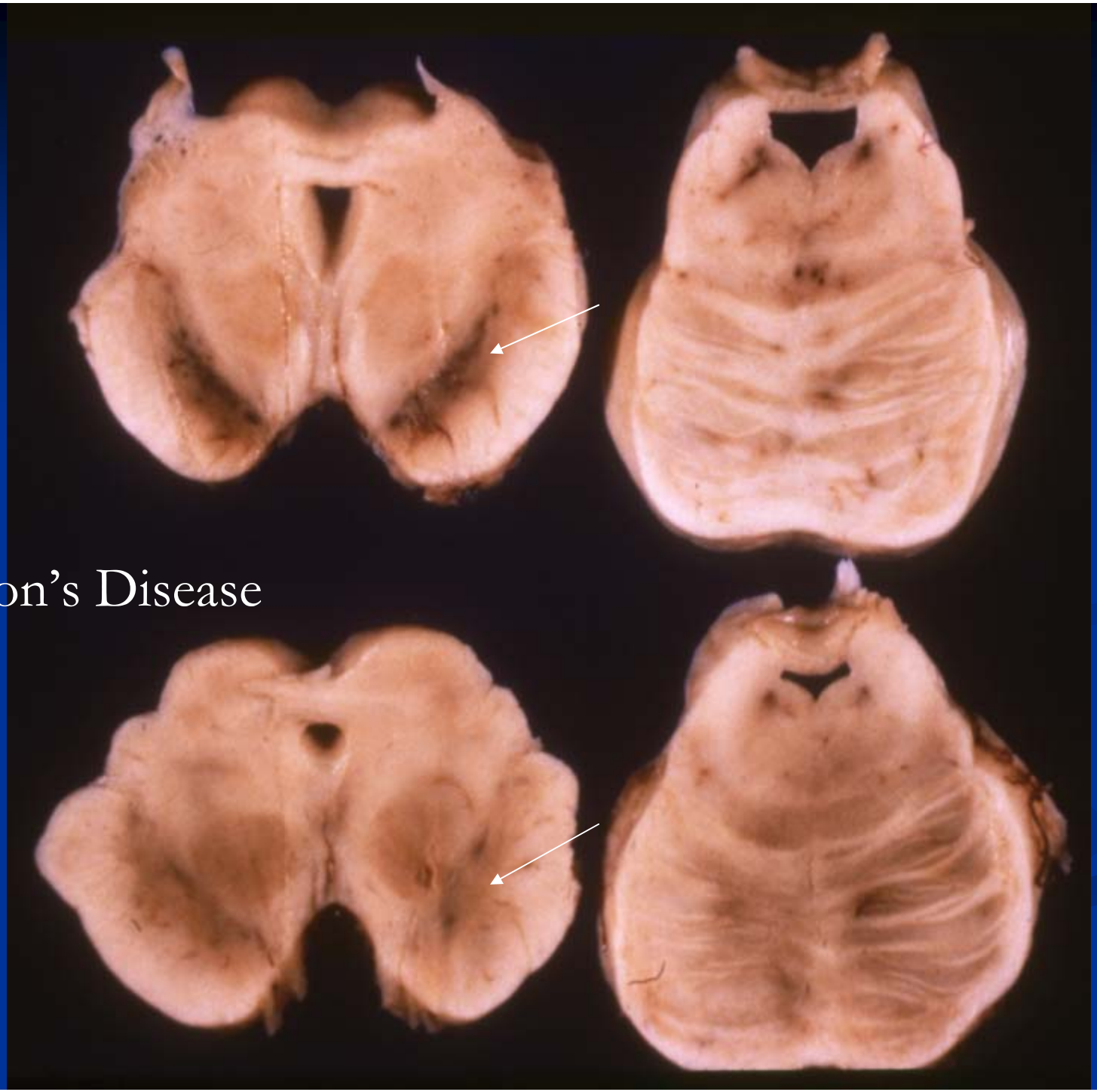
Parkinson's disease: Clinical findings

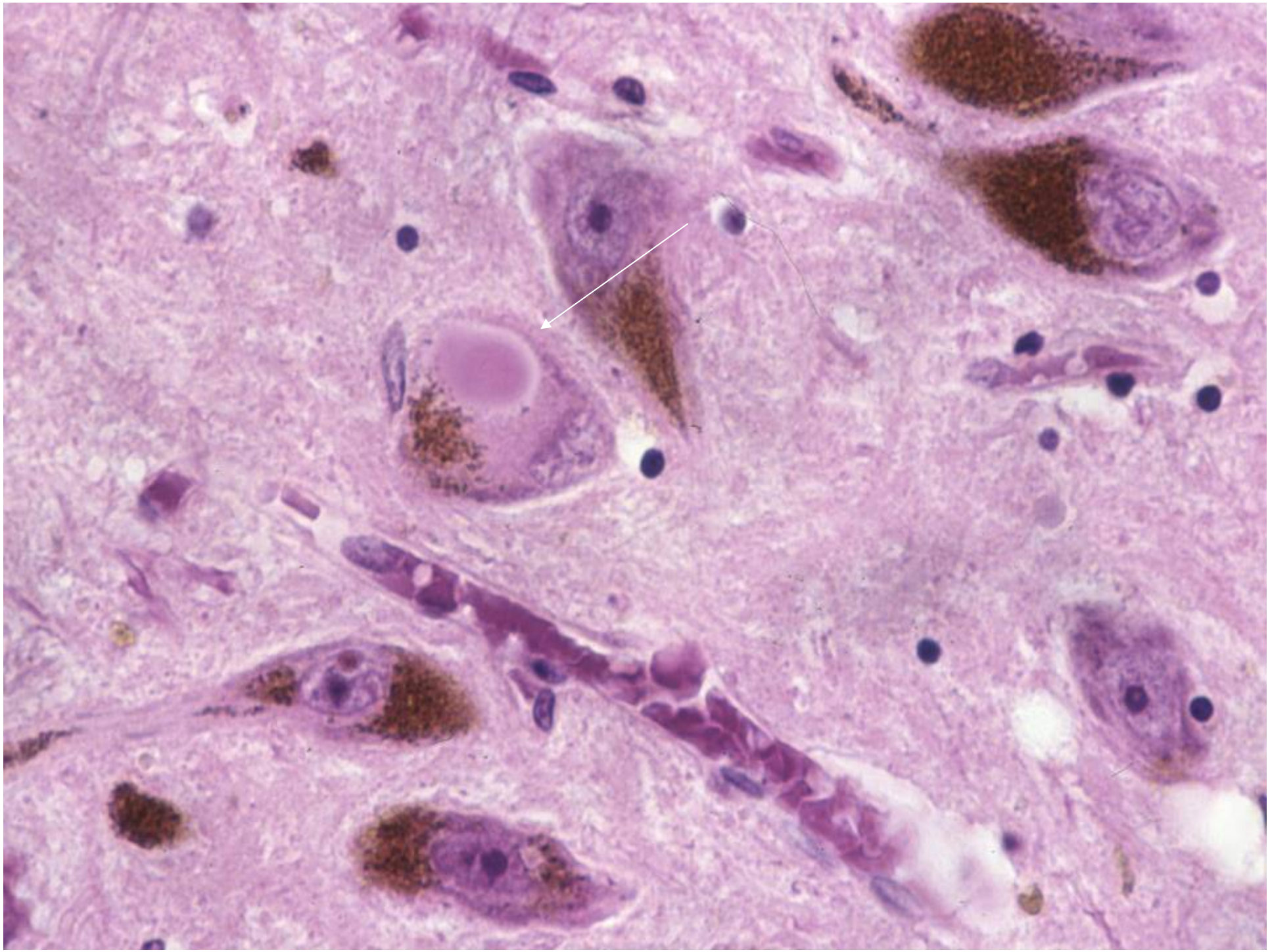
- Idiopathic Parkinson's disease (vs. parkinsonism or parkinsonian syndrome), est 1% of population over 50 years of age
  - **Tremor** (rest)
  - **Rigidity** (cogwheel rigidity)
  - **Bradykinesia** (mask-like facies, loss of arm-swing)
  - Festinating gait (loss of righting reflexes)

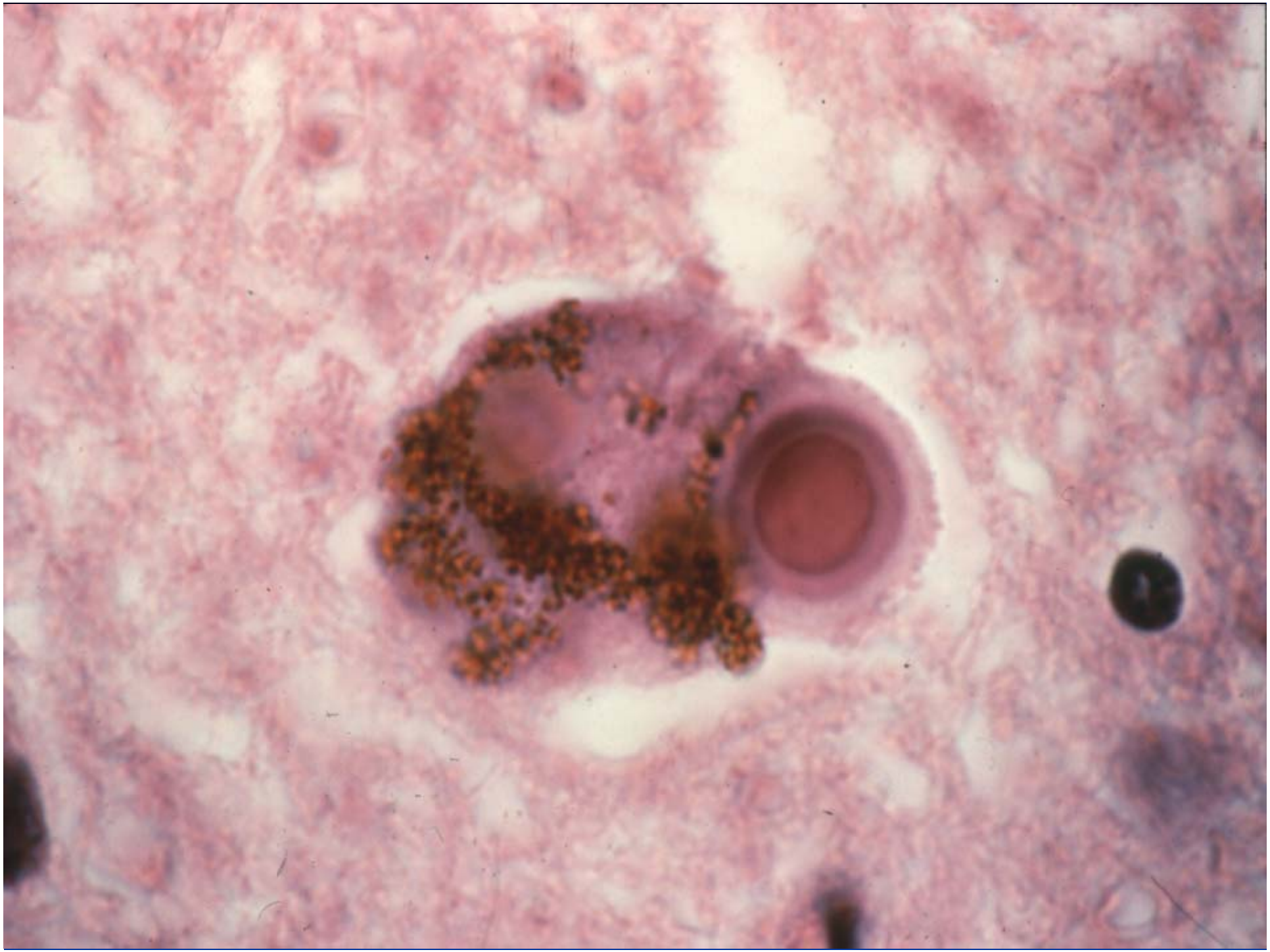
Parkinson's disease: Gross and microscopic findings

- Gross--**loss of pigment** in the **substantia nigra**
- Microscopic--Lewy bodies with pigmented neuronal cell loss and gliosis
  - cortical Lewy bodies present in 80% or more of PD cases

Parkinson's Disease







Other Extrapyramidal Movement Disorders

- Parkinson's disease: Hypokinetic
- Huntington's disease: Hyperkinetic
  - Choreiform movements
  - Intellectual decline
- Multiple Systems Atrophy
  - Parkinsonian features
  - Symptoms suggestive of olivopontocerebellar degeneration
  - Shy-Drager syndrome (parasympathetic dysfunction)

Motor neuron disease

- Amyotrophic lateral sclerosis (Lou Gehrig's disease)
  - Results in progressive weakness, eventually resulting in paralysis of respiratory muscles and death often within 2-5 years of diagnosis
  - Degeneration of upper (motor cortex) and lower (spinal cord) motor neurons

Motor Neuron Disease

- ALS: Adult form of motor neuron disease associated with both upper (brain) and lower (spinal cord) motor involvement
- Werdnig-Hoffman disease: The baby is weak (floppy) at birth. Lower (spinal cord) motor neurons are involved.
- Poliomyelitis: Lower motor neurons are destroyed.

Prion disease (Spongiform encephalopathy): Clinical findings

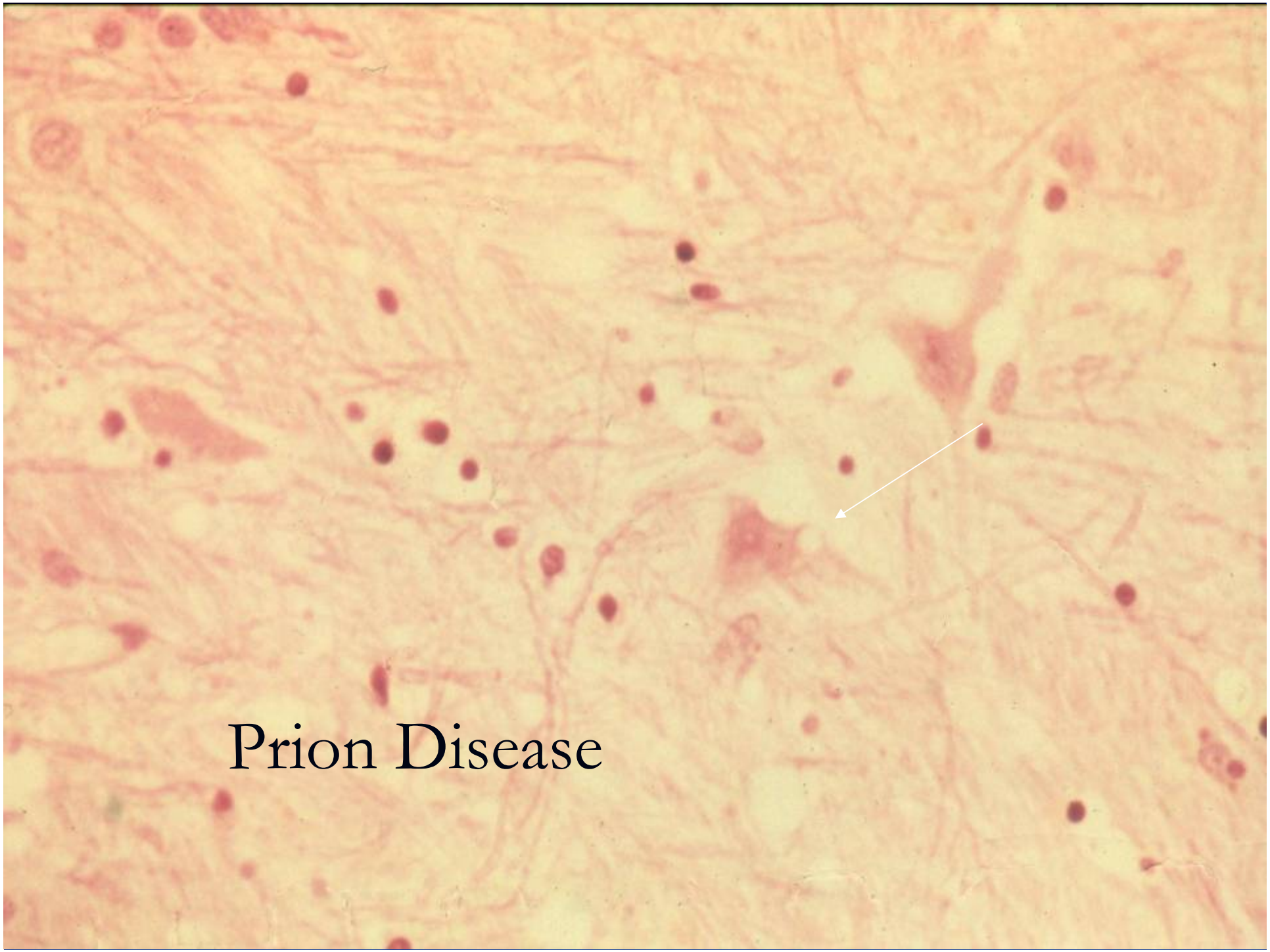
- 50-70 years old, **rapidly evolving dementia**, often with **myoclonus** and a characteristic EEG pattern (of repetitive sharp waves)
- Early symptoms include personality changes, impaired judgement, gait abnormalities, vertigo,
- In some patients cerebellar and visual abnormalities predominate
- Majority **die w/in 6 months**, frequently w/in 3 mo.

Prion disease: Pathogenesis

- Transmissible but not "infectious"
- **Prion protein**, Prusiner--1997 Nobel Prize, (not a "slow virus")
- PrP^{C} -- produced normally in most cells --amino acid sequence is identical to the PrP^{SC} --abnormal protein, the difference is in the secondary conformation (B-pleated vs alpha helical) PrP^{SC} causes post-translational modification of PrP^{C}
- Transmitted by direct inoculation (corneal transplants, dural grafts, pituitary products)

Prion disease: Gross and microscopic findings

- Gross appearance--may be normal due to short duration of disease
- Microscopic appearance--vacuolation of neuropil, vacuoles are within nerve cell bodies and neuronal processes
  - cell loss and gliosis may be prominent


Prion Disease

Summary: Neurodegenerative diseases

- Dementia
  - Alzheimer's disease: common, amyloid hypothesis, plaques and tangles, gross brain atrophy
  - Prion disease: rare, "transmissible" protein, rapidly progressive, vacuolar changes
- Movement disorders
  - Parkinson's disease: hypokinetic, loss of dopaminergic cells substantia nigra, Lewy bodies
  - Huntington's disease: choreiform movements, caudate atrophy, nuclear inclusions
- Motor neuron disease (ALS): Loss of upper and lower motor neurons, progressive over 2-5 years

Pediatric Neuropathology

Developmental Abnormalities
Neuronal Storage Diseases
Familial Tumor Syndromes
Perinatal Lesions/Infections
Trauma: shaken baby syndrome

Developmental Abnormalities: Pathology

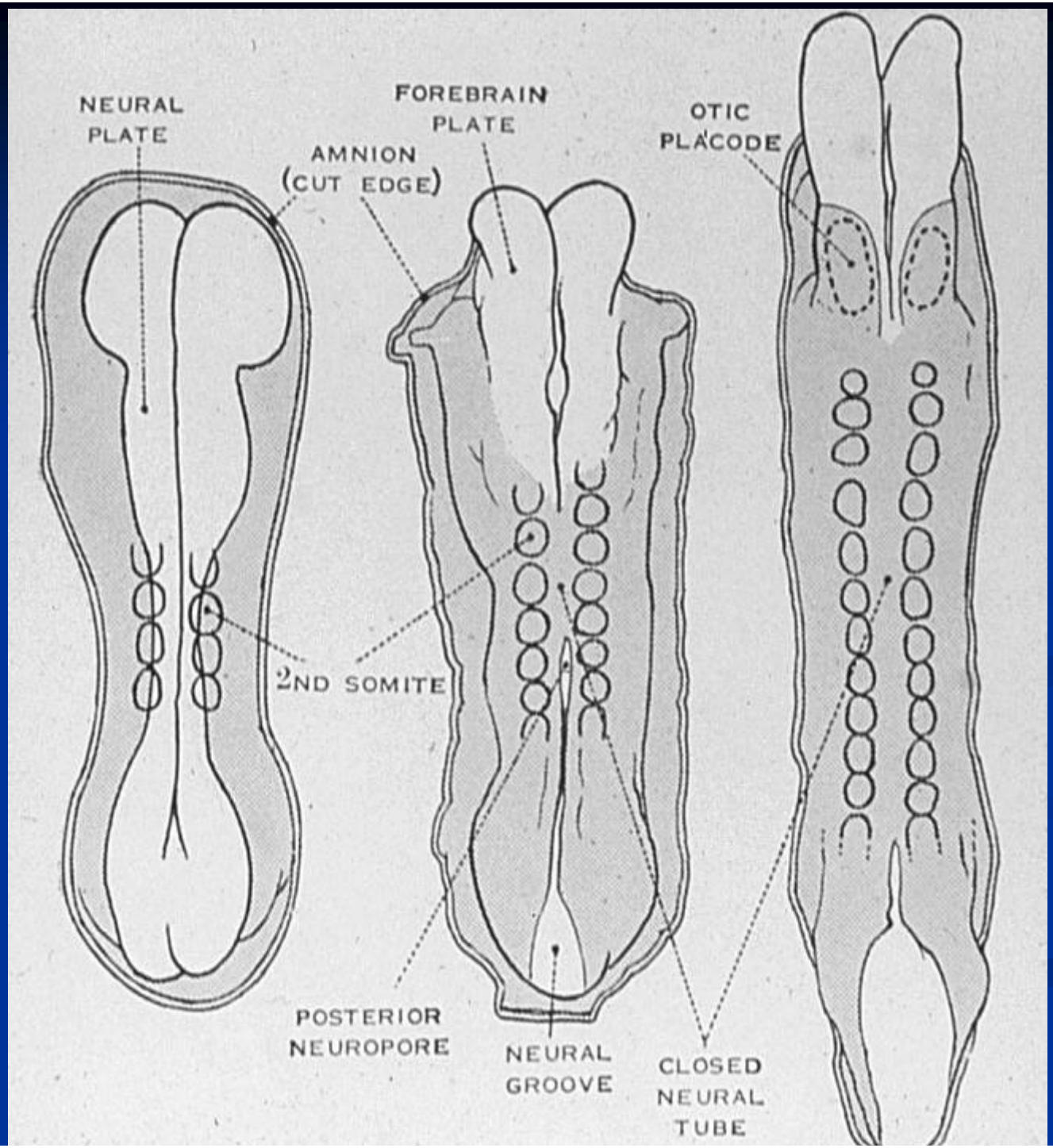
- **Organ induction** (2.5-6 weeks): neural tube defects: anencephaly, spinal dysraphism, encephalocele, holoprosencephaly
- **Neuronal (glial) migration** (3-6 months): lissencephaly, microcephaly, polymicrogyria, agenesis of the corpus callosum

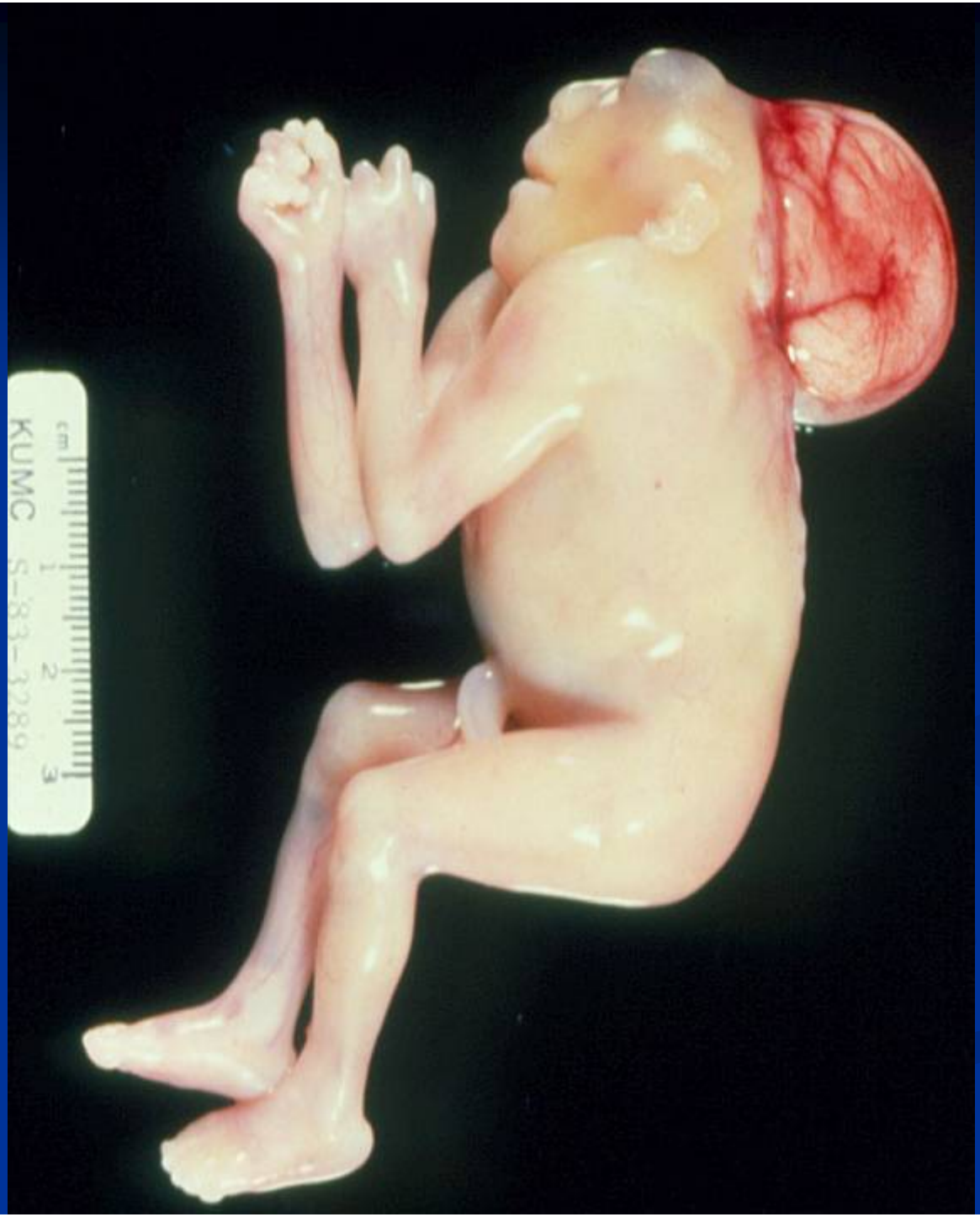
- **Myelination** (2 months-juvenile)
- **Synaptogenesis** (20 week gestation-adulthood): trisomy 21, fragile X, cretinism

In general, **earlier insults cause more severe structural damage**

Organ Induction:
Dysraphic Disorders

- Failure of neural tube folds to close during development
  - Prenatal testing may reveal an elevated maternal serum AFP
  - Folate deficiency: Folic acid supplementation prior to conception may reduce the incidence of neural tube defects up to 70%
  - Neural tube defects range from small bony defects in the lumbosacral region (spina bifida occulta) to craniorachischisis.
  - Myelomeningoceles occur most commonly in the lumbosacral region


NEURAL PLATE
AMNION (CUT EDGE)
FOREBRAIN PLATE
OTIC PLACODE
2ND SOMITE
POSTERIOR NEUROPORE
NEURAL GROOVE
CLOSED NEURAL TUBE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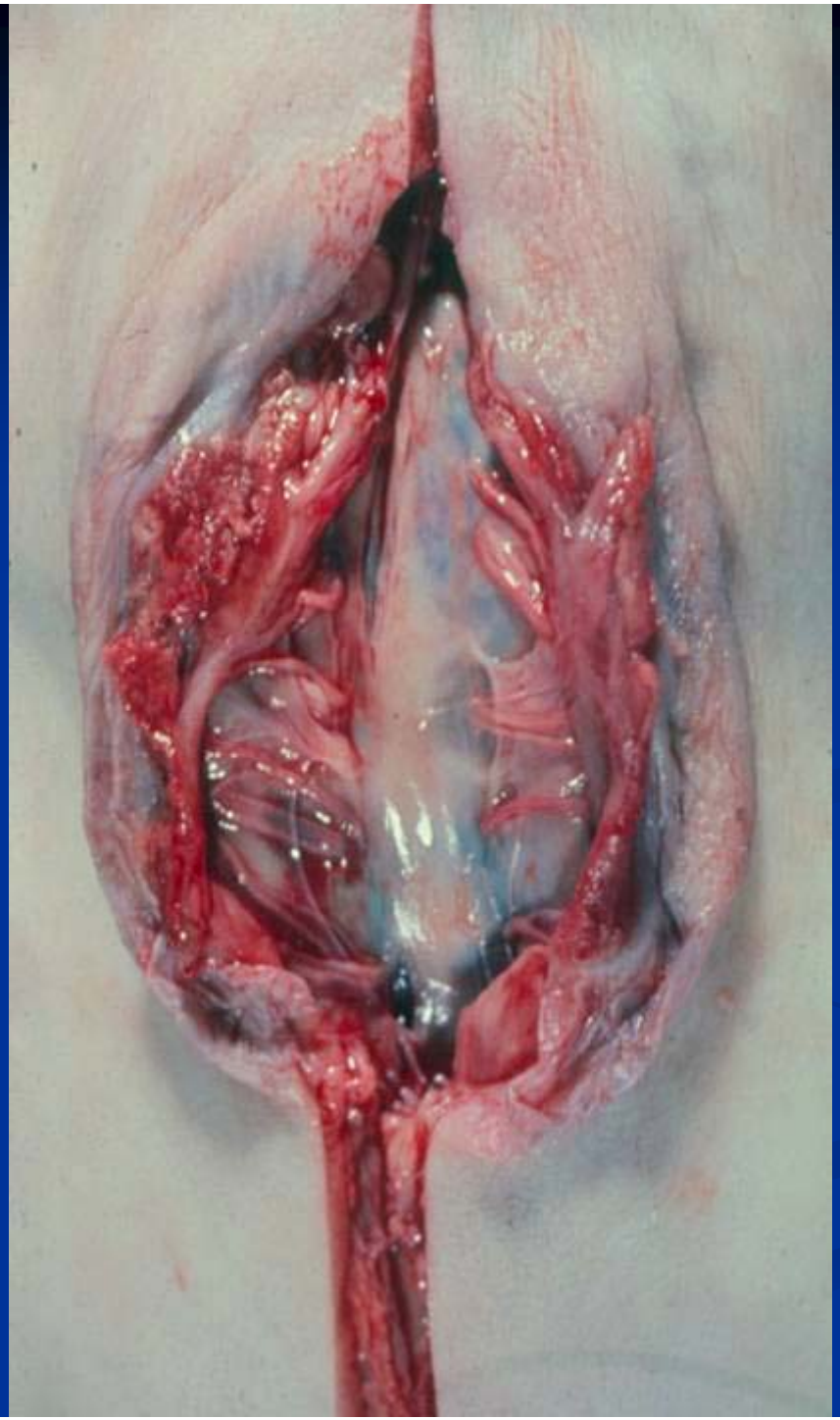
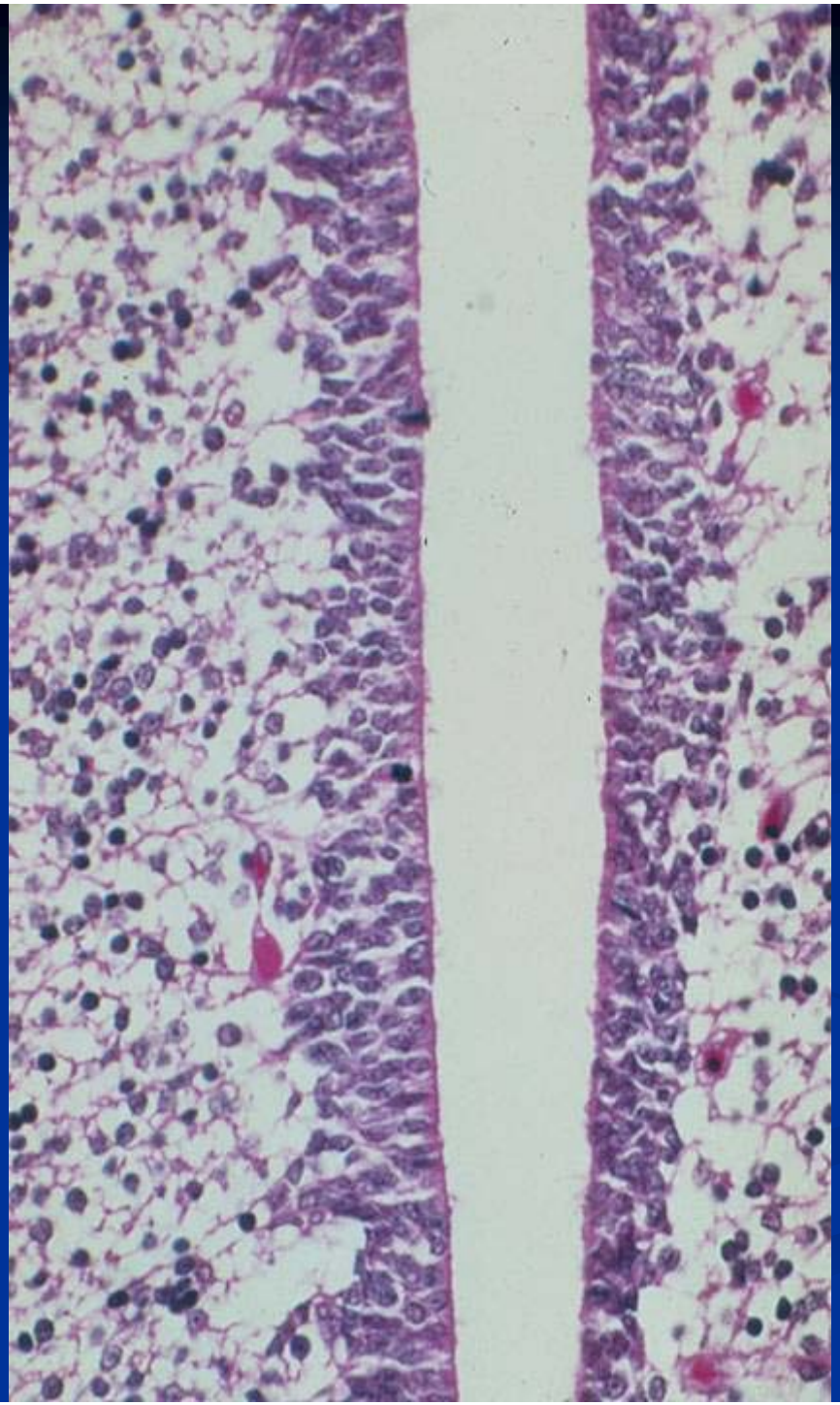


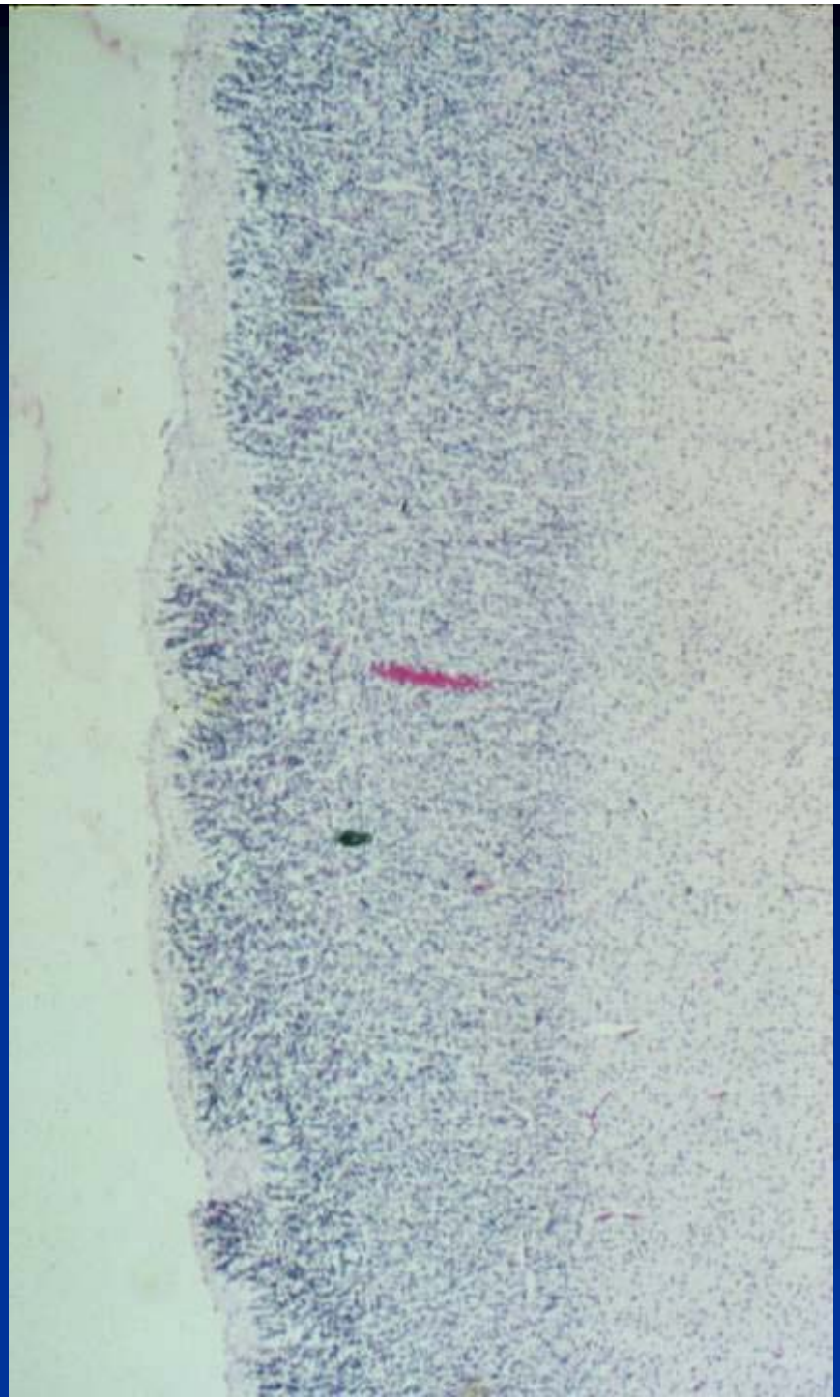
Neuronal migration disorders

- Lissencephaly (smooth brain)/pachygyria (few enlarged gyri
- Polymicrogyria (many small gyri)
- Heterotopias (circumscribed collections) and dysplasias (disorganized lamination)
  - Occur with other developmental abnormalities for example in patients with chromosomal abnormalities
  - May be the focus of seizure activity

Seizures

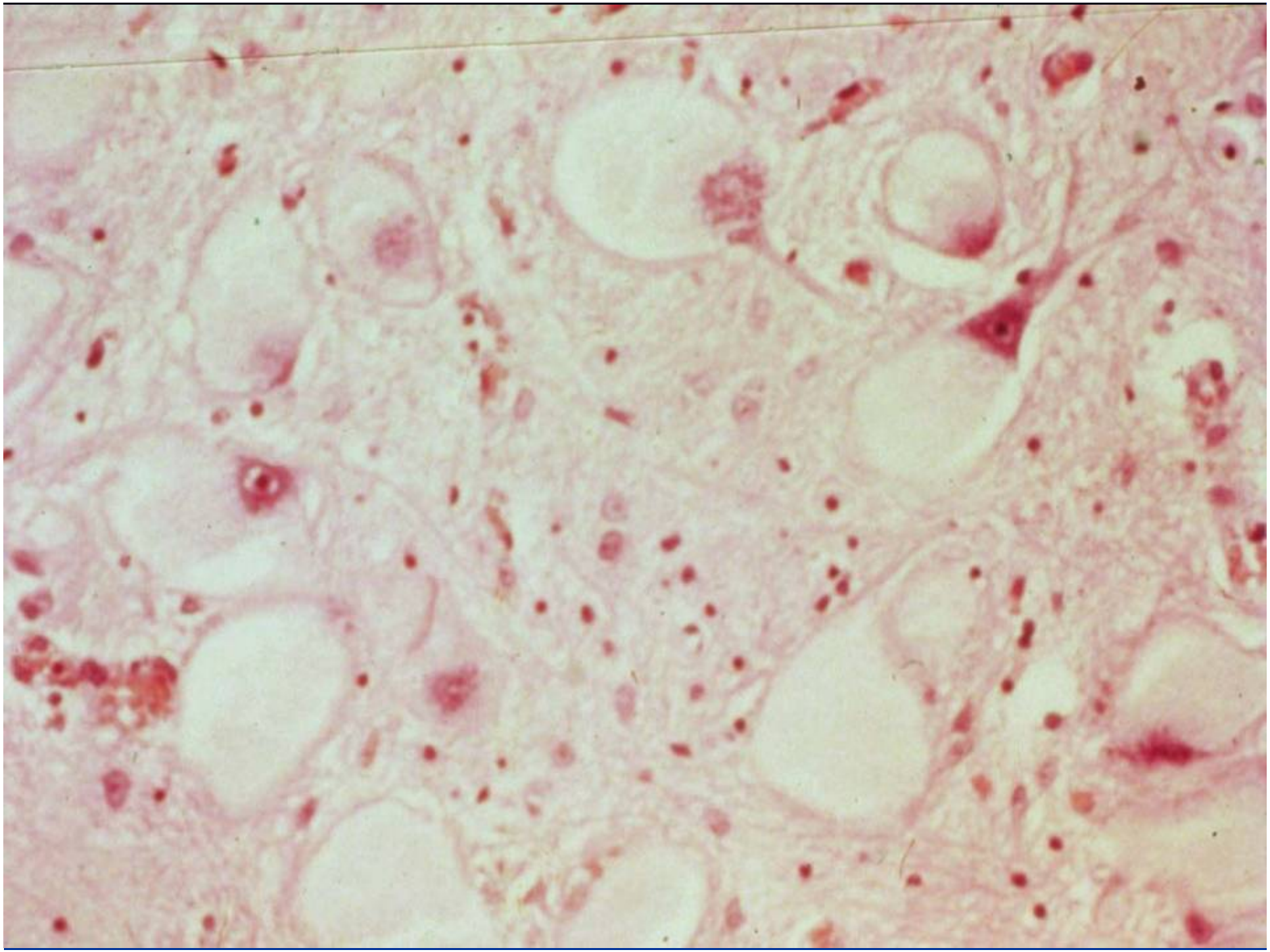
- Result from abnormal electrical activity of a group of brain cells and cause an altered mental state or tonic clonic movements. May be partial (focal) or generalized.
- In children seizures may result from neuronal migration abnormalities or from abnormalities acquired subsequent to brain damage (such as inflammation)
- A first time seizure in an adult would warrant an imaging study to rule out tumor or other structural abnormality





Neuronal Storage Disease

- Result from inborn errors of metabolism (deficient enzyme or abnormal lysosomal function)
- Progressive, poor treatment options (bone marrow transplant)
- Accumulation of metabolic products in the neuron
  - Tay Sachs disease
  - Neuronal ceroid lipofuscinosis
  - Glycogen storage disease



Concentric Multilamellar membranous cytoplasmic bodies (MCB’s)

Familial Tumor Syndromes

- Neurofibromatosis
  - NF-1: (most common) multiple peripheral neurofibromas
  - NF-2: bilateral acoustic schwannomas and meningiomas
- Tuberous Sclerosis: subcortical and cortical hamaratomas(tubers)

-Autosomal dominant

-Tumor suppressor gene mutations

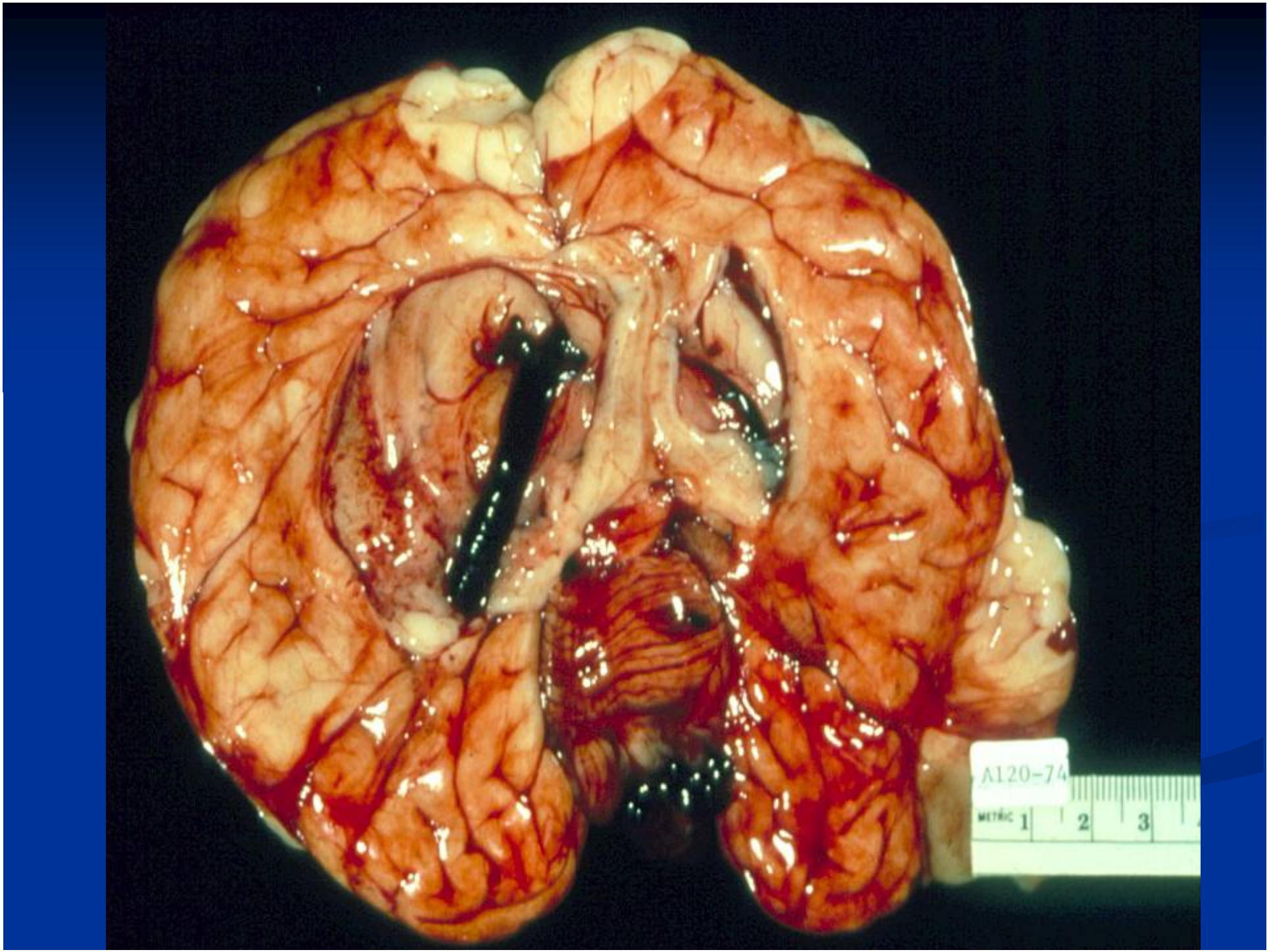
-Cutaneous findings

Perinatal Lesions of the CNS

Hemorrhage

Hypoxic/Ischemic

Infectious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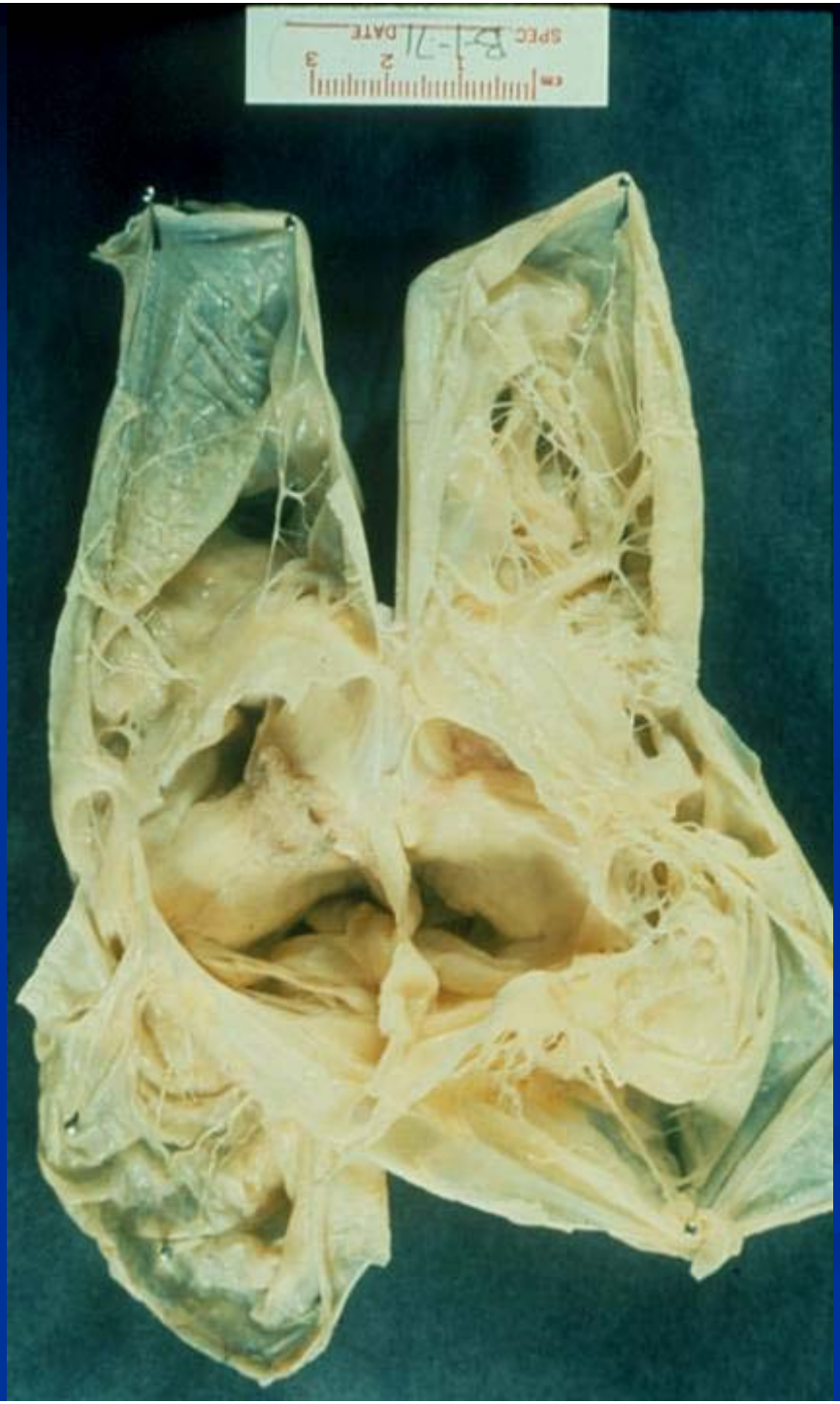
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Congenital/Perinatal Infections

TORCH

- Toxoplasmosis
- Other: syphilis, TB, listeria monocytogenes; other viruses (VZV, HepB)
- Rubella (rare—immunizations)
- Cytomegalovirus, Chlamydia trachomatis
- Herpes simplex (usually type 2); HIV

Shaken Baby Syndrome

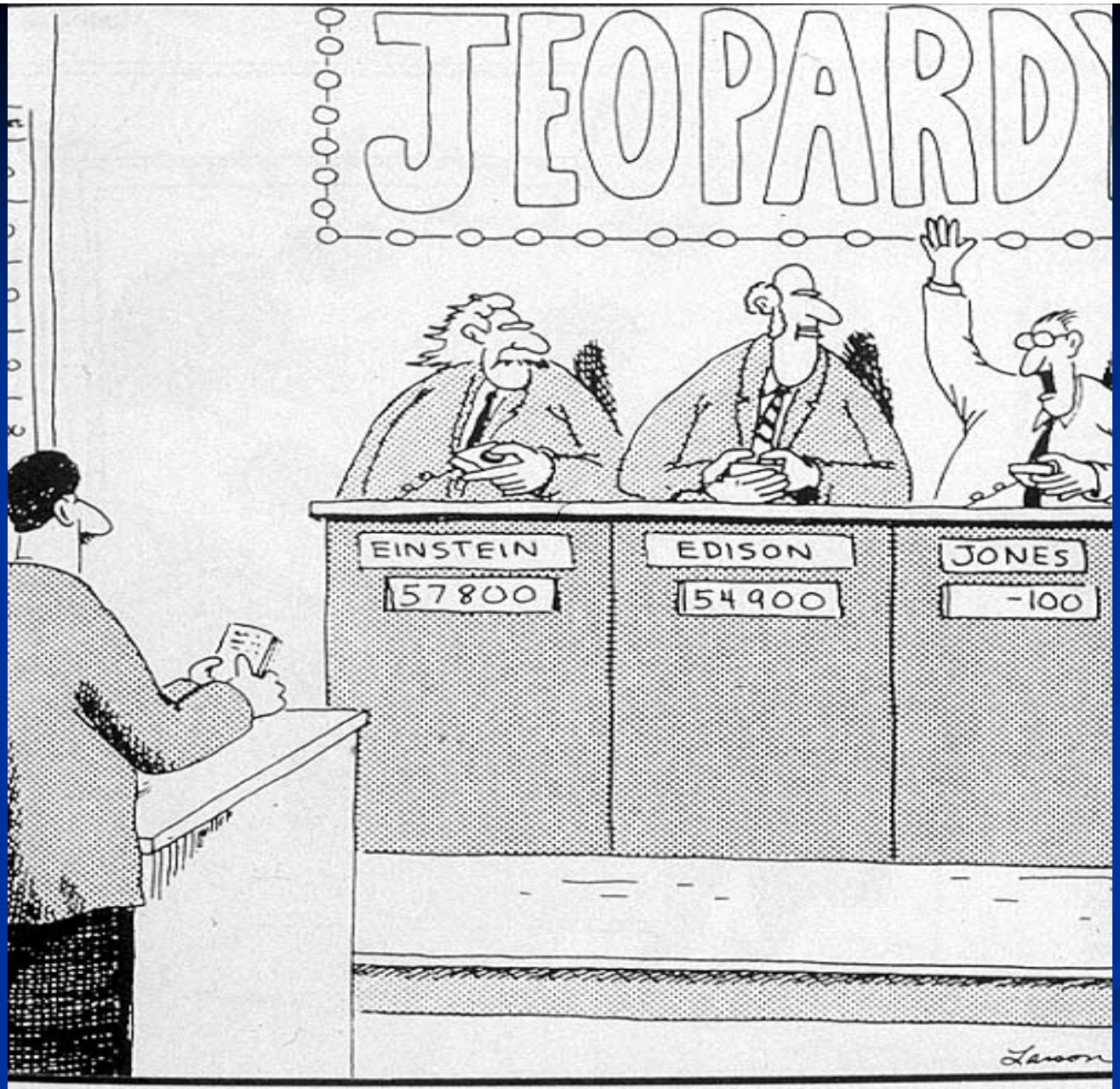
- General: Violent shaking causes acceleration (**shearing**) injury of axons: **diffuse axonal injury**
- Neurologic: Blindness/mental retardation in infants less than 1 year of age. Present with apnea, seizures, lethargy, bradycardia, respiratory difficulty, coma.
- Pathology: **Oculo-cerebral damage can occur without external evidence of head injury. Retinal and optic nerve sheath hemorrhage—ophthalmoscopic exam important**
- Microscopic: Axonal spheroids

Summary: Pediatric neuropathology

- Developmental abnormalities: Neural tube defects (anencephaly, spina bifida), migrational defects (mental retardation, seizures)
- Inborn errors of metabolism: Neuronal storage diseases and leukodystrophies
- Other: Familial tumor syndromes, hemorrhage, hypoxic/ischemic injury, shaken baby syndrome

Pathology of the Nervous System

- Introduction
- Increased intracranial pressure
- Vascular and circulatory disorders
- Trauma
- Infections
- Tumors
- Demyelinating diseases
- Degenerative diseases
- Developmental Abnormalities



"Excuse me ... I know the game's almost over, but just for the record, I don't think my buzzer was working properly."