Degenerative Disorders

Neurodegenerative Diseases

- Group of disorders associated with **progressive loss of neurologic function** affecting **selective groups of functionally related neurons**.
- Most are ***sporadic***, some are ***familial***.
- No effective treatment

General features

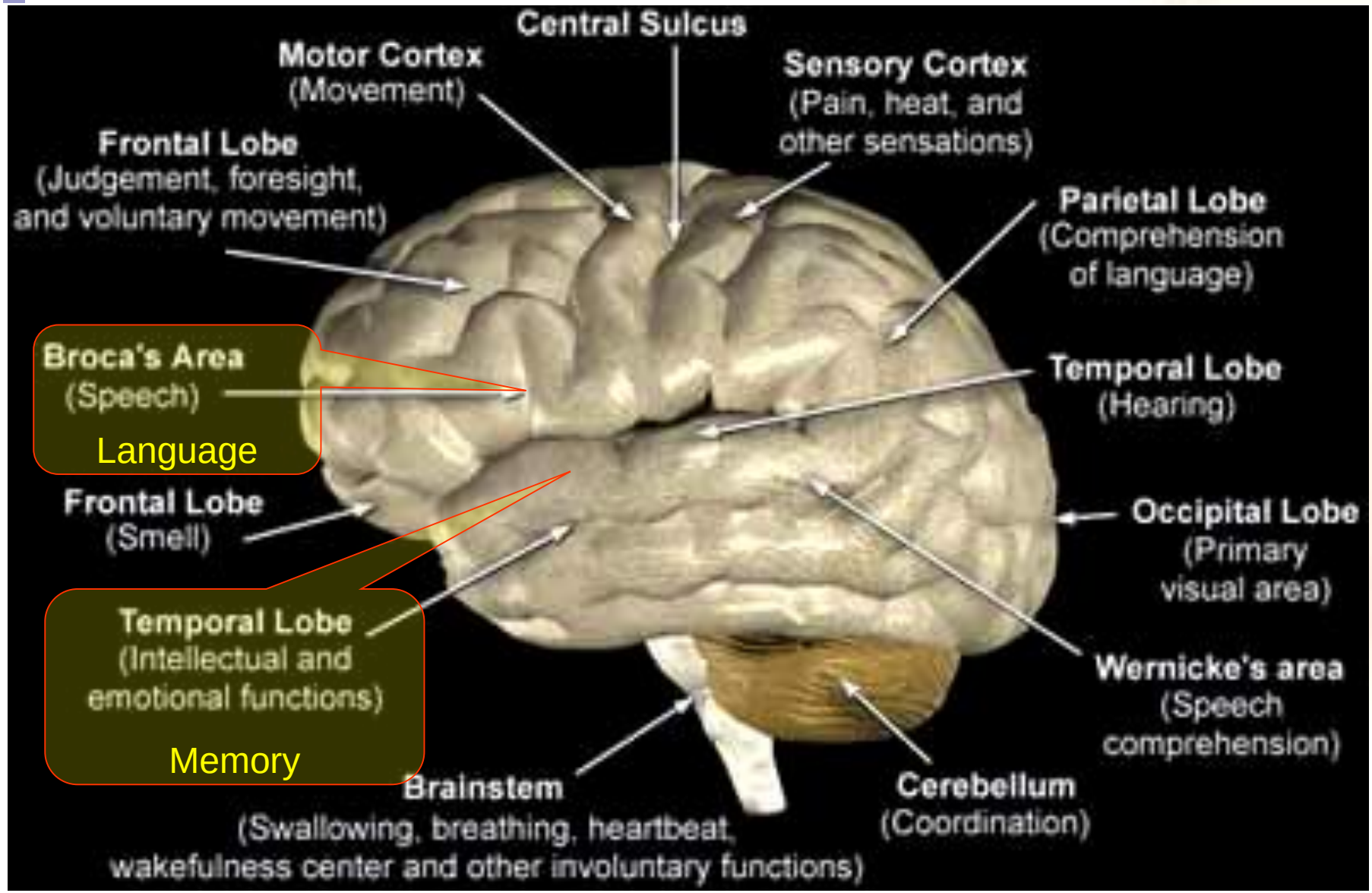
1. **Pathologically**, most of NDD are associated with accumulation of abnormal **protein aggregates** (forming *cellular inclusions*):
   - **Cause:** Usually unknown.
   - **Lead to**: Indirect stress response, direct neurotoxic effect OR prions-like effect (???).
   - **Examples:** Tangles, plaques, Lewy bodies …

2. **Clinically**; symptoms reflects the patterns of brain involvement (**NOT** type of inclusions):
   - See table.

Group	Usual location	Clinical features	Example
Dementia	Cerebral cortex	Memory & cognitive deficit	• Alzheimer disease • FTLD • Parkinson disease • 2nd (multiple infarction, infections, chronic hematoma …)
Movement disorders	Basal ganglia	Abnormal gait or movements	Some types of Parkinsonisms
Cerebellar ataxias	Cerebellum	Ataxia	Many
Motor neuron disease	Motor neurons	Weakness + features of UMN or LMN injury	Amyotrophic lateral sclerosis

Development of memory impairment and other intellectual or cognitive deficits (as language, insight, planning…) severe enough to ↓ the affected person's capacity to function at the previous level ***despite a normal level of consciousness***.

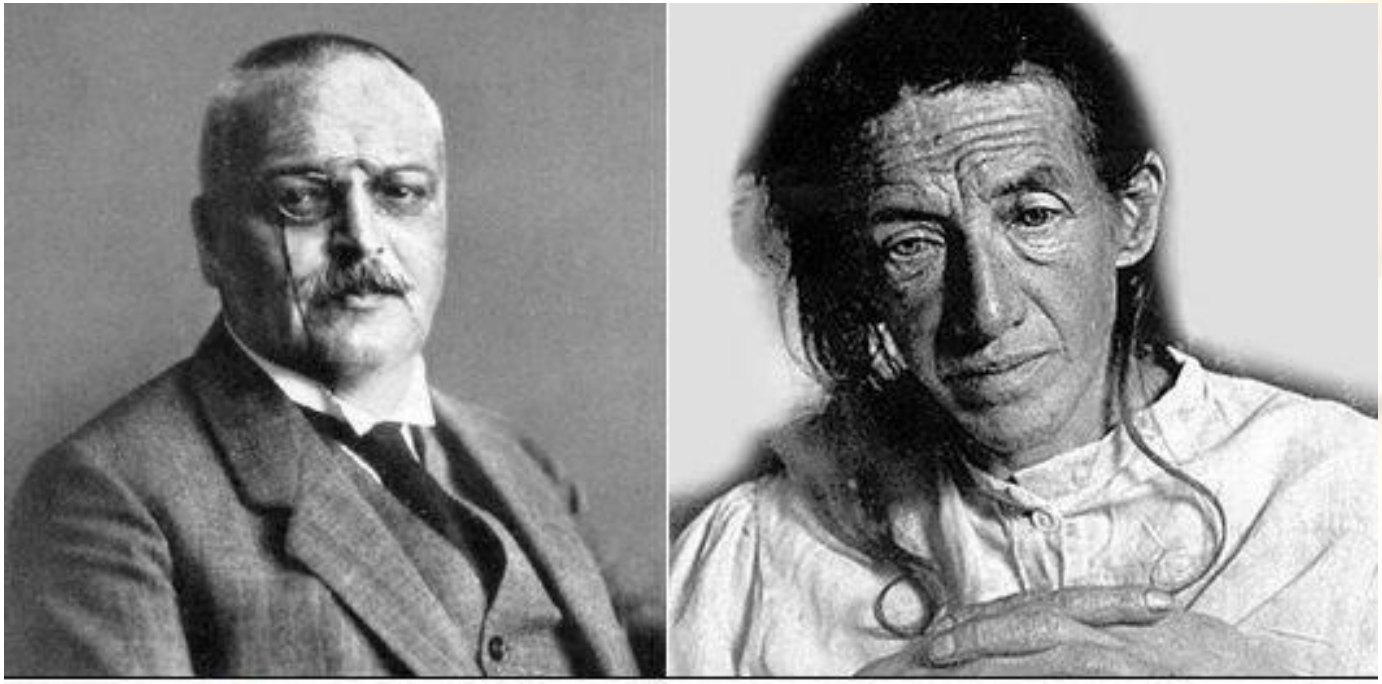
Brain : Functional areas.



1. Alzheimer's disease (AD):

- **Commonest** cause of dementia in elderly.
- Incidence ↑ with **AGE** (65-75 →~3%; > 85 → >50%).
- Usually **sporadic** (>50y) >> **familial**.
- Insidious onset of memory loss (starting with *short-term memory*) along with impaired cognition, mood & behavior → then progress to disorientation, memory loss & aphasia → then pt become disabled, mute & immobile… (within ~10y) → death.
- **Pathology:**
  - Significant cortical atrophy
  - Secondary ventricular enlargement
  - Extracellular Aβ amyloid deposition → Neuritic plaques & Amyloid angiopathy
  - Intracellular Tau deposition → Neurofibrillary tangles (within neurons).

Alois Alzheimer:



Alois Alzheimer

Auguste Deter

Alois Alzheimer's first Patient

AD – Pathogenesis:

- The fundamental abnormality is the accumulation of two proteins:
  - **Aβ** (extracellular) → form ***plaques***.
  - **tau** (intracellular) → form ***tangles***.

- **Aβ generation is the critical initiating event** for the development of AD.
  - Aβ is created by **amyloidogeneic** pathway when the transmembrane protein amyloid precursor protein (**APP**) is sequentially cleaved by the enzymes β-amyloid converting enzyme (**BACE or β-secretase**) **and γ-secretase** →instead of α & γ-secretases.

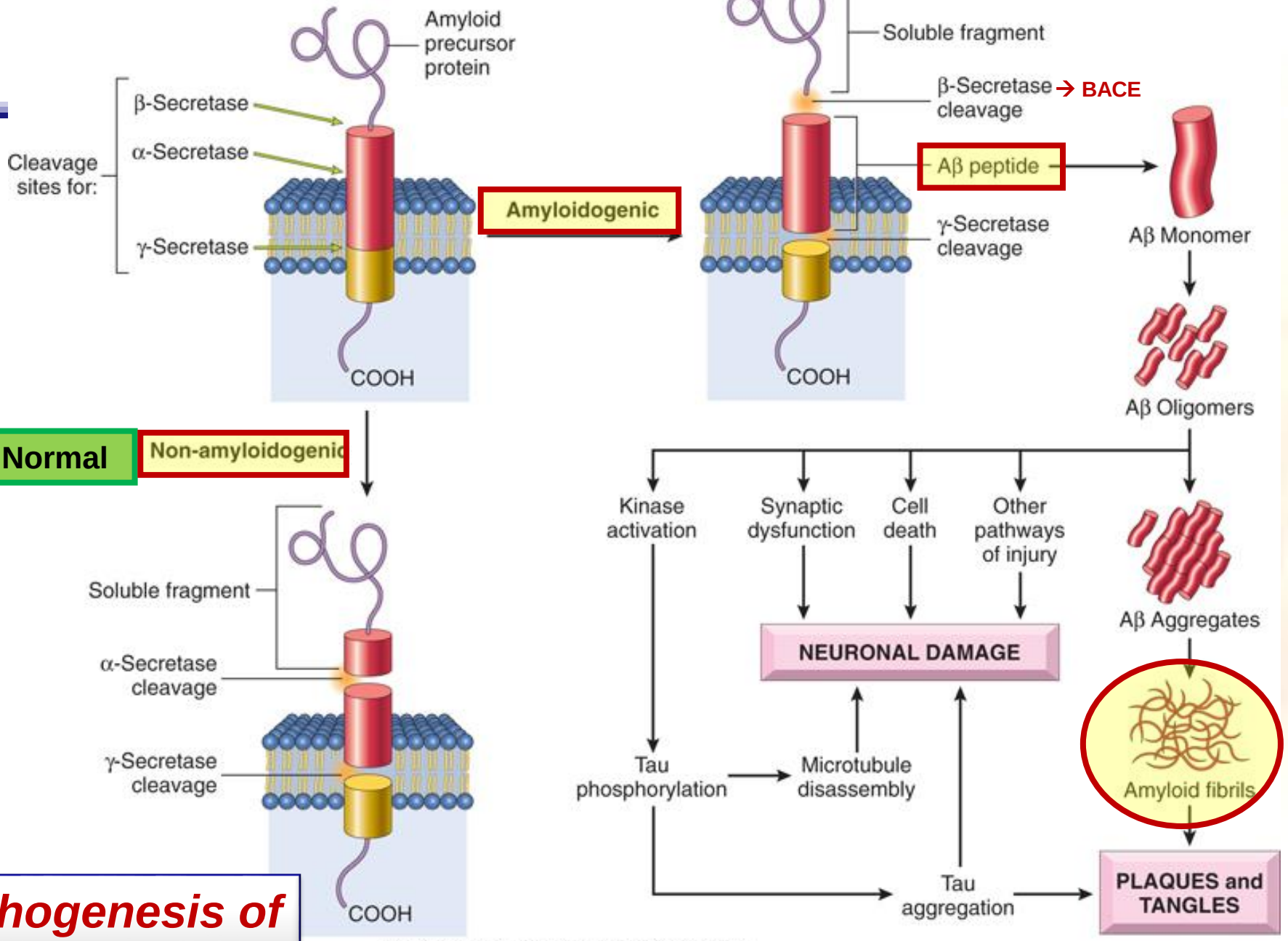
AD – Pathogenesis:

- Small aggregates of Aβ → alter neurotransmission and are toxic to neurons and synaptic endings.

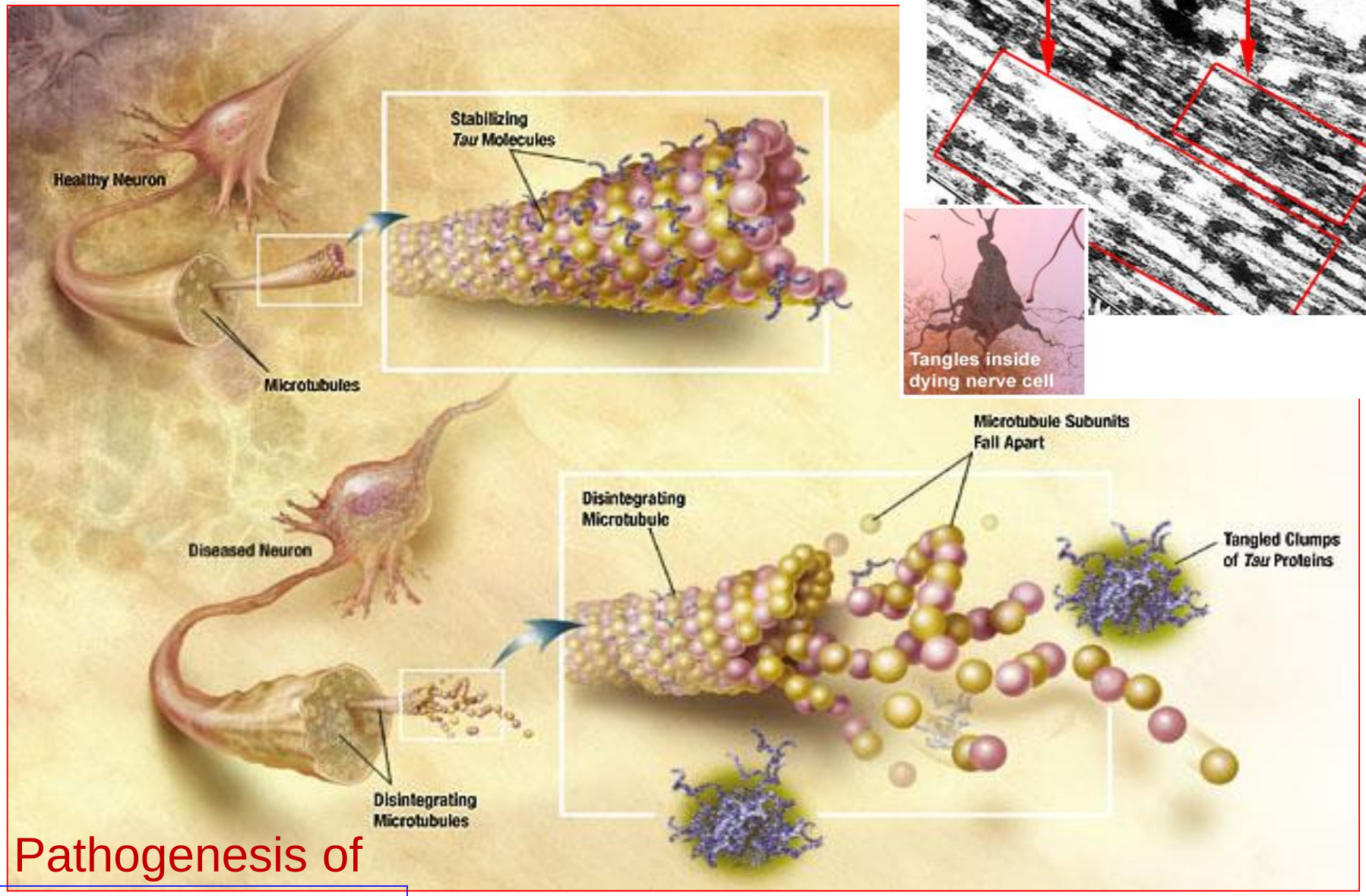
- Large deposits of Aβ (**plaques**) → cause neuronal death, elicit a local inflammatory response* ± altered region-to region communication**.

- Aβ also cause hyperphosphorylation of neuronal microtubule binding protein tau → redistribution of tau from axons into dendrites and cell bodies, where it aggregates (tangles) which also contribute to neuronal dysfunction and cell death.

- http://youtu.be/NjgBnx1jVIU (pathogenesis video)



Pathogenesis of AD



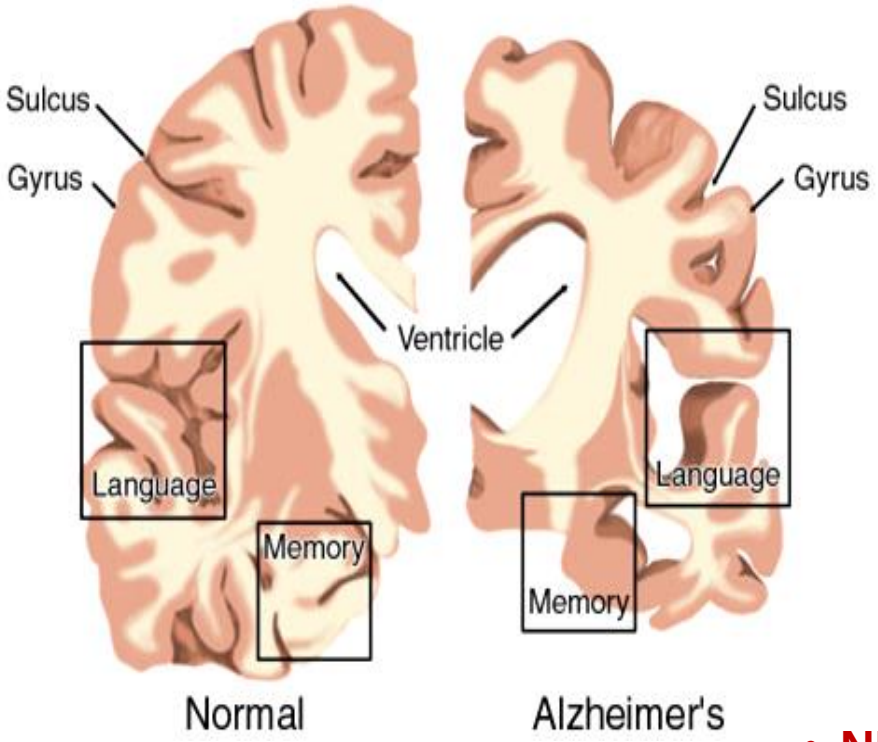
Pathogenesis of Neurofibrillary Tangles

Familial AD

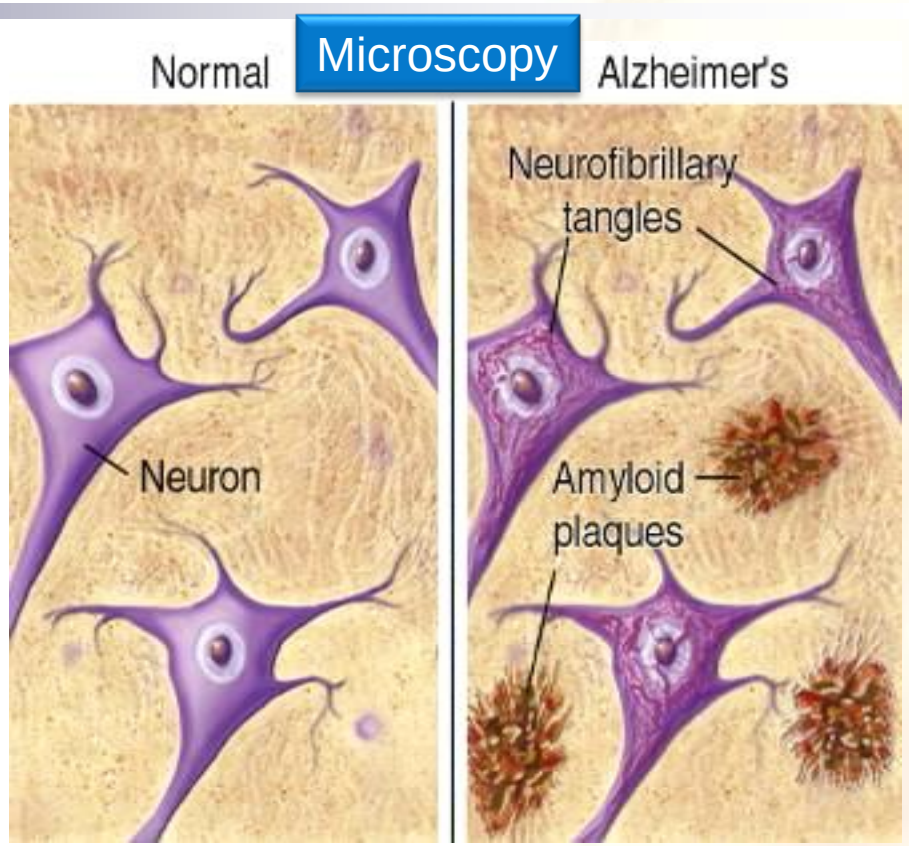
- 5-10% of AD cases.
- Manifests at *earlier* age than sporadic AD.
- Many genetic mutations have been identified (*& many are unidentified*):
  - **APP gene** (on chr. 21) → extra copy in as in DOWN syndrome → dementia by 40's.
  - **γ-secretase genes** (presenilin-1 or presenilin-2).
  - **Apolipoprotein E - E4** (ApoE4) on chr. 19 →↑ Aβ amyloid deposition → X4 risk of AD.

AD : Morphology

Gross



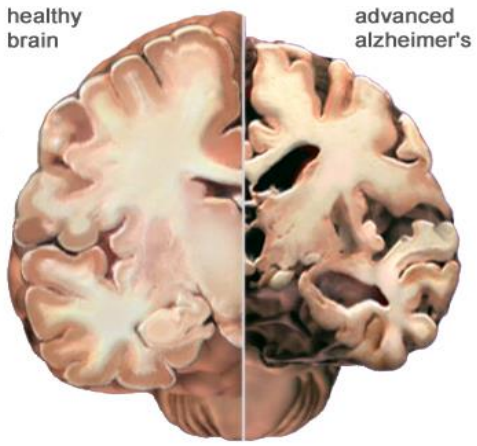
Microscopy

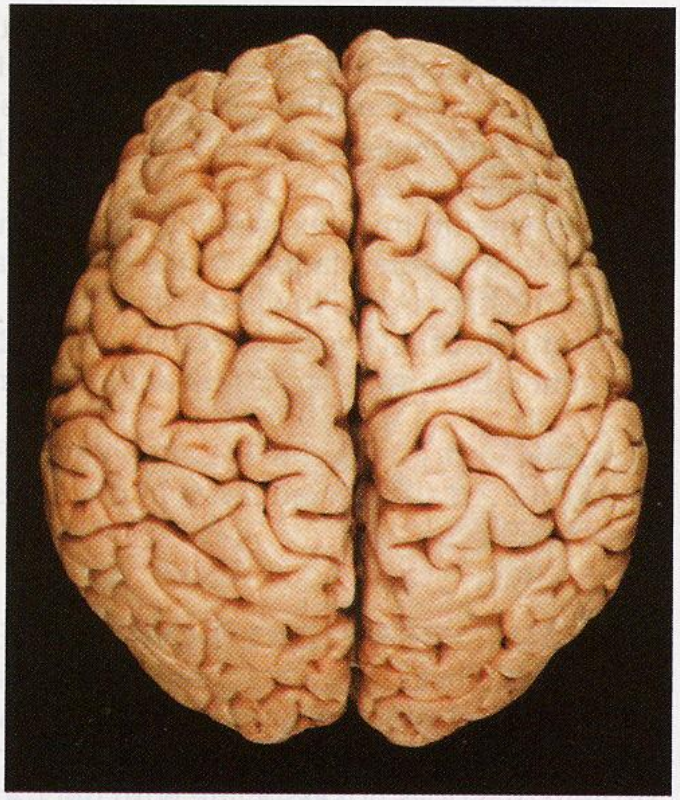


- **CORTICAL ATROPHY:**
- Then involves frontal, parietal, temporal …→ usually spares motor and sensory cortices
- Hydrocephalus ex vacuo .

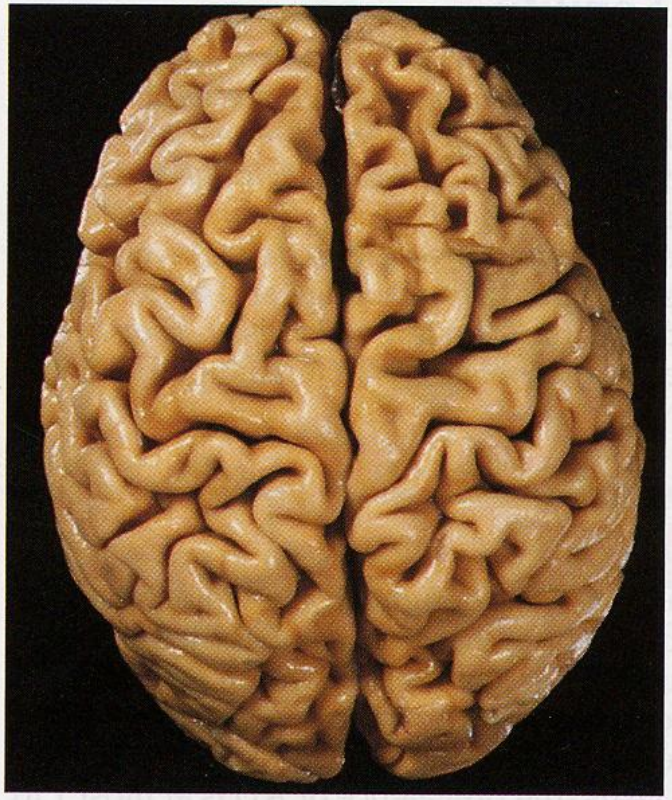
- **NEUROFIBRILLARY TANGLES** →Intracellular
- **NEURITIC PLAQUES & AMYLOID ANGIOPATHY** → Extracellular
- Loss of neurons with gliosis.

→ First start in *entorhinal cortex & hippocampus*.





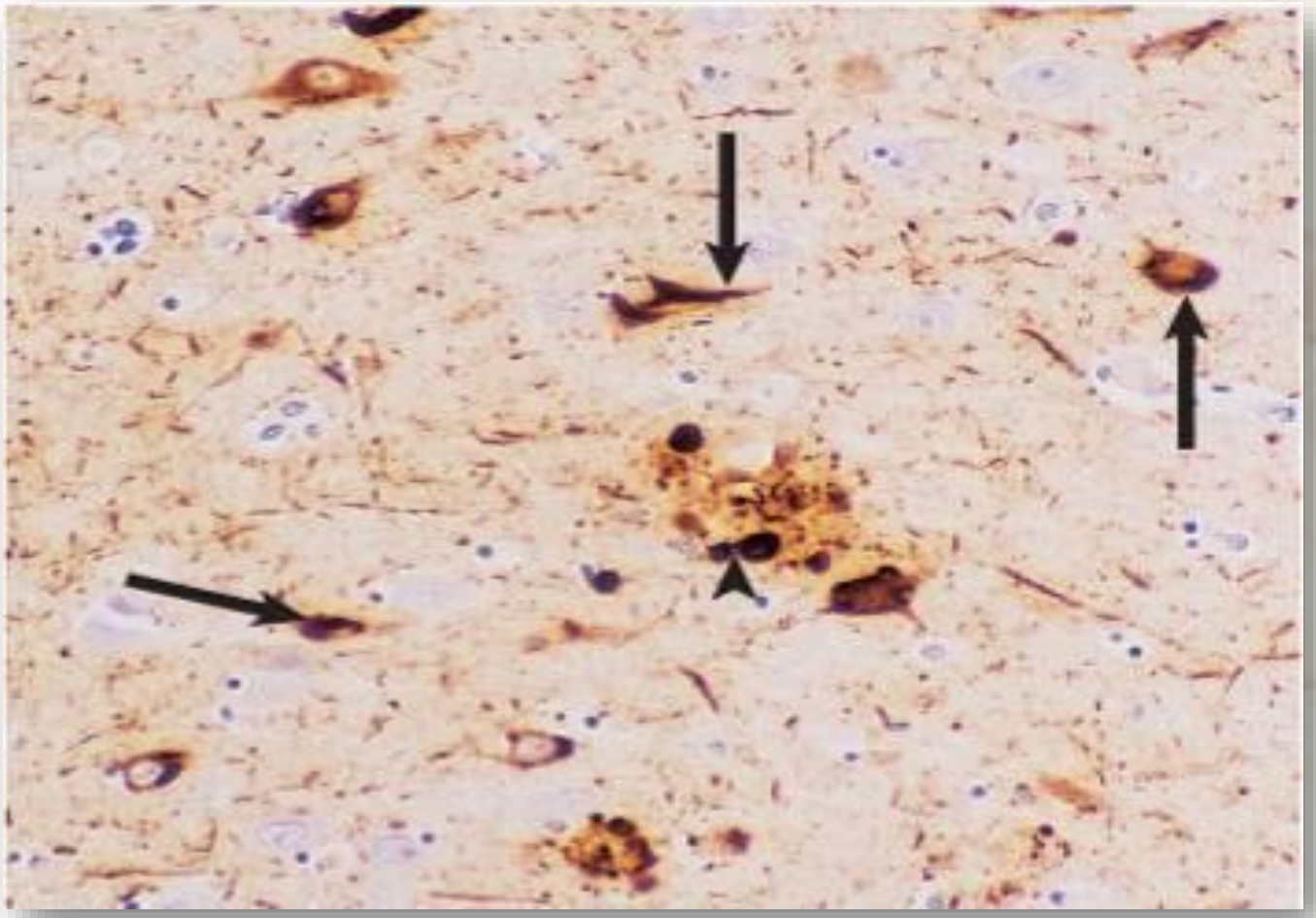
A



B

FIGURE *28-123*
Alzheimer disease. A. Normal brain. B. The brain of an AD patient shows cortical atrophy with thin gyri and prominent sulci.

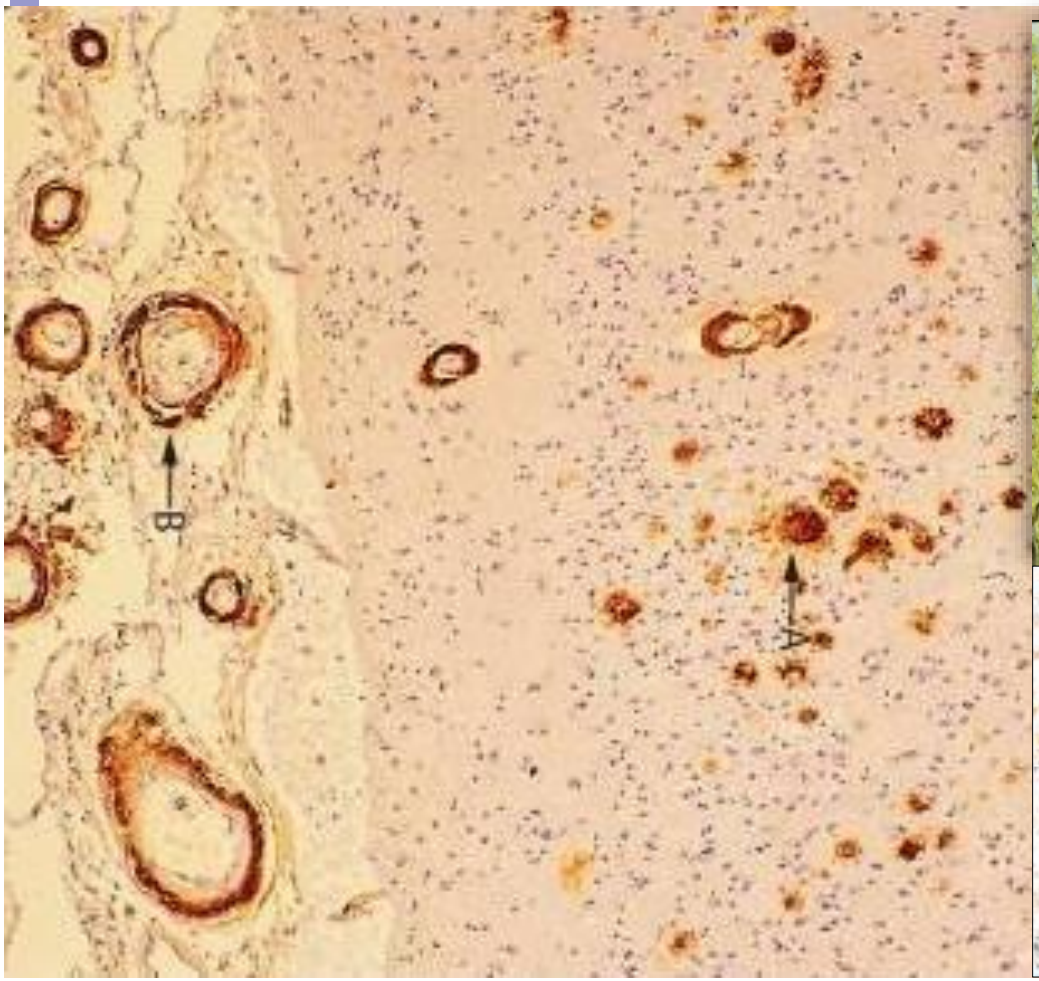
AD - Microscopy

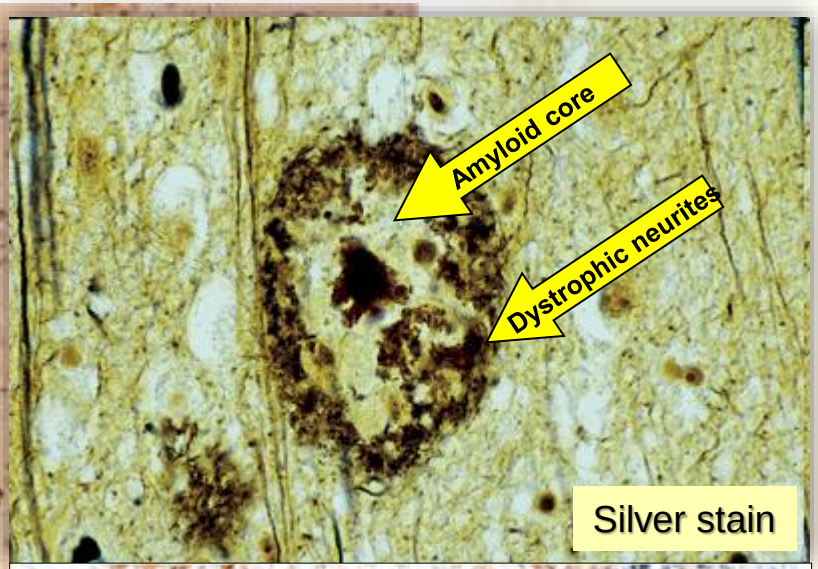


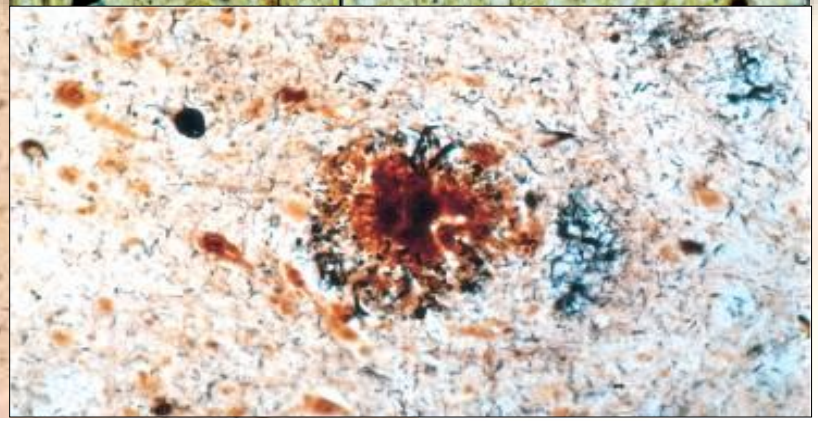
Plaques & around BV.
Aβ Amyloid

NF Tangles-Intracellular
tau protein

Neuritic plaques & Amyloid Angiopathy





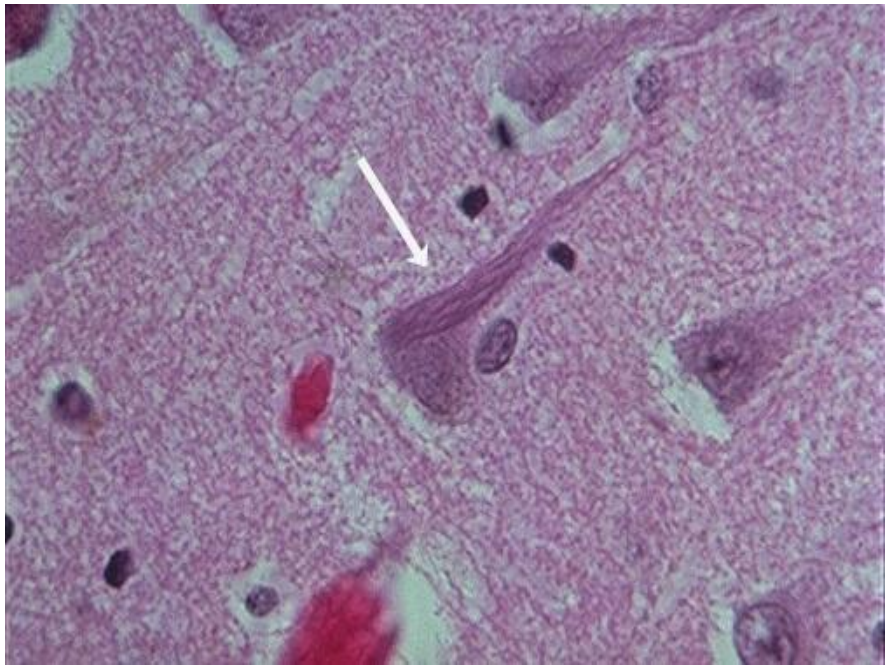


Amyloid deposits in: **A**. Plaques in brain substance – composed of tortuous neuritic processes surrounding a central amyloid core of **Aß protein** → **specific for AD**

B. and in blood vessel walls

Neurofibrillary tangles

- Fibrillary structures (tau protein) in the cytoplasm of the neurons that displace or encircle the nucleus.
- Tangles are **NOT specific** to AD.



Diagnosis of AD

- **Clinical picture:**
  - Progressive memory loss (short term memory is affected 1st) and cognitive deficits with increasing inability to participate in daily living activities.
- **Radiological methods**
- **Brain biopsy**

→ **The final diagnosis is made pathologically by examination of the brain at autopsy.**

AD & Intelligence….!

- In early life, higher skills in grammar and density of ideas are associated with protection against AD in late life.

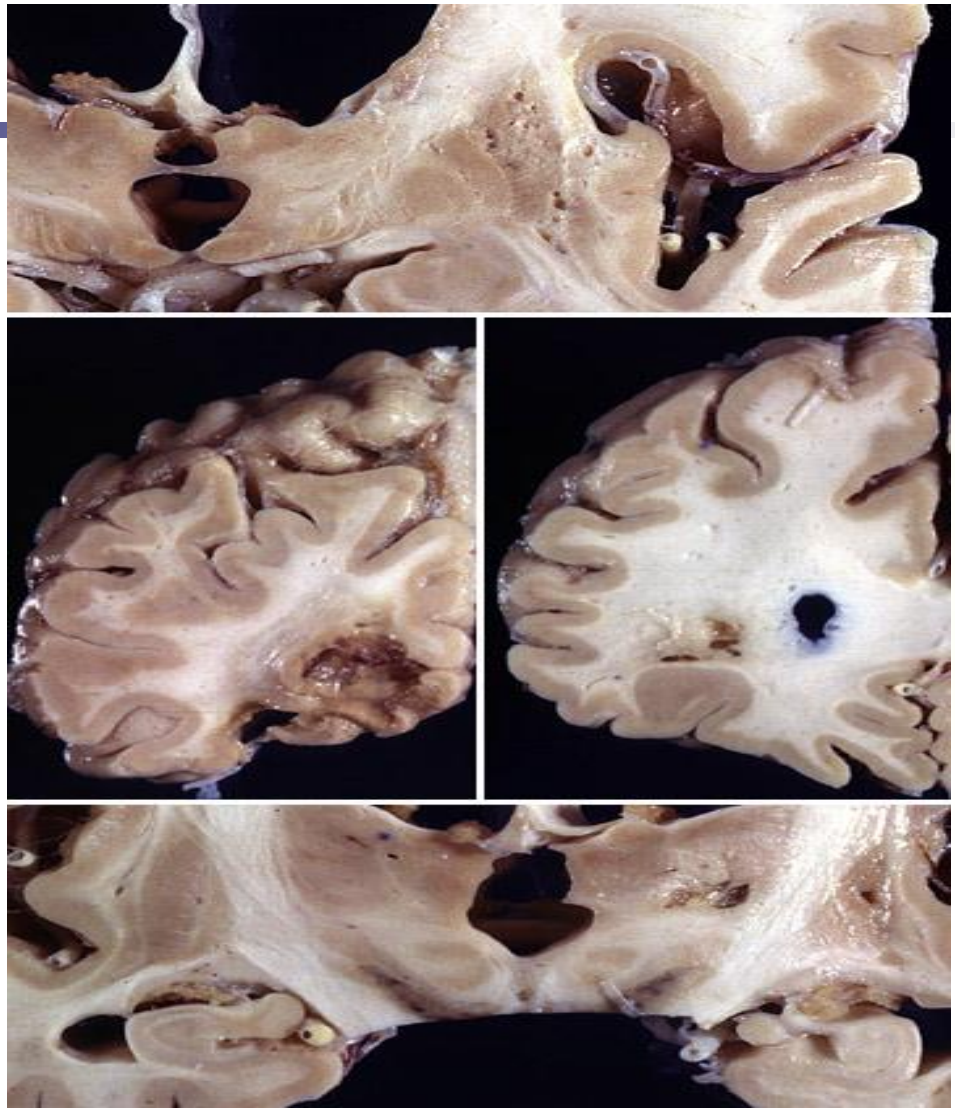
- Mentally stimulating activity protects against AD.

- Use it or loose it…..!

- *Coffee protects against Alzheimers ???*
- *Tea protects against Parkinsons ???*

2. Vascular dementia

- **2nd commonest** form of dementia after AD.
- Associated with multiple infarcts, hence the name **(Multiple Infarct Dementia):**
  - **Lacunar infarcts**
  - **Cortical microinfarcts**
  - **Multiple embolic infarcts**
- MRI show **grey matter lesions** rather than white (as in MS).



MULTI INFARCT DEMENTIA

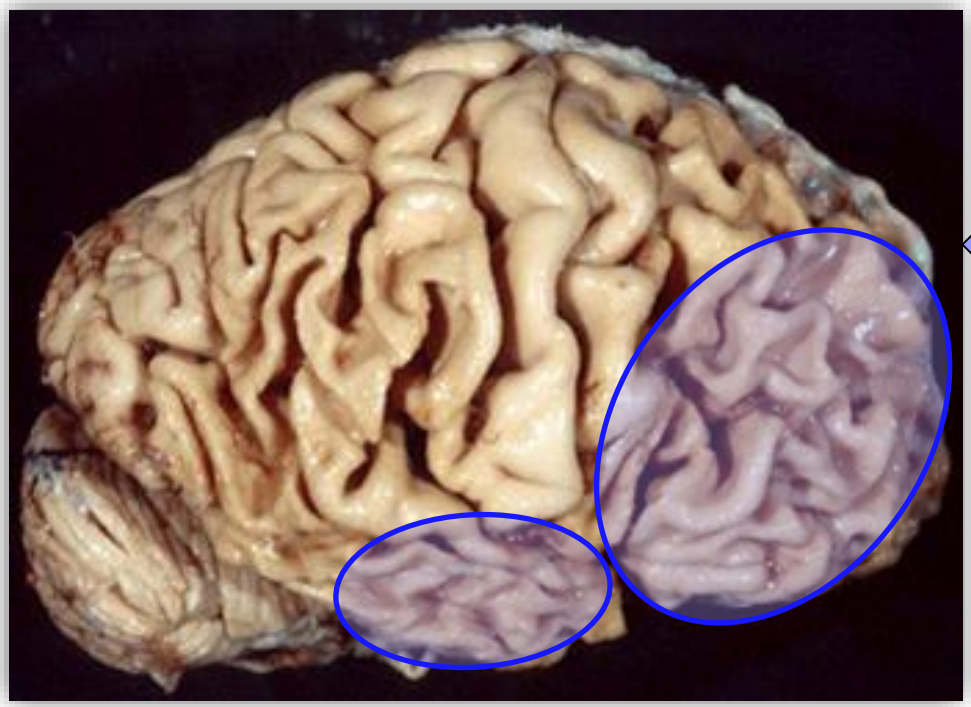
3. Fronto-Temporal Lobar Degeneration/Dementia (FTLD)

- Progressive disease characterized by **dementia** with degeneration of:
  - *Frontal lobe* → leading to behavioural changes.
  - *Temporal lobe* → leading to language problems.

- Memory loss seen **late** in the disease (differ from AD).

- Many sub types (according to nature of inclusions):
  - **Pick's Disease:** FTLD-tau common.
  - **FTLD-TDP43:** DNA/RNA-binding proteins (2nd common).

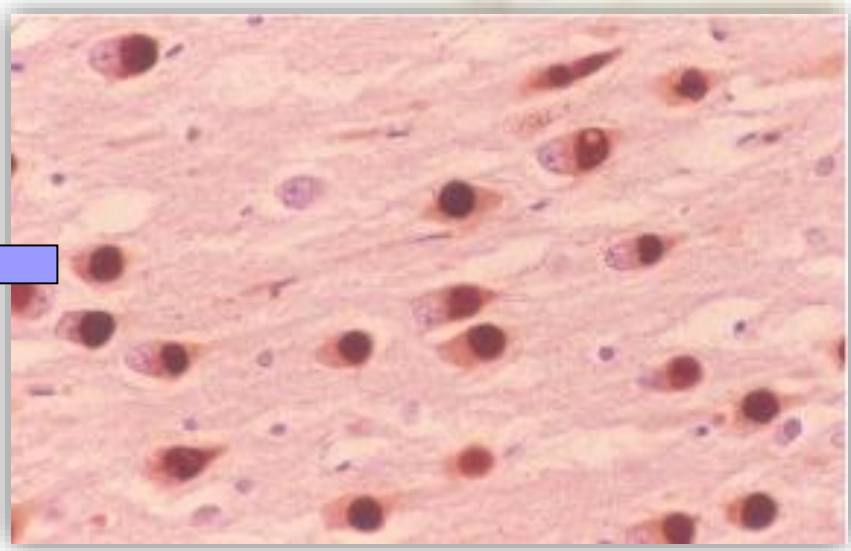
FTLD - Morphology



Atrophy of frontal & temporal lobes

Pick's bodies:

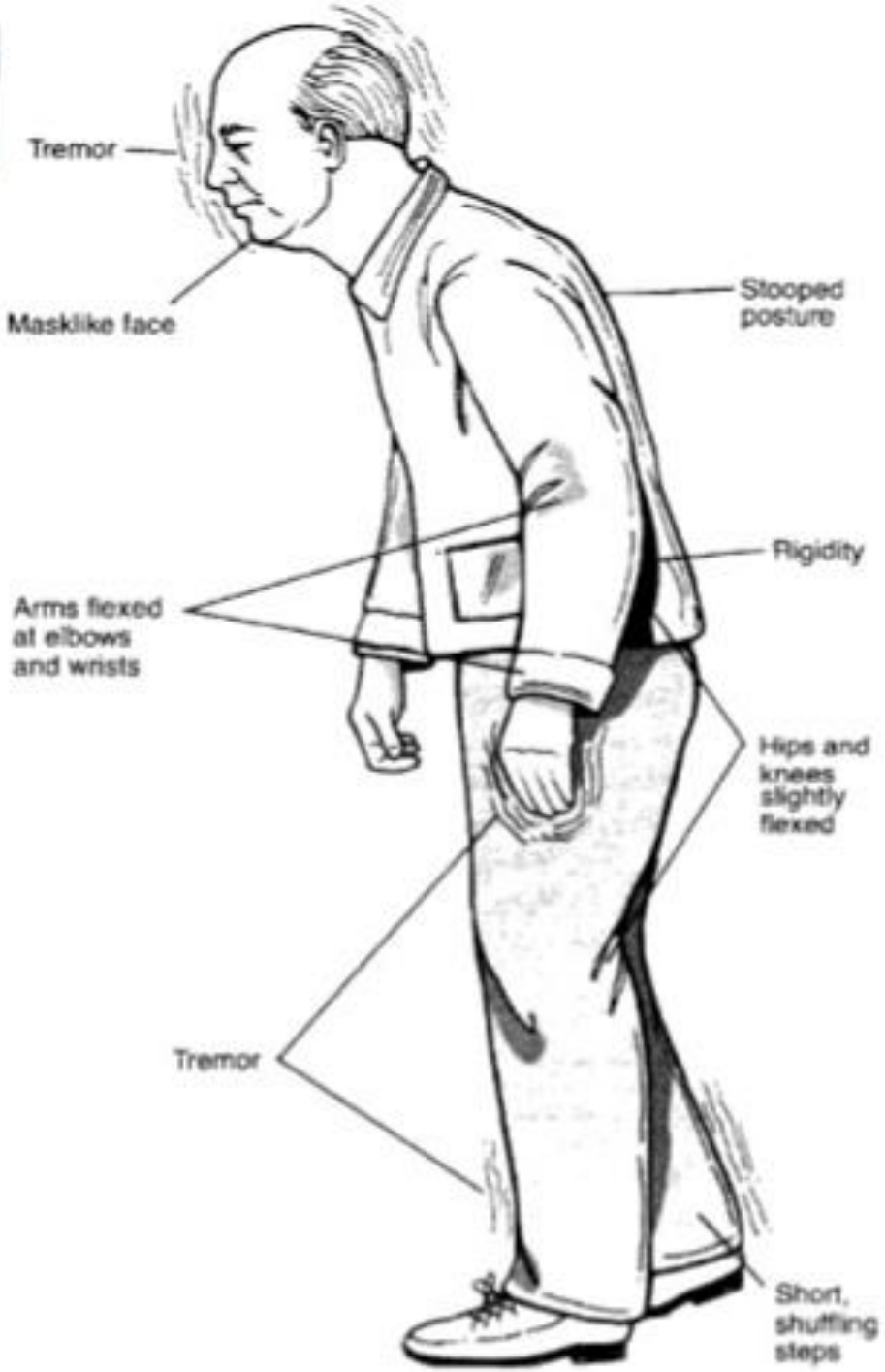
Neurons with round intracytoplasmic inclusions (containing tau protein)



4. Parkinson disease

- **Parkinsonism:** A clinical syndrome characterized by tremor (resting / pill-rolling), rigidity, bradykinesia and instability **+** stooping gate, expressionless faces, shuffling gait with small steps.

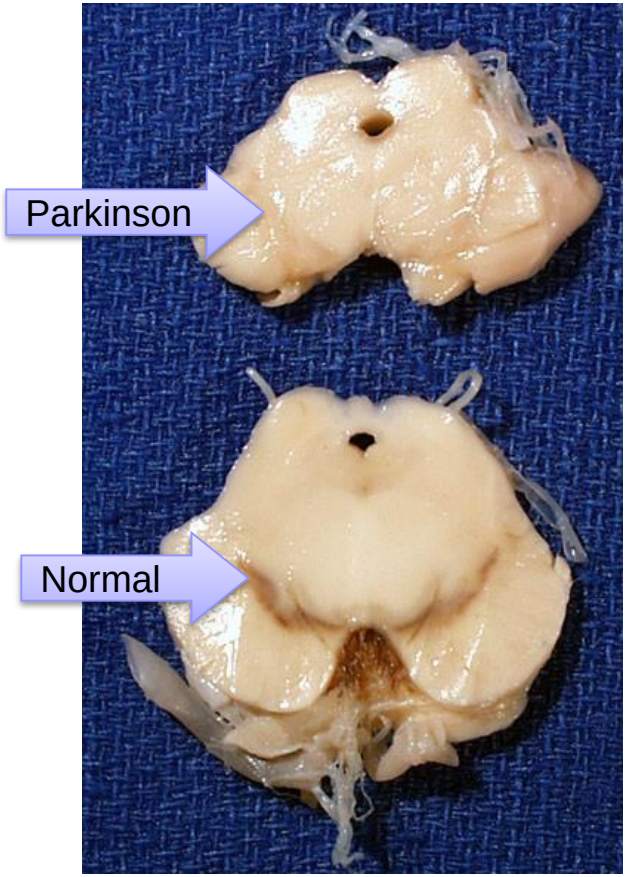
- **Cause:** Damage of **dopaminergic neurons** in **substantia nigra**.


Tremor
Masklike face
Stooped posture
Rigidity
Arms flexed at elbows and wrists
Hips and knees slightly flexed
Tremor
Short, shuffling steps

Parkinson disease

- **Types:**
  - **Secondary: Antidopaminergic drugs, trauma, vascular disorders, viral encephalitis, neurotoxic agents.**
  - **Primary (Parkinson disease*):**
    - Associated with characteristic neuronal inclusions containing ***α-synuclein*** (**Lewy bodies**).
    - **Sporadic** (mostly) or **familial** (mutation in α synuclein gene involved in synaptic transmission OR other genetic abnormalities some related to **Tau** protien).
    - Adults, 60s.

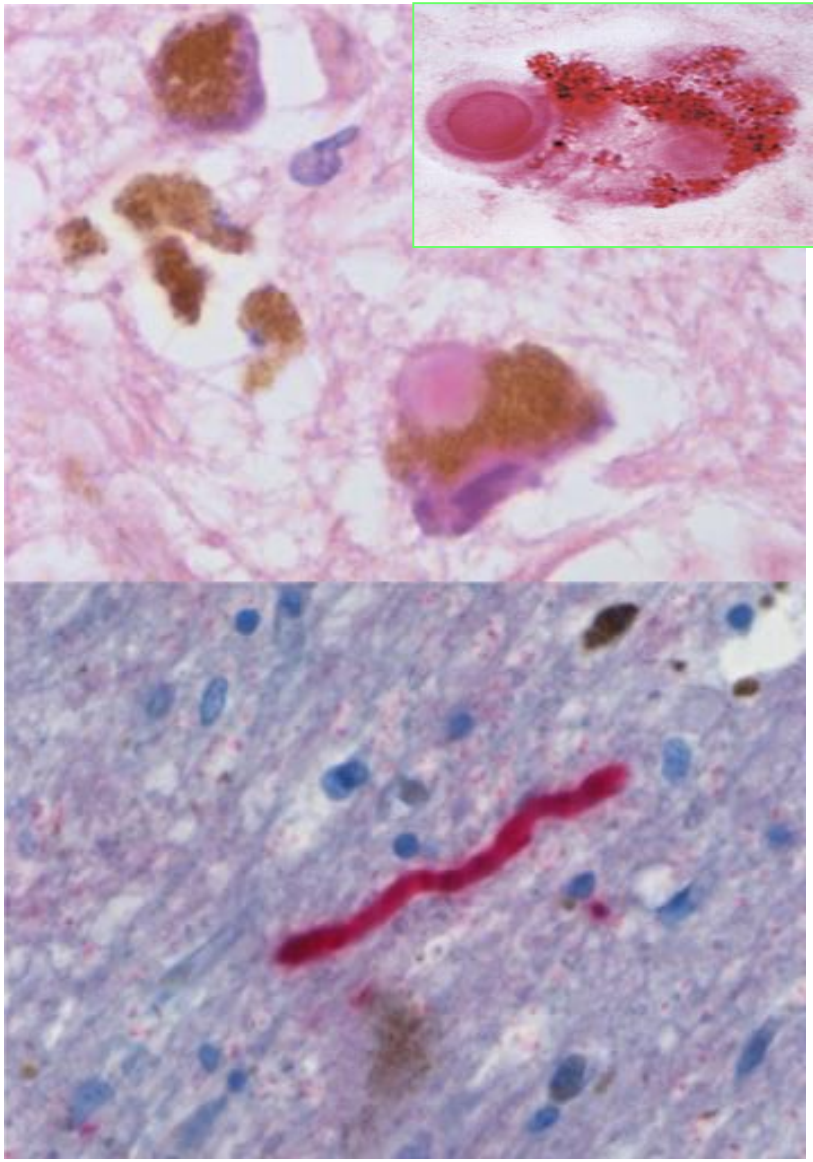
Parkinson disease - Gross

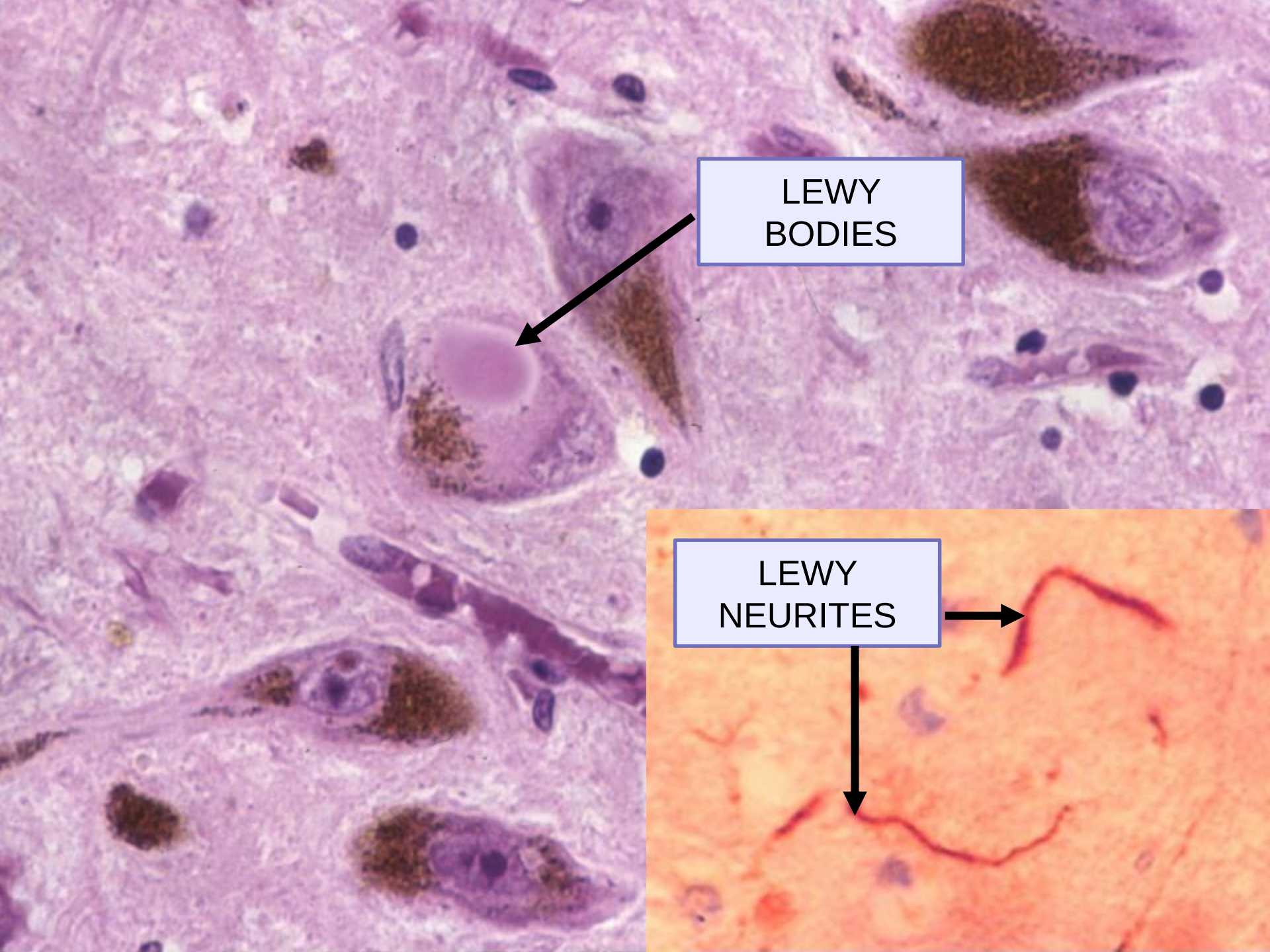


Loss of pigment in the **substantia nigra**

Parkinson disease - Microscopy

- **Loss of pigmented neurons** in substantia nigra with gliosis.
- **Lewy bodies** in remaining neurones → Concentric eosinophilic inclusions in the cytoplasm with dense core surrounded by halo.
- **Lewy neurites** contain abnormal aggregates of α-synuclein.




LEWY
BODIES
LEWY
NEURITES

Lewy body dementia

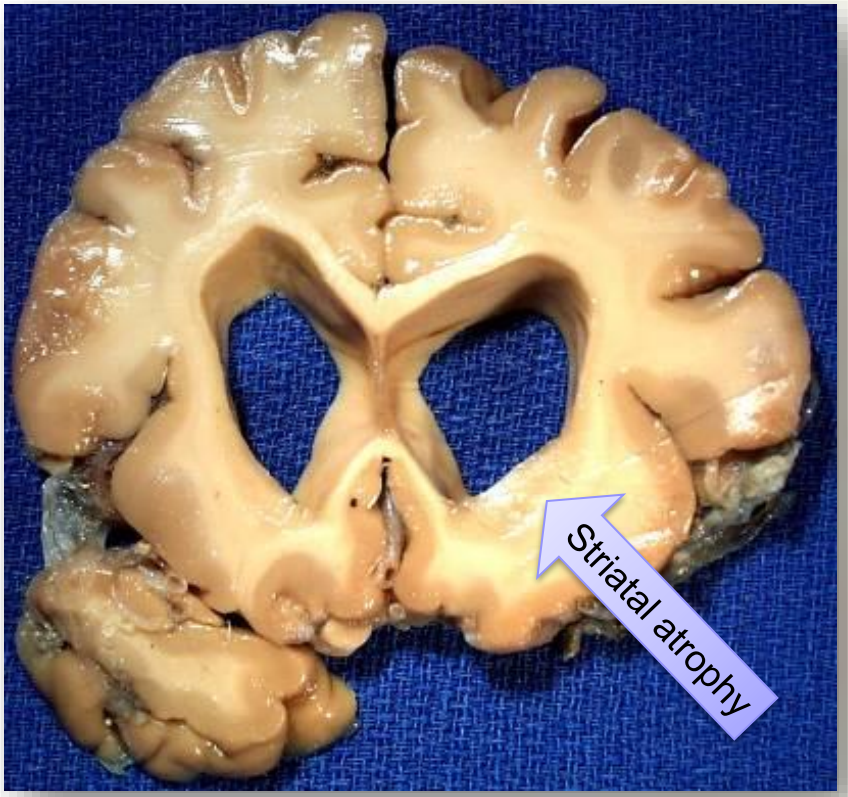
- Dementia emerges in many persons with Parkinson disease → arises within **1 year** of the onset of motor symptoms.

- Attributable to involvement of the **cerebral cortex** → Lewy bodies & neurites appear in the cortex (**DIFFUSE LEWY DISEASE**).

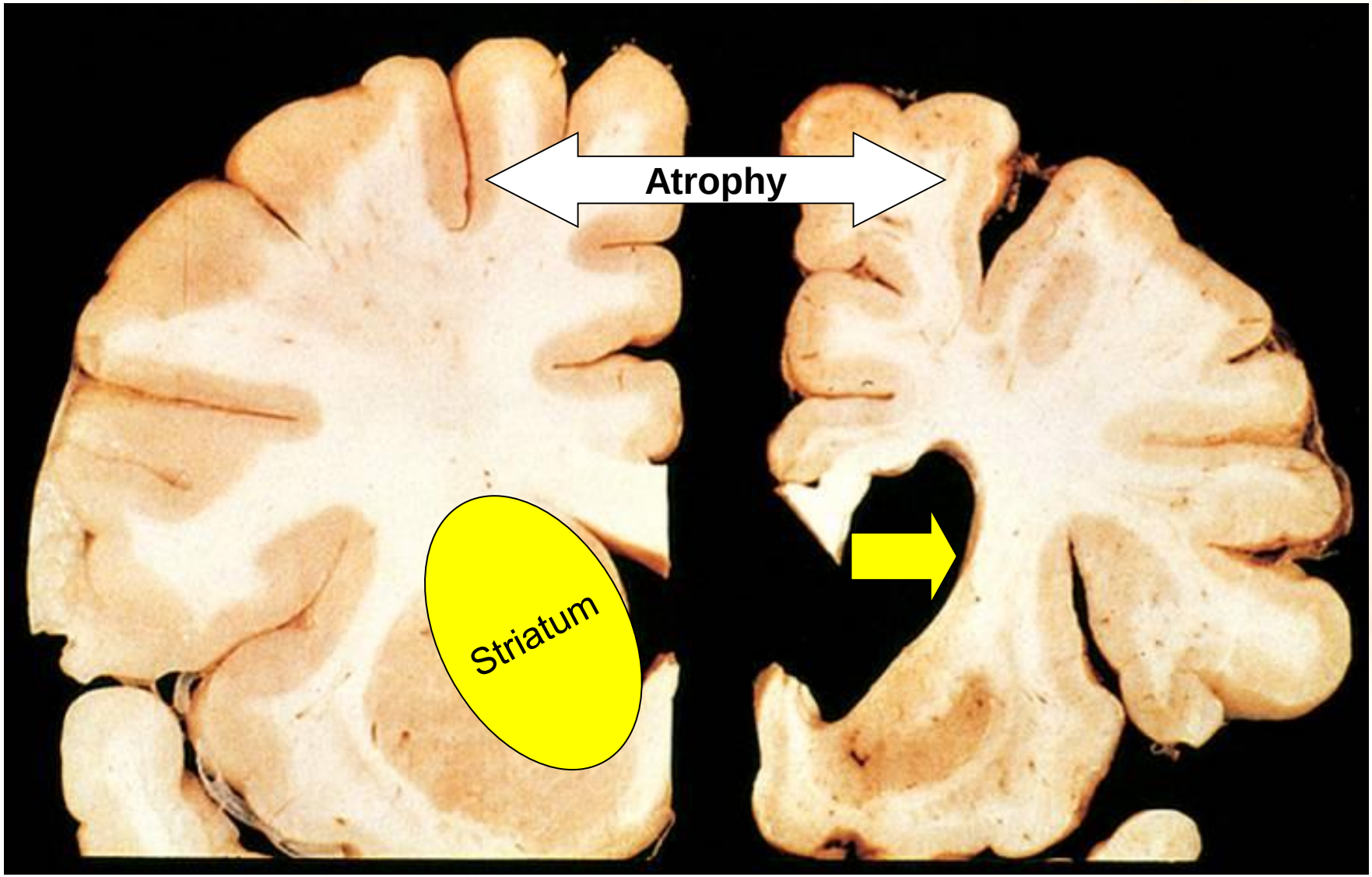
- Overlapping clinical features between parkinsonism + dementia.

5. Huntington's Disease

- Hereditary (**AD**) progressive disease. **5th** decade.
- **Cause:**
  - **CAG trinucleotide repeat expansions of HUNTINGTIN gene located on 4p.**
- **Characterized by:**
- **Choreiform** (jerky or dance like) movement.
- Memory & language problems.
- Ends with severe dementia → death (within ~ 15 yrs).
- **Gross:**
  - Atrophy of striatum (***caudate > putamen***) with compensatory **hydrocephalus** (ex vacuo) dilatation of the anterior horns of the lateral ventricles*.
  - Atrophy of cortex.

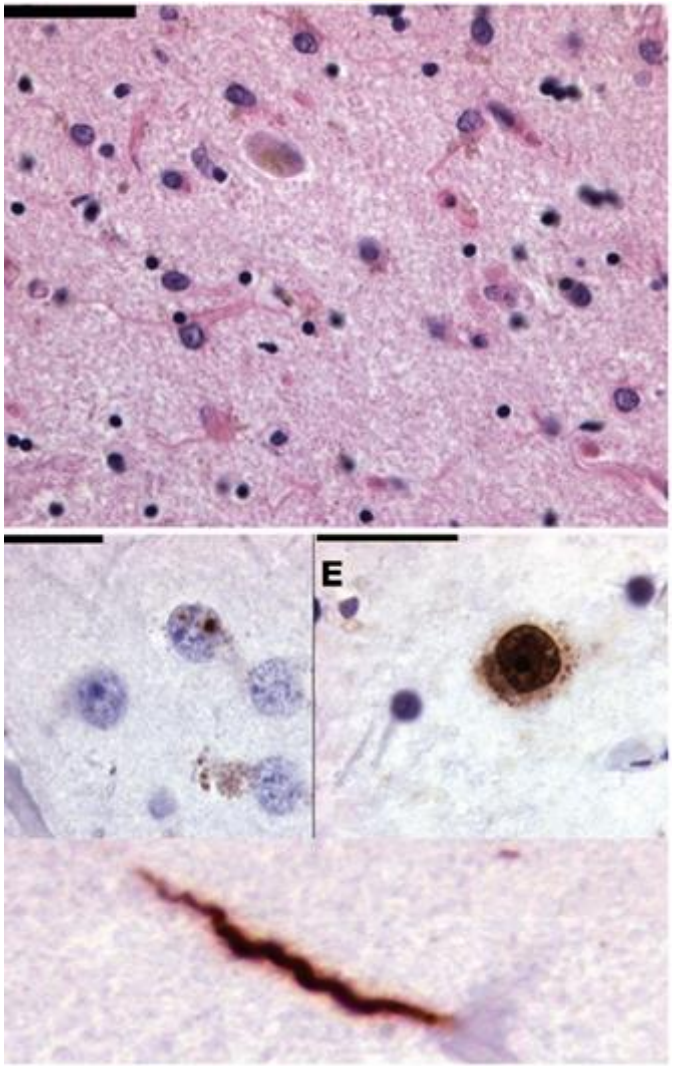


Normal - Huntington's



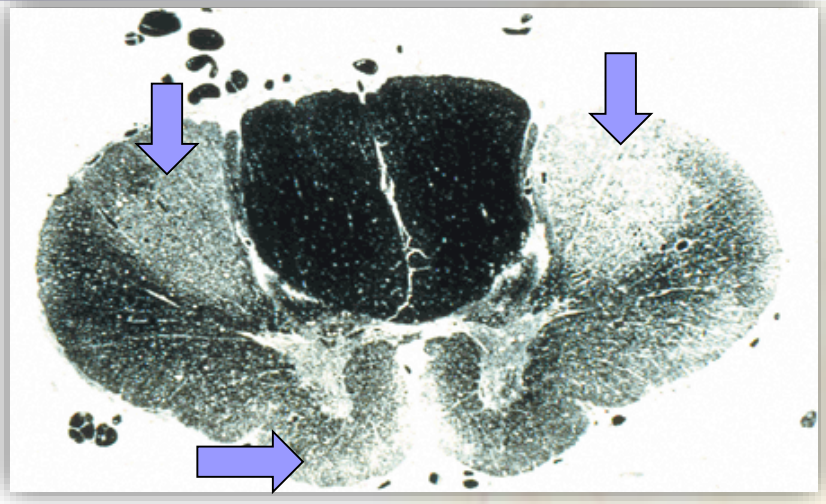
Huntington's - Histology

- Severe ***loss of neurons*** in striatum → esp. GABA type.
- Fibrillary ***gliosis***.
- Remaining neurons show ***intranuclear inclusions*** (by accumulation of huntingtin protein).



6. Amyotrophic Lateral Sclerosis (ALS)

- M>F, >50 yrs.
- Mostly **sporadic** (unknown cause), **familial** (AD - < 10%).
- **Genetic:** Many genes (20% SOD1 gene on chr. **21**.



Degeneration of lateral corticospinal tracts (myelin stain).

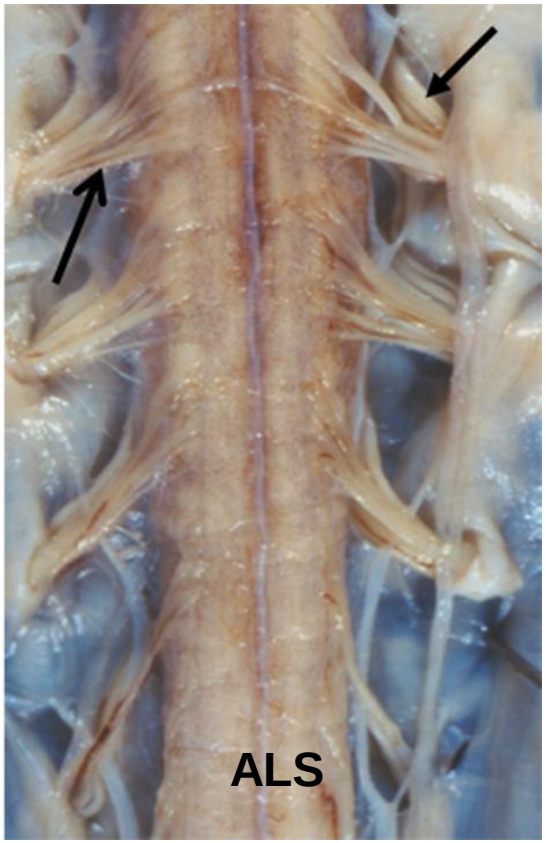
- ALS caused by death of:
  - ❖**LMN** in the SC & brain stem →neurogenic muscle atrophy, asymmetric weakness & fasciculation.
  - ❖**UMN** (Betz cells) in the motor cortex → paresis, hyperreflexia, spasticity, & +ve Babinski sign.
- Ass. with degeneration of the corticospinal tracts in the **lateral** portion of the SC **("lateral sclerosis")**.
- Sensation & bowel/bladder control is usually *unaffected***.

ALS

Lou Gehrig

Stephen Hawking

ALS - Morphology



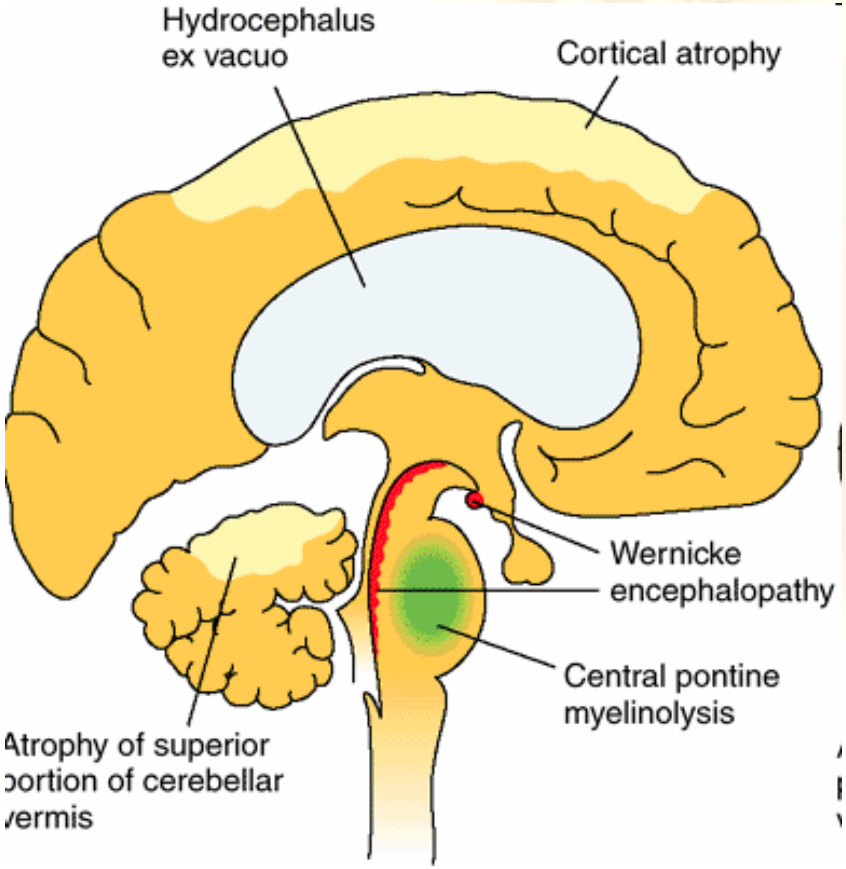
- Thinning of SC anterior roots ± precentral gyrus atrophy.
- **Microscopic**: ↓ anterior horn cell neurons + reactive gliosis ± Bunina bodies.

JAMES COOK UNIVERSITY
AUSTRALIA

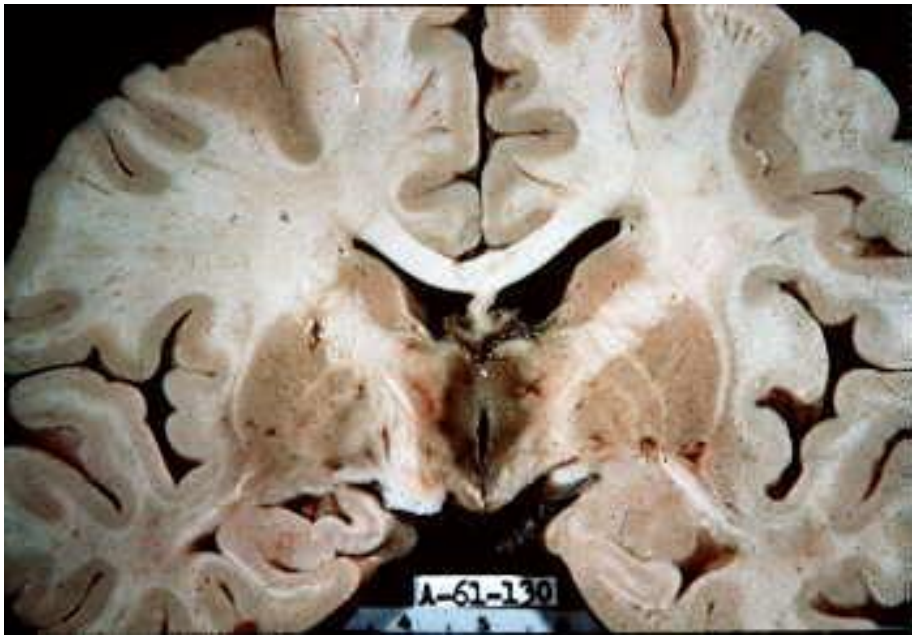
Acquired Metabolic & Toxic Disorders

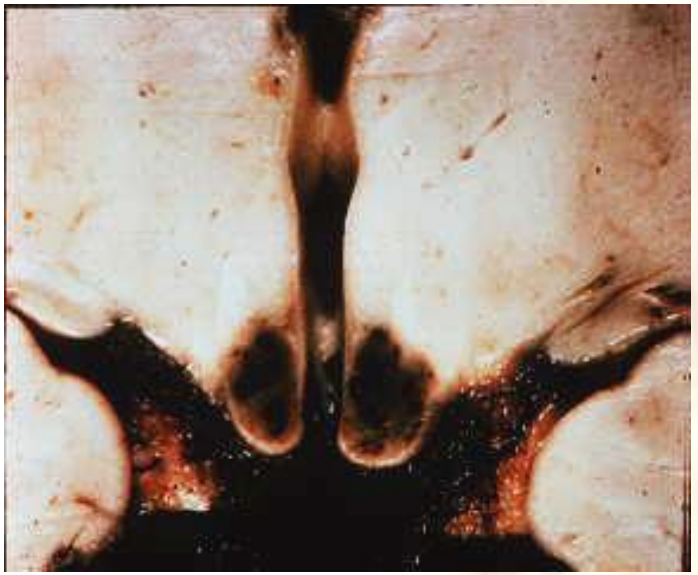
Metabolic CNS Disorders:

- Alcoholism induced CNS disorders:
  - Wernicke syndrome (vit B1 thiamine def.) – ataxia, confusion.
  - Korsakoff syndrome (memory)
  - Central pontine myelinolysis
  - Cortical atrophy
  - Atrophy of vermis of the cerebellum.



Wernicke's encephalopathy:



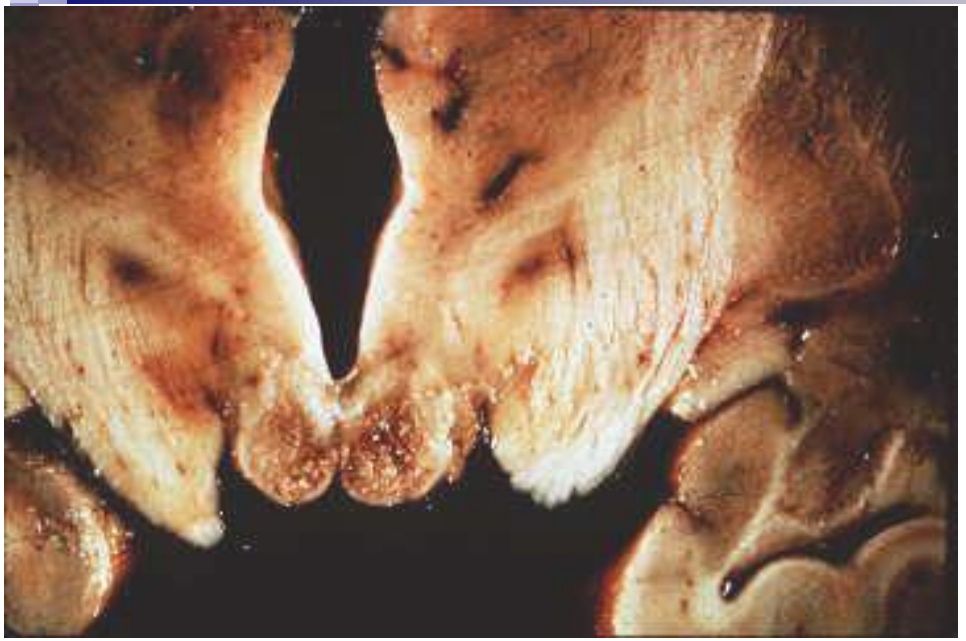


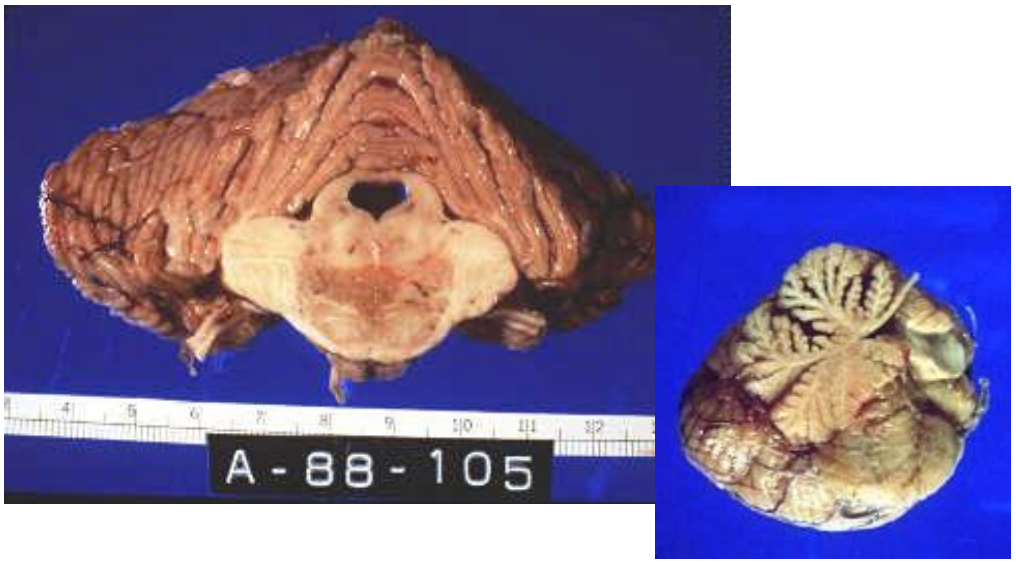
Recurrent petechial hemorrhages in the hypothalamus, mamillary bodies with atrophy.

Wernicke's Sy: Altered Thermal regulation & consciousness, ophthalmoplegia, nystagmus.

Korsokoff Psychosis: Loss of recent memory compensated by confabulation.

Korsakoff's disease:



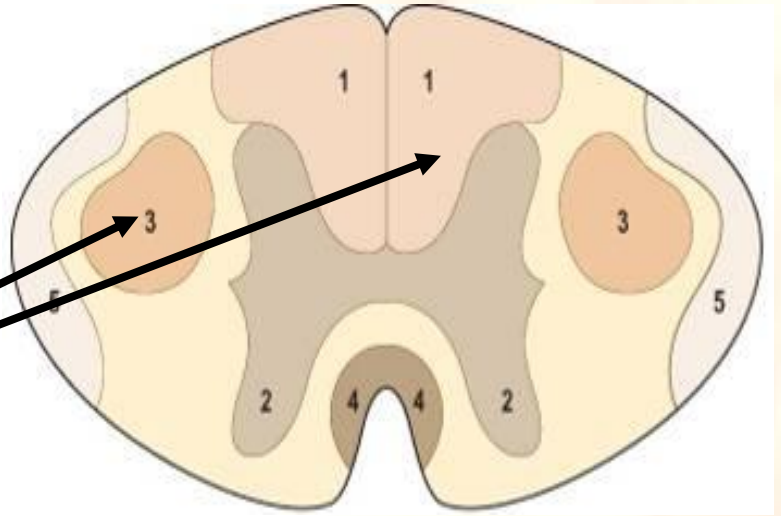


Korsakoff's disease.
Central pontine myelinolysis. Demyelination of the center of the pons. Shrunken, brown mammillary bodies (indicating chronic stage). Cause is unknown but usually seen in chronic alcoholics and associated with rapid over-correction of hyponatremia.

Alcoholic cerebellar atrophy. Shrunken folia and widened fissures of the anterior, superior vermis of the cerebellum. Another change which may be found in chronic alcoholics.

Vitamin Def & Neuropathy:

- **A** - Benign intracranial hypertension (rare)
- **B1** Wernicke-Korsakoff syndrome
- **B2** Peripheral neuropathy, ataxia,dementia
- **B6** Convulsions in infants
- **B12** Weakness and paraesthesiae in the lower limbs (1 & 3)
- **C** Scurvy
- **E** Weakness, sensory loss, ataxia, nystagmus

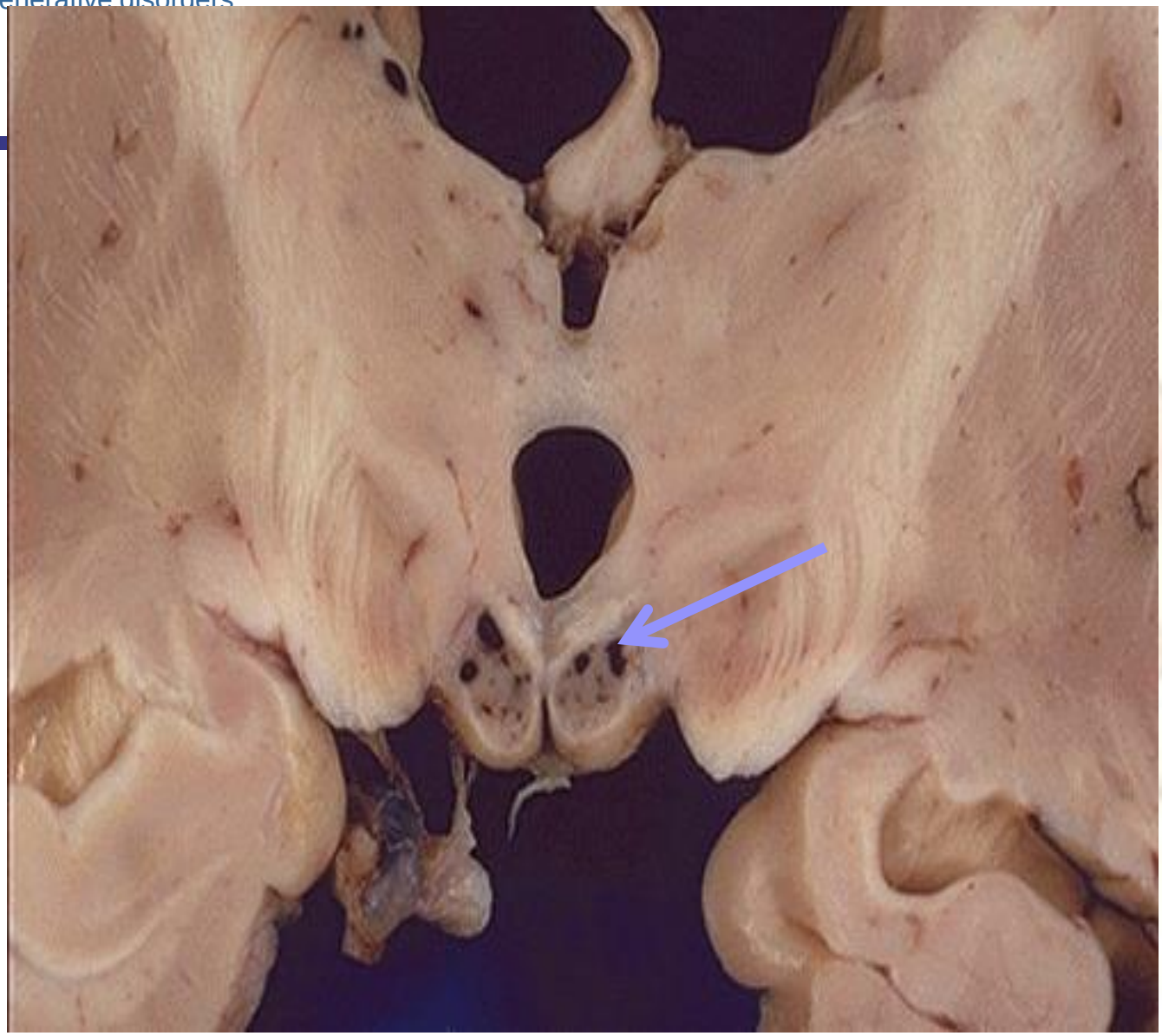


A- Nutritional Diseases :

1- Thiamine deficiency:

Beriberi & alcoholism

- **Pathology : Wernicke encephalopathy**
  - **hemorrhage in mamillary bodies**
  - **hemosiderin deposition**
  - **gliosis**
- **Symptoms**
  - **Memory loss**
  - **Peripheral neuropathy**



- **2 - Vitamin B12 deficiency**
  - **Pernicious anemia**
  - **Subacute Combined Degeneration of spinal cord**

Pathology :

Myelin loss in dorsal & lateral columns

Symptoms :

Result in motor & sensory loss

B- Acquired Metabolic Disorders

- **1- Hypoglycemia :**
  - **Changes similar to Global hypoxia specially in hippocampus.**
  - **Cerebellar Purkinje cells more resistant.**

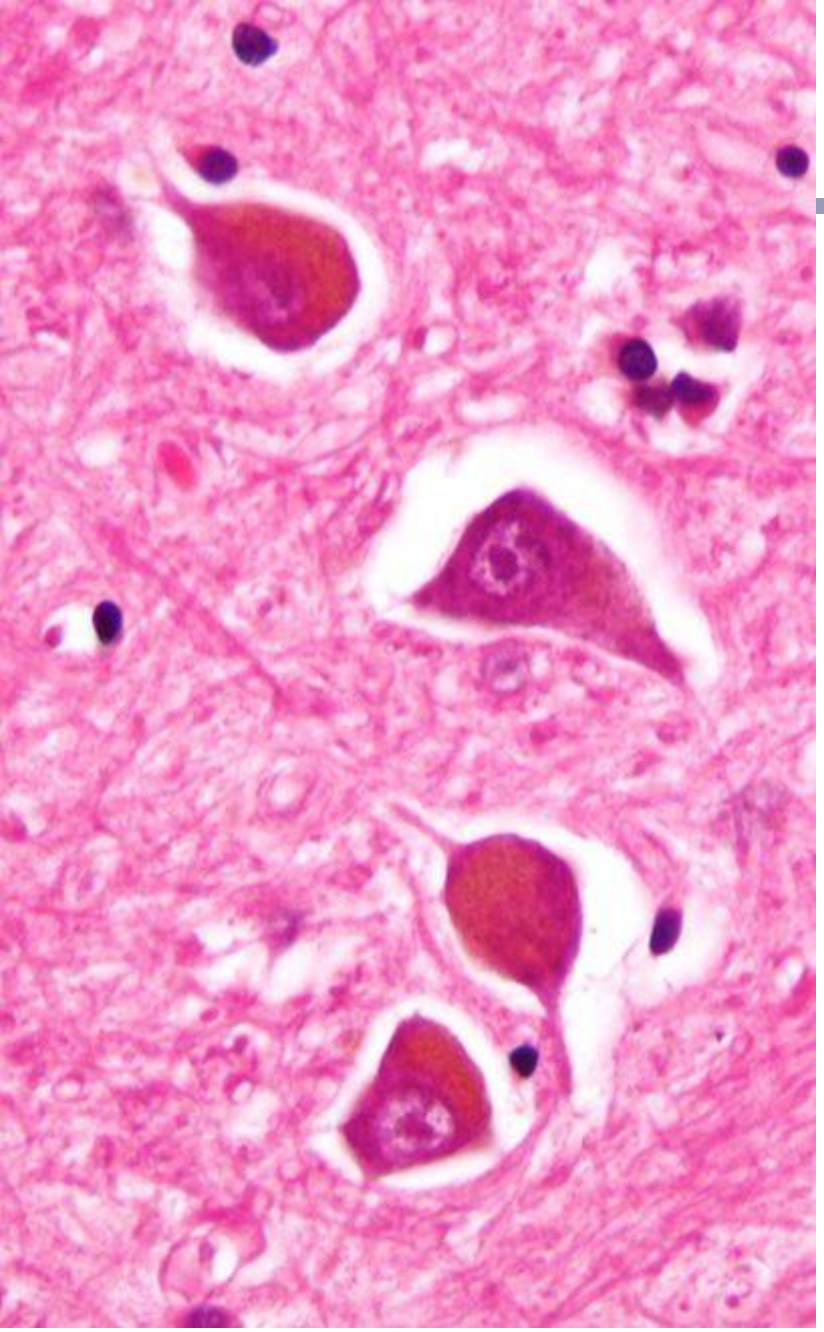
- **2- Hyperglycemia :**
  - **Ketoacidosis in uncontrolled Type I**
  - **Hyperosmolar coma in Type II**
  - **Result → coma due to accumulation of water in neurons → cerebral edema**

3- Liver disease :

- **Metabolic dysfunction of astrocytes → inability to detoxifying accumulated amonia → Hepatic Encephalopathy and 'Flapping tremor'**

- **Pathology :**

Glial response with formation of Alzheimer type II astrocyte in cortex & basal ganglia

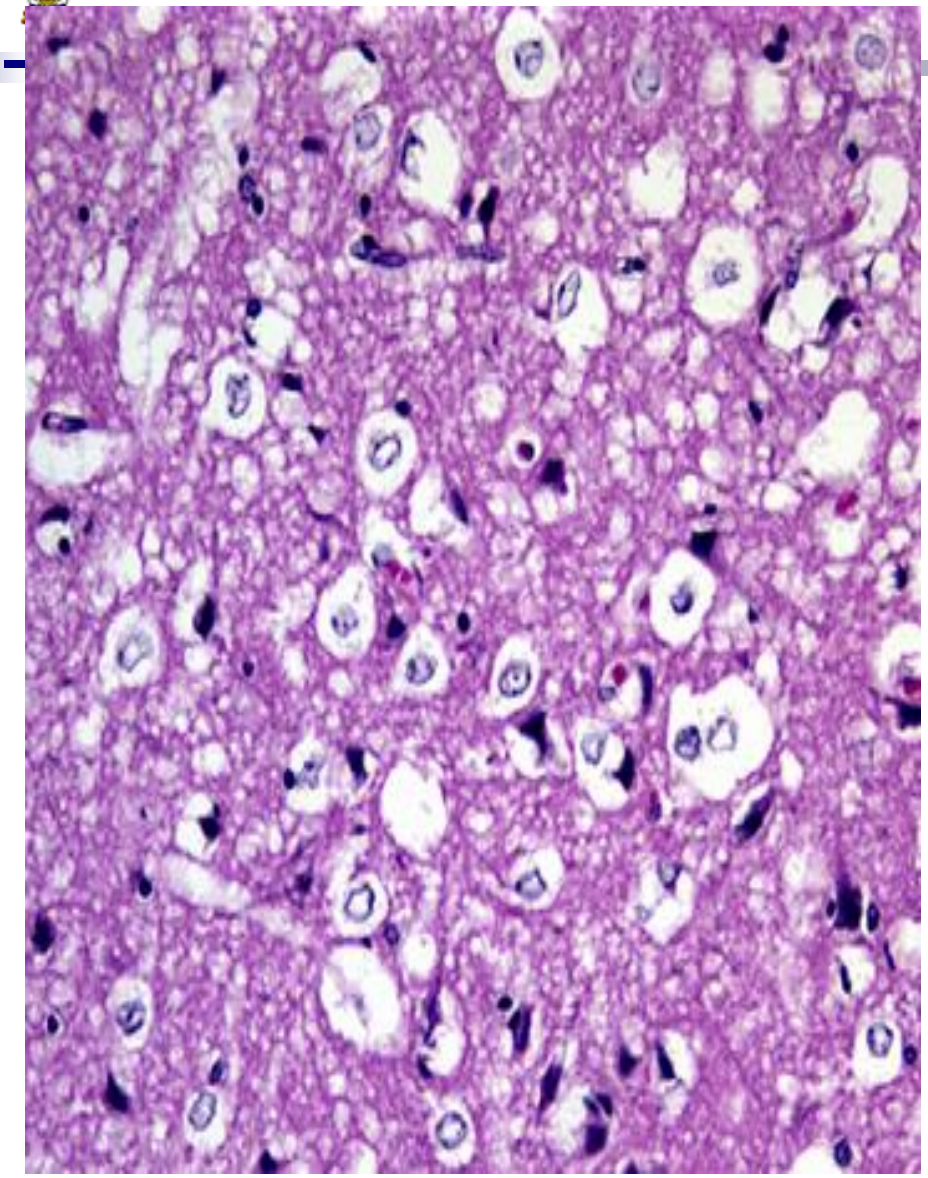


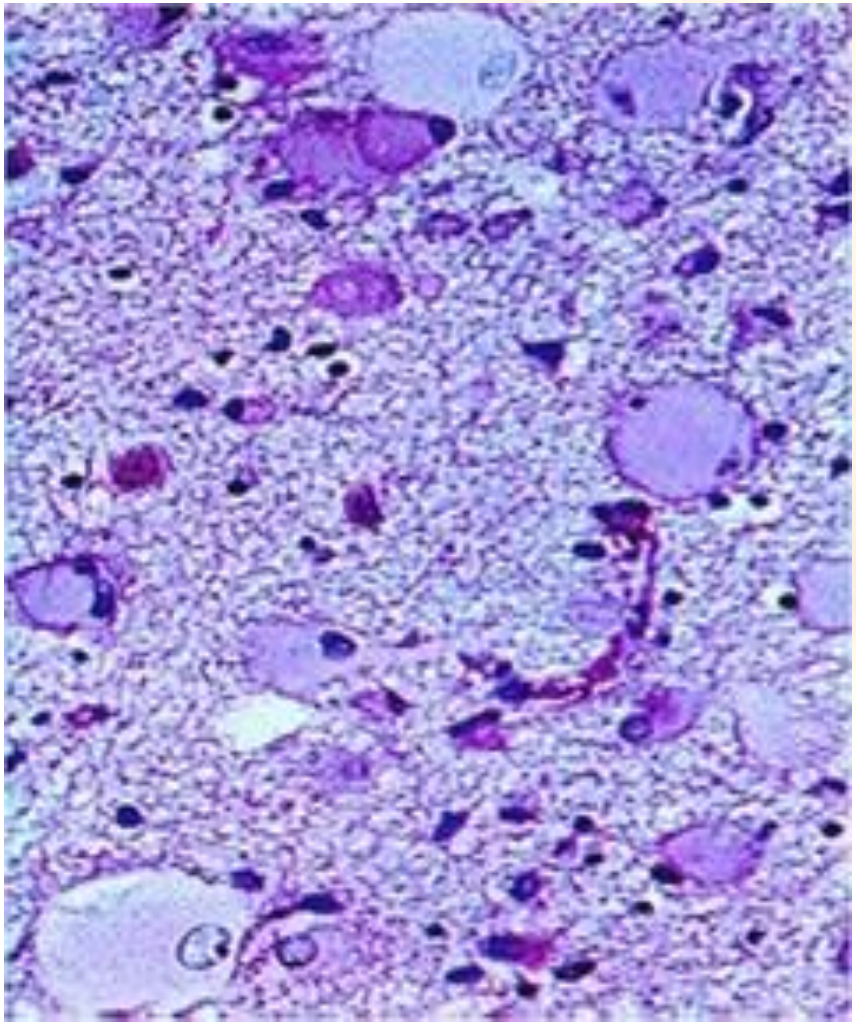
Pathology :

Glial response with formation of

Alzheimer type II astrocyte in cortex & basal ganglia.

- Seen in chronic alcoholics & in Wilson's disease.





C- Toxic Disorders :

- **Metals & Industrial chemicals → blindness, neurotoxicity, diffuse encephalopathy…**
- **Chronic Alcoholism → cerebellar dysfunction**
  Acute ethanol → cerebral edema
- **Methotrexate →white matter demyelinization**
- **Ionizing radiation → white matter ischemia**

Thank you