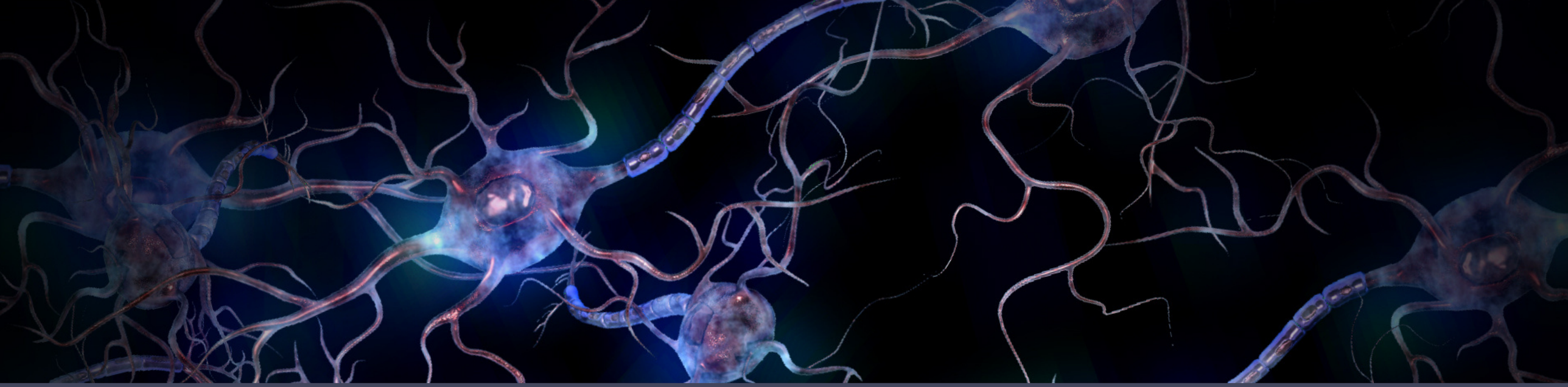

YU - Medicine

Passion Academic Team

Sheet# 3 - Pathology

Lec. Title : Neurodegenerative Diseases

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If you come by any mistake , please kindly report it to shaghafbatch@gmail.com

PERIPHERAL NERVOUS SYSTEM

Degenerative Disorders I

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.

some drugs slow the progression of the disease.

General features

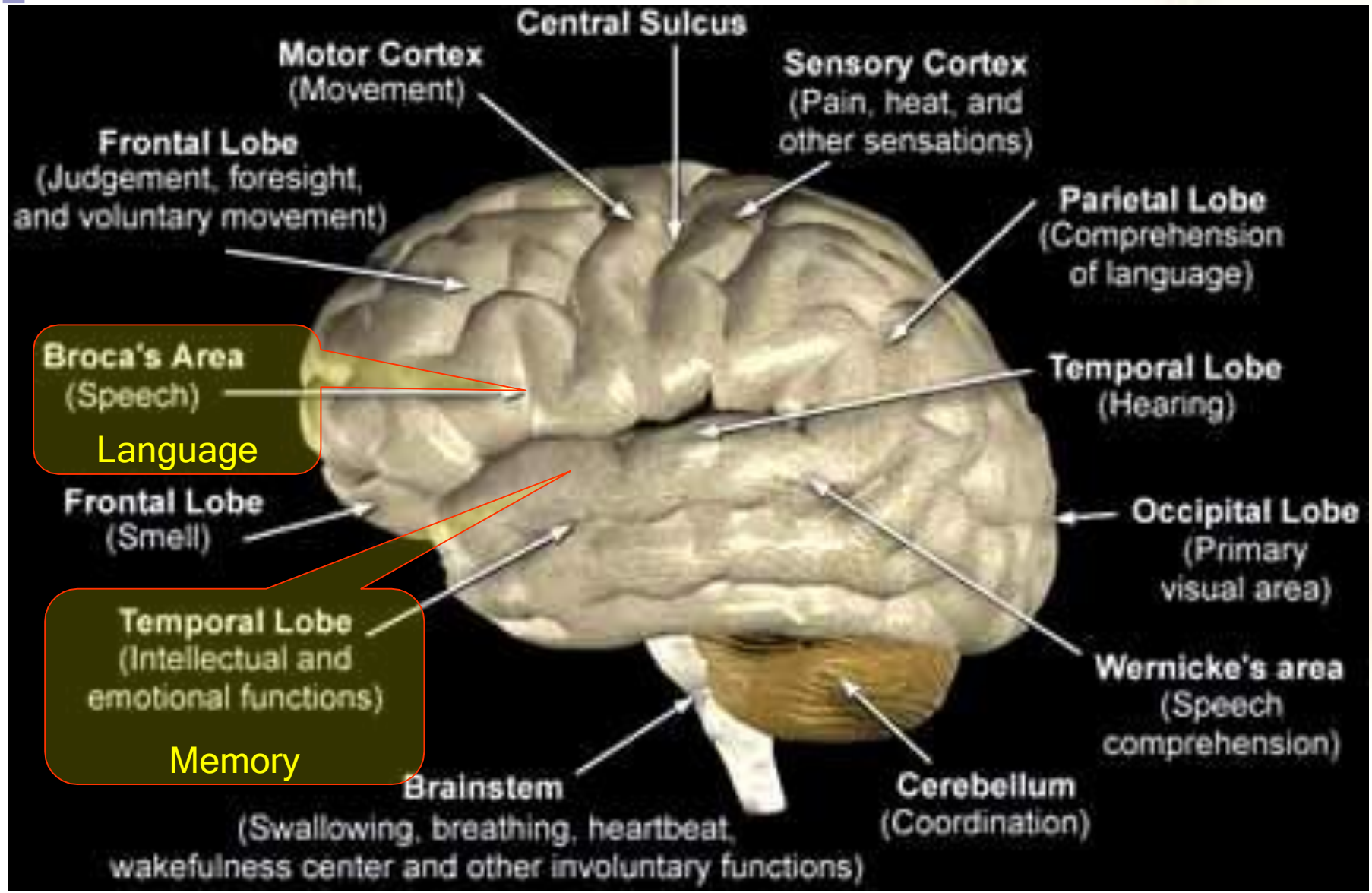
1. **Pathologically**, most of NDD are associated with accumulation of abnormal **protein aggregates** (forming *cellular inclusions*):
   - **Cause:** Usually unknown.
   - **Lead to**: Indirect stress response, direct neurotoxic effect OR prions-like effect (???).
   - **Examples:** Tangles, plaques,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

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

depend of the selective group of neurons that involved .

جدول

rain : 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**. 60y-70y
- 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)

Onset : It develops gradually overtime Less memory in mild form then come severe form .

Aphasia: lose their ability to speech.

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***.

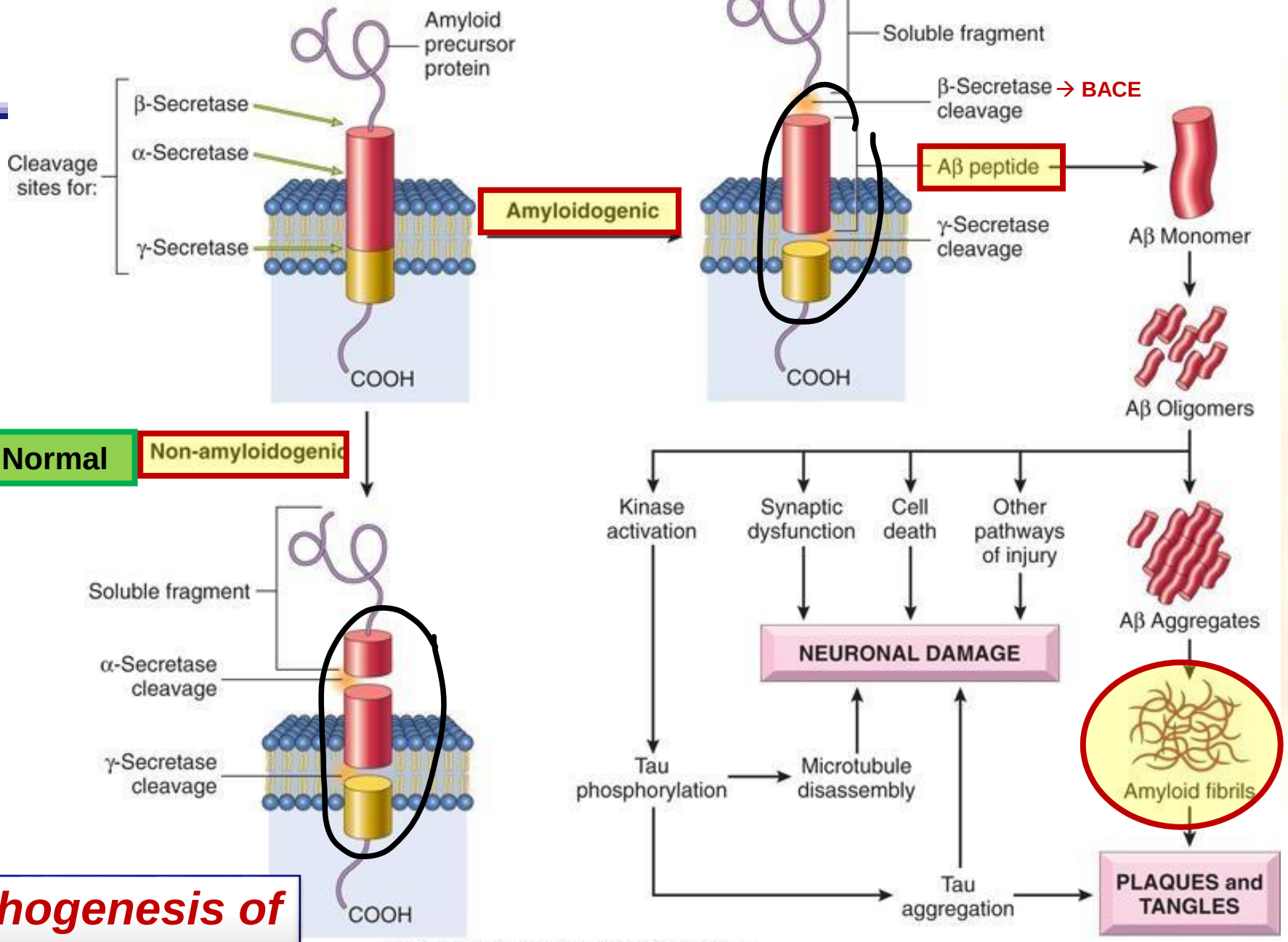
↑Death of neurons → ↑toxicity → ↑ severe disease.

- **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.

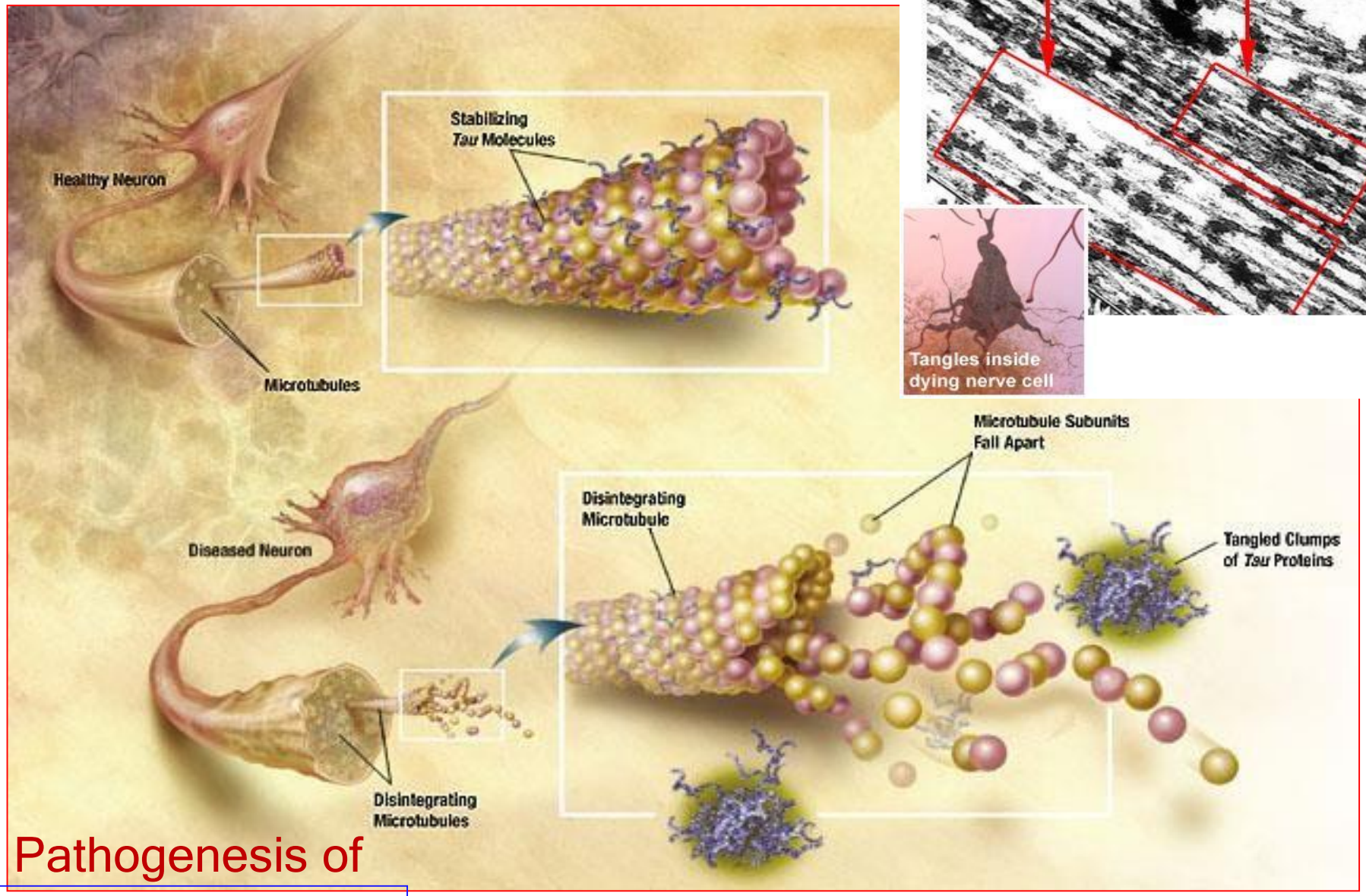
AD – Pathogenesis:

- 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



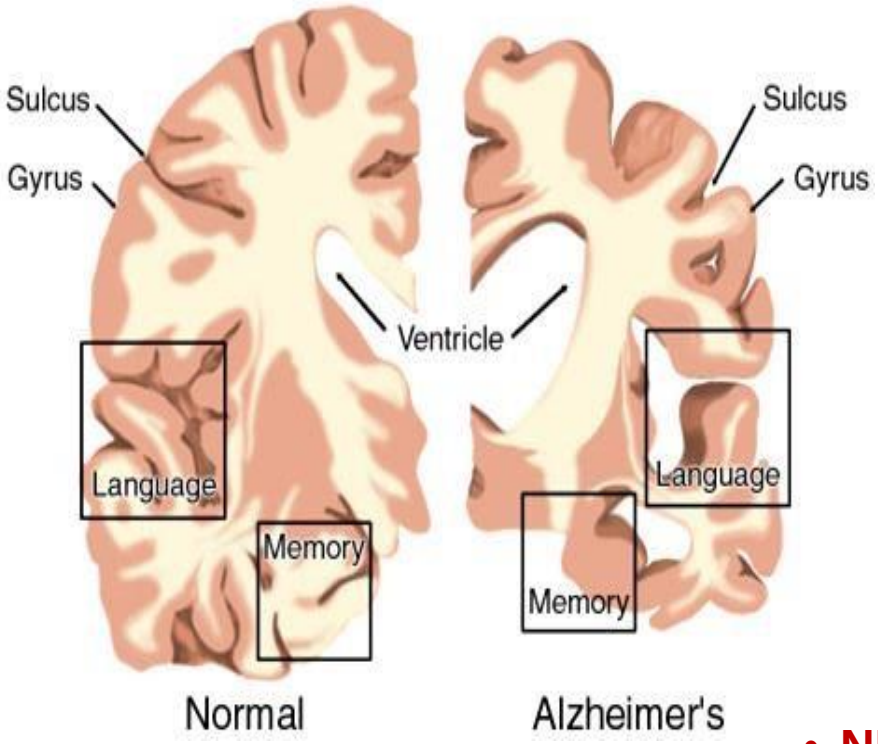
Pathogenesis of Neurofibrillary Tangles

Familial AD

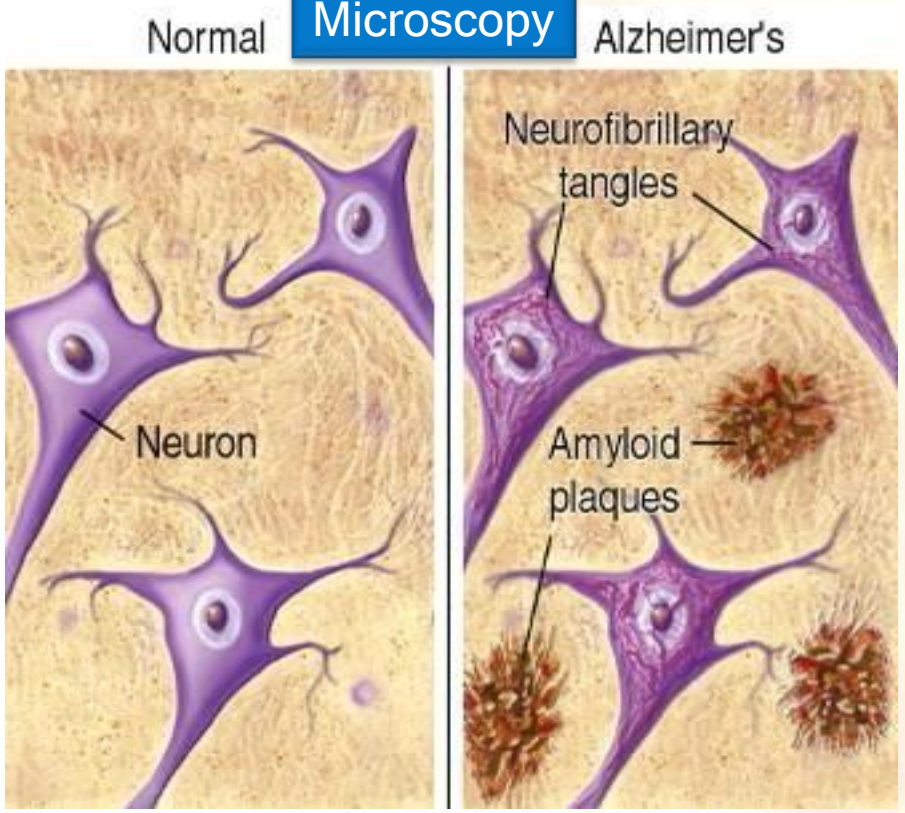
- 5-10% of AD cases.
- Manifests at *earlier* age than sporadic AD.
- Many genetic mutations have been identified (*& many are unidentified*):
  - **APP gene** (on chr. 21) → extra copy in as in DOWN syndrome → dementia by 40's.
  - **γ-secretase genes** (presenilin-1 or presenilin-2).
  - **Apolipoprotein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

AD : Morphology

Gross



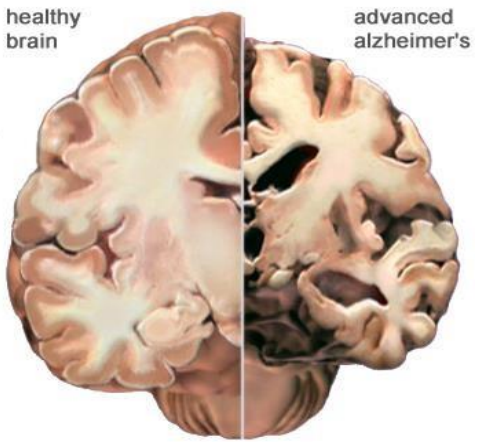
Microscopy

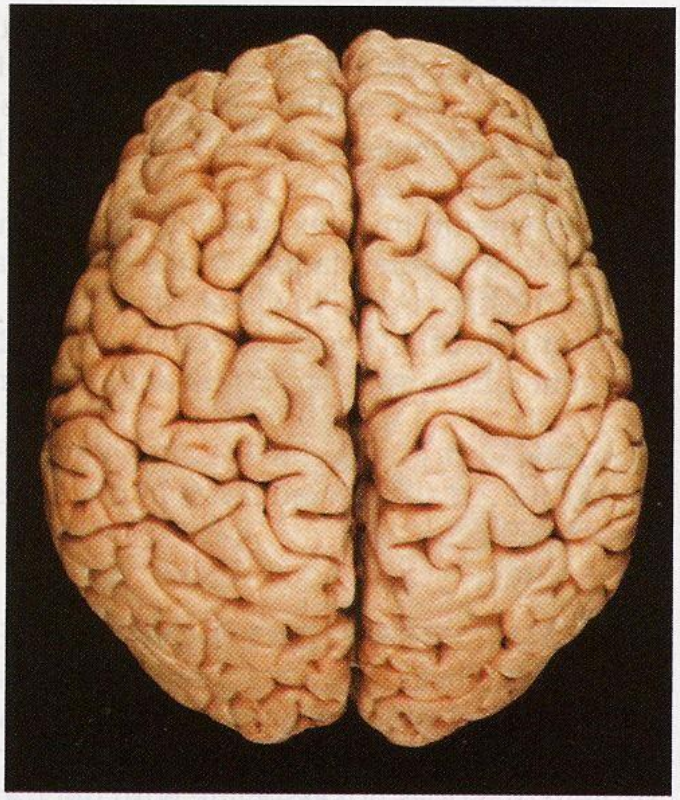


- **CORTICAL ATROPHY:**
- Then involves frontal, parietal, temporal …→ usually spares motor and sensory cortices
- Hydrocephalus ex vacuo .

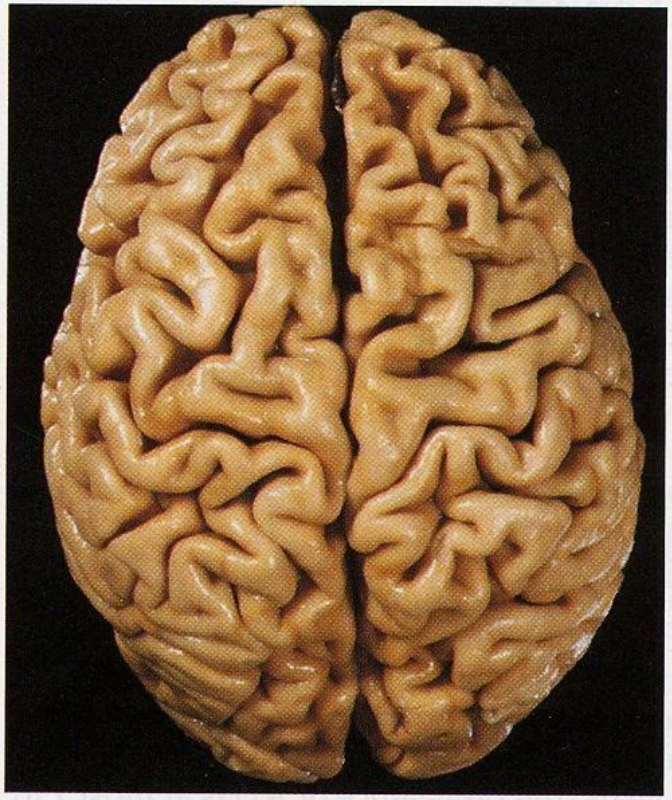
- **NEUROFIBRILLARY TANGLES** →Intracellular
- **NEURITIC PLAQUES & AMYLOID ANGIOPATHY** → Extracellular
- Loss of neurons with gliosis.

→ First start in *entorhinal cortex & hippocampus*.





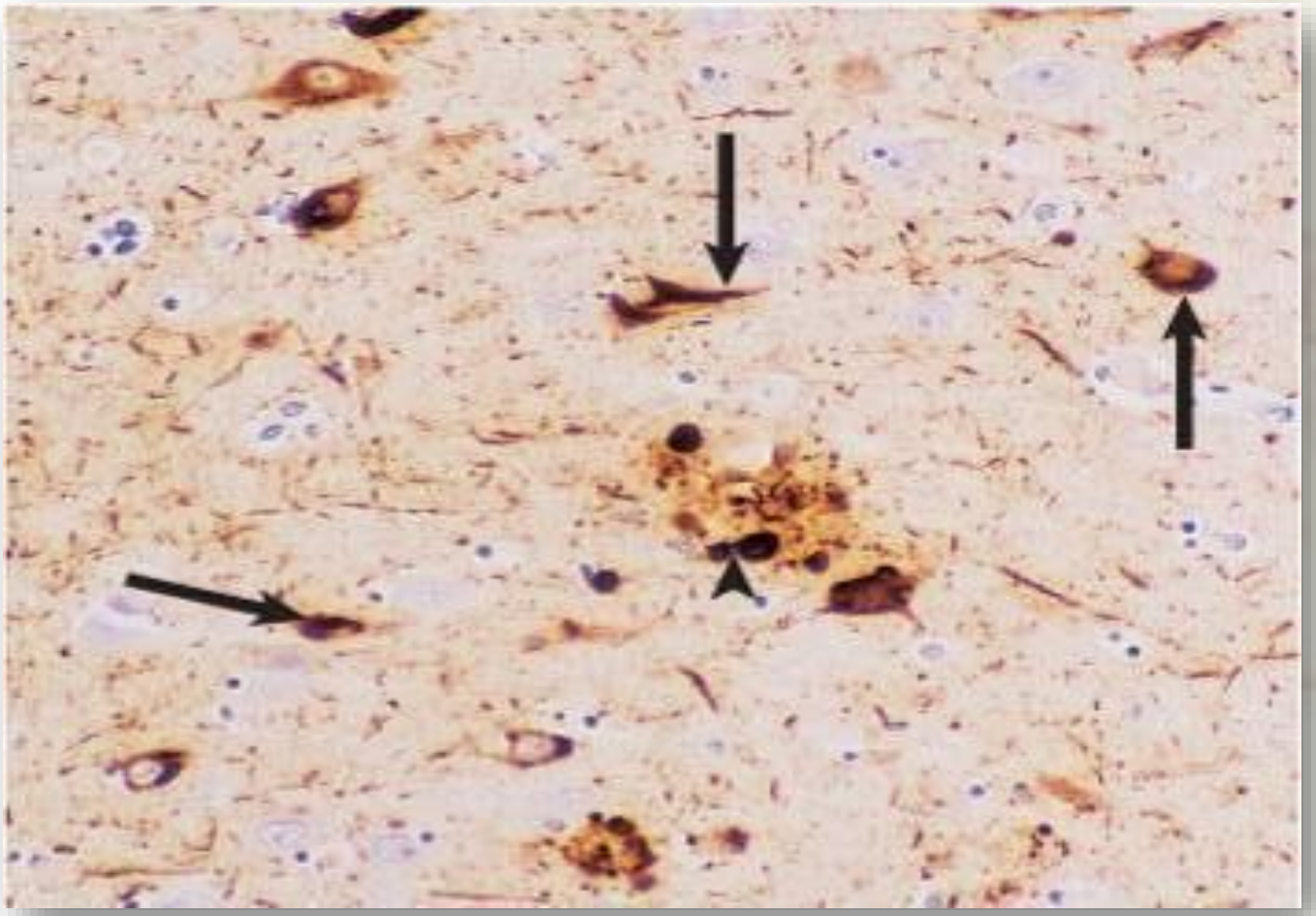
A



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.

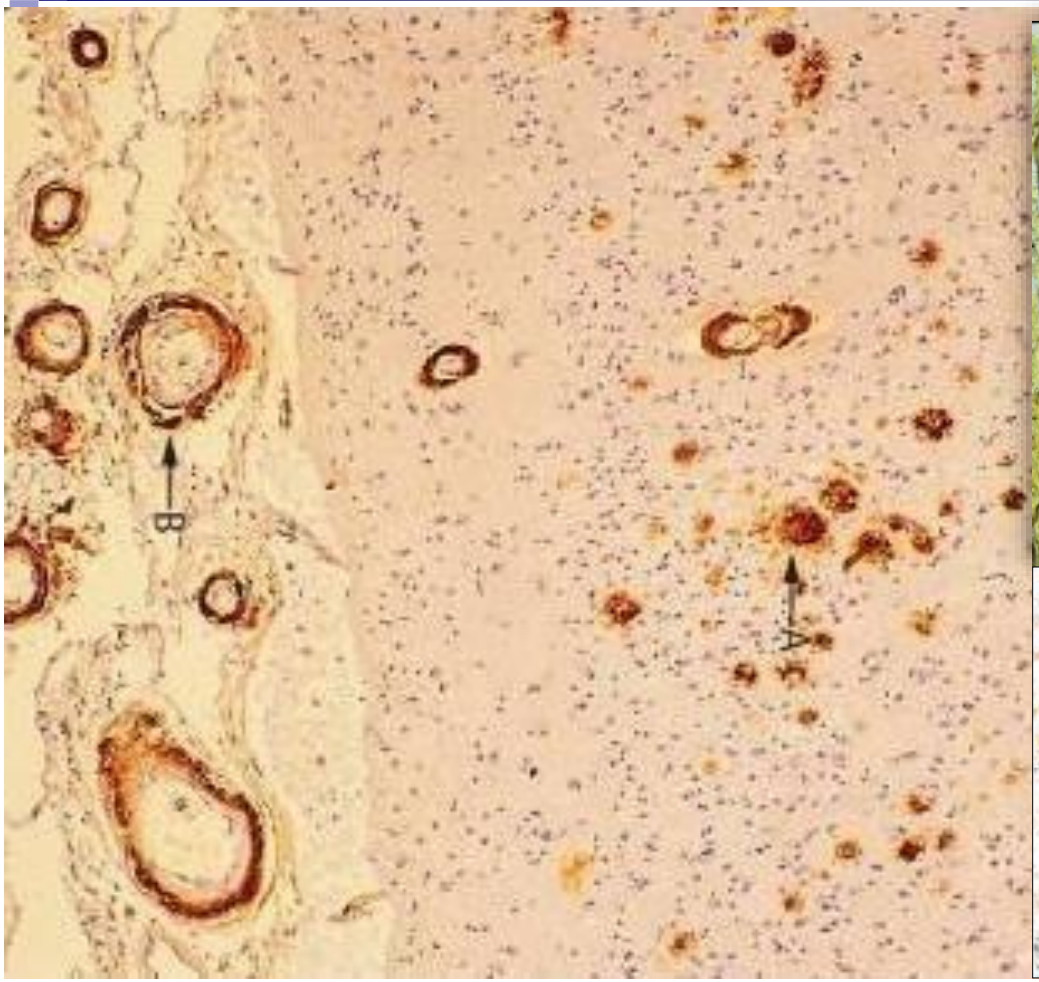
AD - Microscopy

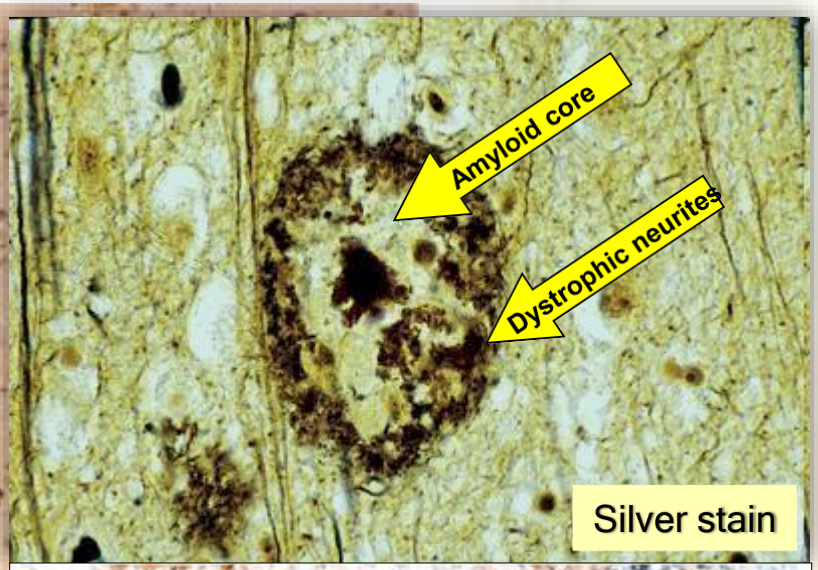


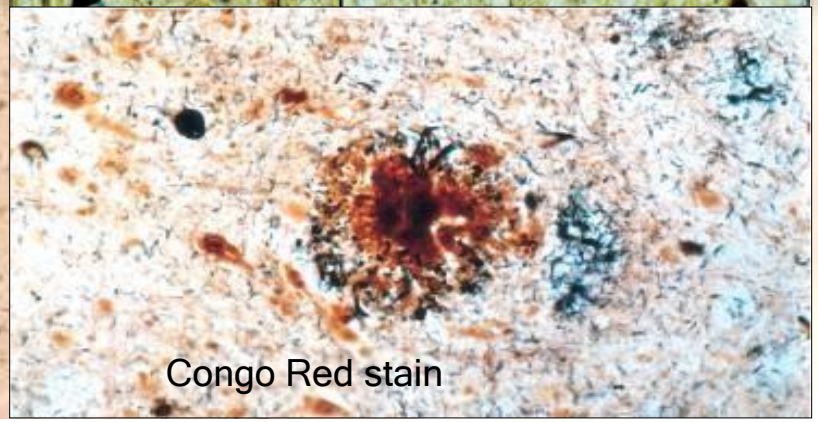
Plaques & around BV.
Aβ Amyloid

NF Tangles-Intracellular
tau protein

Neuritic plaques & Amyloid Angiopathy







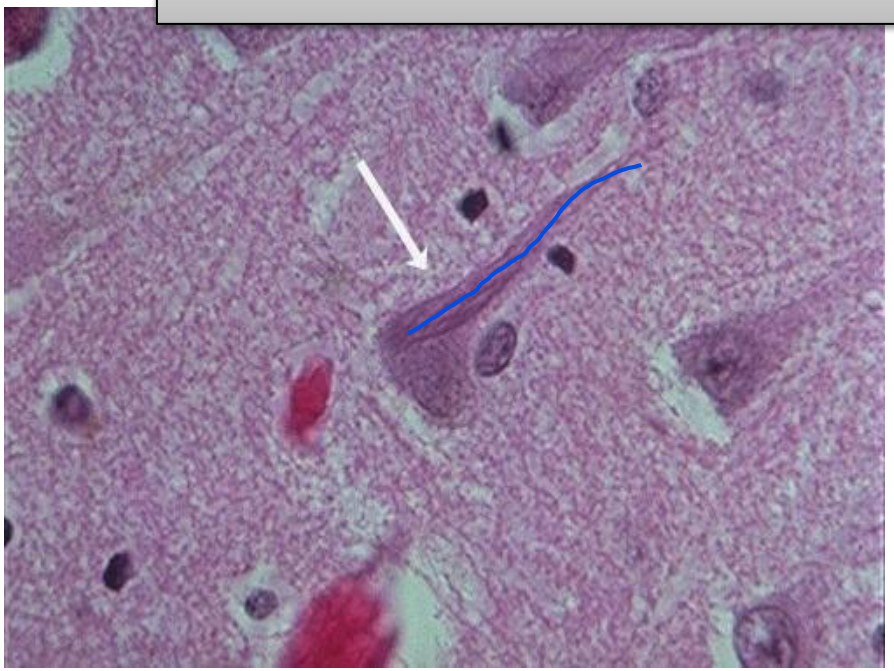
Amyloid deposits in: A . Plaques in brain substance – composed of tortuous neuritic processes surrounding a central amyloid core of **Aß protein** → **specific for AD**

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.

Aβ Amyloid deposition is specific to AD .
وجودها يدل بوجود مرض الزهايمر. Aβ Amyloid



Diagnosis of AD

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

Clinical picture:
يمكن يتذكر احداث صارت من ٢٠ سنة او اكثر يعني امور كثير قديمة
بس ما بتذكر شو صار معه امبارح او بالفترة القريبة .

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

لازم اخد عينة من المخ بعد وفاة الشخص ل أشوف تحت المايكروسكوب :

* **Aβ** (extracellular) → form ***plaques***.
* **tau** (intracellular) → form ***tangles***.

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…..!

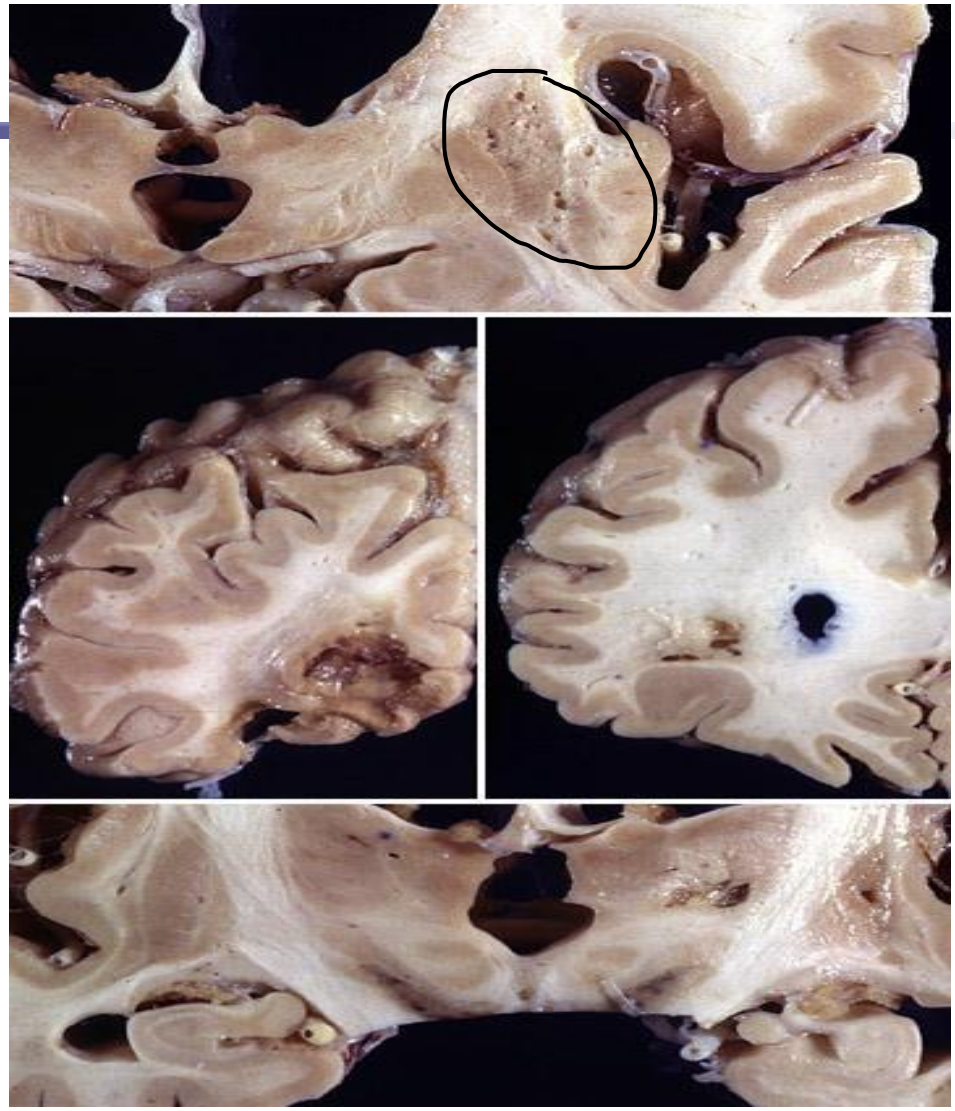
- *Coffee protects against Alzheimers ???*
- *Tea protects against Parkinsons ???*

Stimulate the brain.(Because it contains caffeine).

Contains a high level of antioxidants.

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).



It occurs in people with hypercoagulation and older people from 60 to 65 years.

MULTI INFARCT DEMENTIA

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

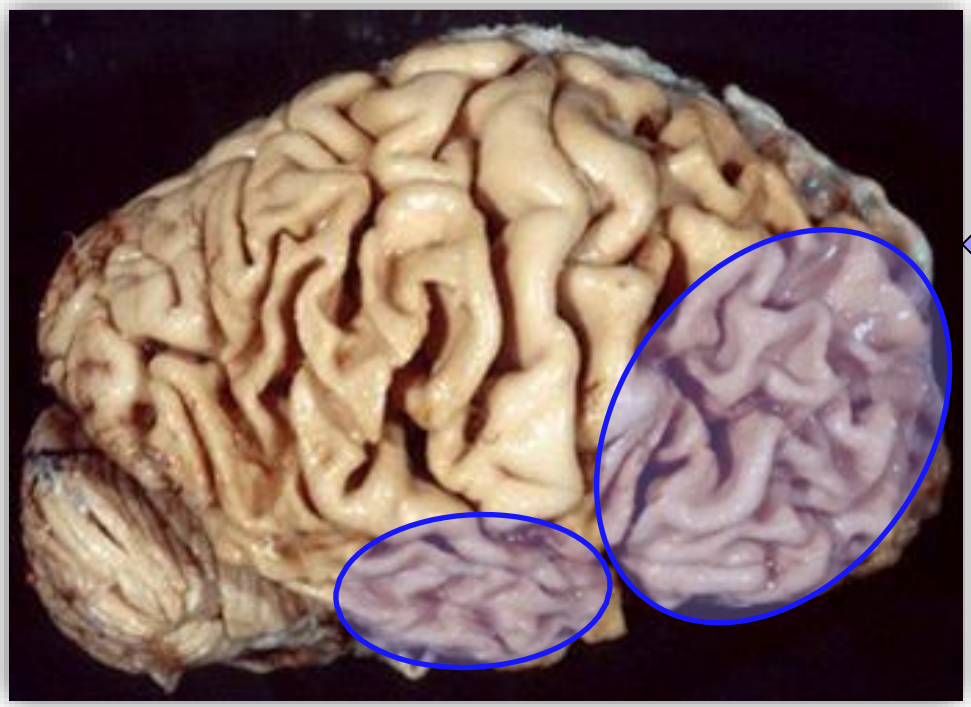
- Progressive disease characterized by **dementia** with degeneration of:
  - *Frontal lobe* → leading to behavioural changes.
  - *Temporal lobe* → leading to language problems.

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

هاد المرض ما بيجي لحاله لا بيجي معه عدة امراض من ضمنها:
* **Pick's Disease** and **FTLD-TDP43**.

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

FTLD - Morphology

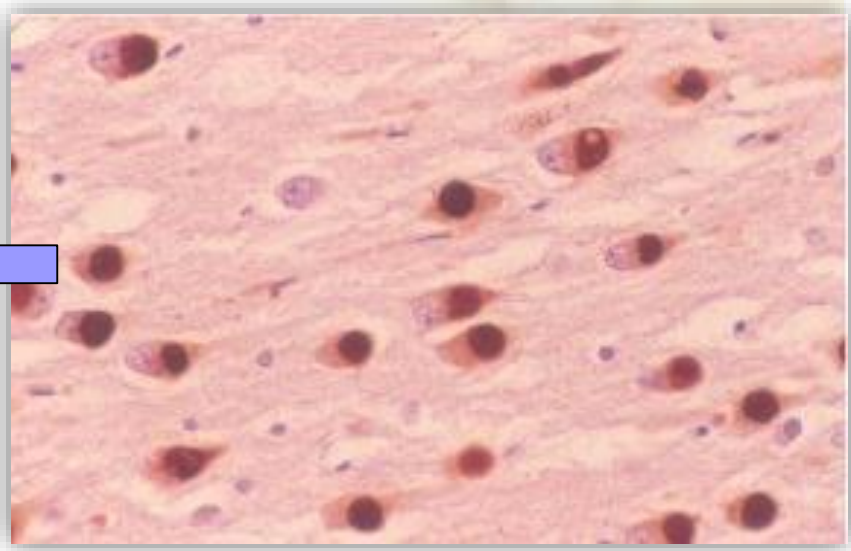


Atrophy of frontal & temporal lobes

Affected more severely.

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.

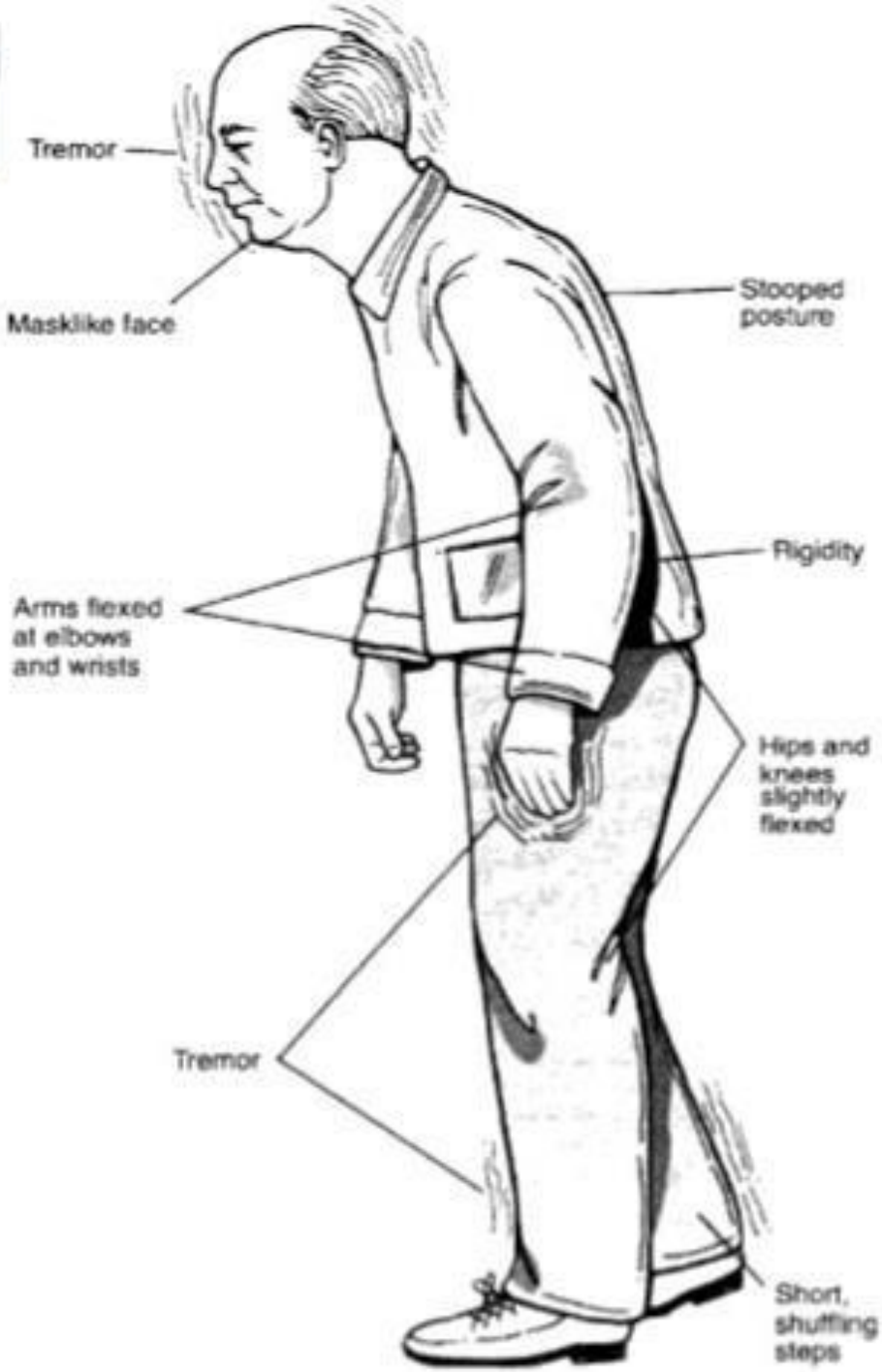
- **Cause:** Damage of **dopaminergic neurons** in **substantia nigra**.

Tremor: رعشة

Bradykinesia: حركتهم بطيئة
stooping gate: خطواتهم قريبة

expressionless faces :mask face.

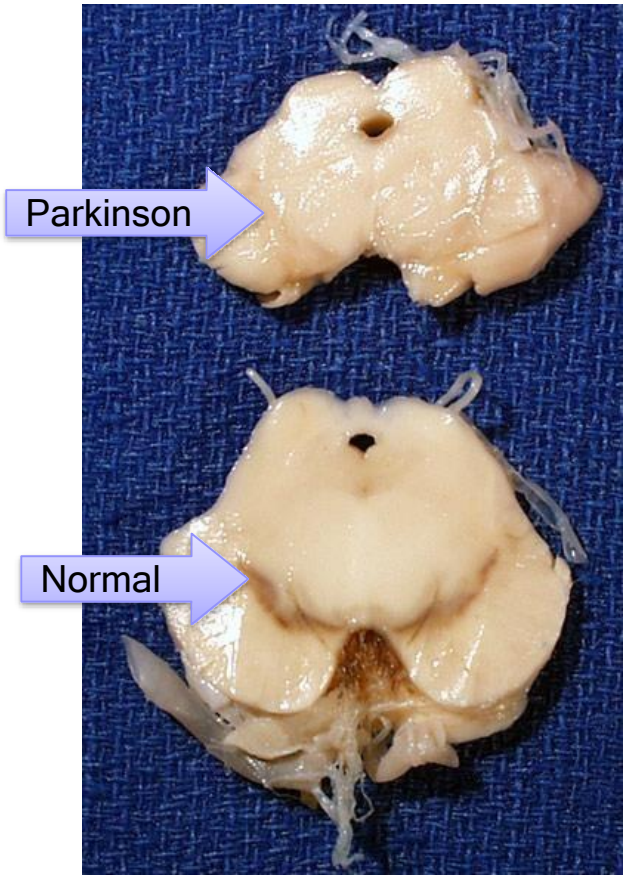
pill-rolling : circle movement.
حركة ايديهم دائرية متل الي بحرك ب ايده وقت السباحة.
the muscles are hypertonic.


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**