NEURODEGENERATIVE DISEASES

- no cure
- worser with time.

2/3/25

due to accumulation it'll affed the liver.

- Progressive loss of neurons, affecting groups of neurons with functional interconnections.
- All Caused by the accumulation of protein aggregates,
- The clinical phenotype is determined more by the **distribution of the aggregates** than by the nature of the aggregating protein.
- Many of the protein aggregates are capable of spreading to healthy neurons.(like prions).

i.e misfolded proteins.

NEURODEGENERATIVE DISEASES

- What causes the aggregates:

Production

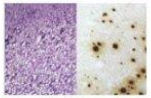
1- Mutations that (a) alter protein's conformation or (b) disrupt pathways involved in processing or clearance of the proteins.

2- A subtle imbalance between protein synthesis & clearance (due to genetic, environmental, or stochastic factors) →allows gradual accumulation

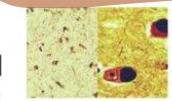
- Aggregates often are resistant to degradation by normal cellular proteases, accumulate within cells, elicit an inflammatory response, & may be directly toxic to neurons.

initiate apoptosis.

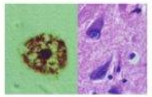
The classification will be BY LOCATION



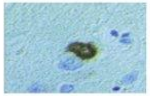
Prion disease
Location: diffuse cortical
Macro: cerebral atrophy
Micro: spongiosis, PrP deposits



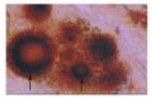
FTD
Location: frontotemporal
Macro: cerebral atrophy
Micro: tau deposits, Pick bodies



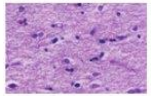
AD Alzheimer disease
Location: temporoparietal
Macro: cerebral atrophy
Micro: Aβ plaques, tangles



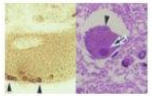
LBD
Location: frontotemporal
Macro: cerebral atrophy
Micro: Lewy bodies



PD
Location: midbrain
Macro: pallor of substantia nigra
Micro: Lewy bodies

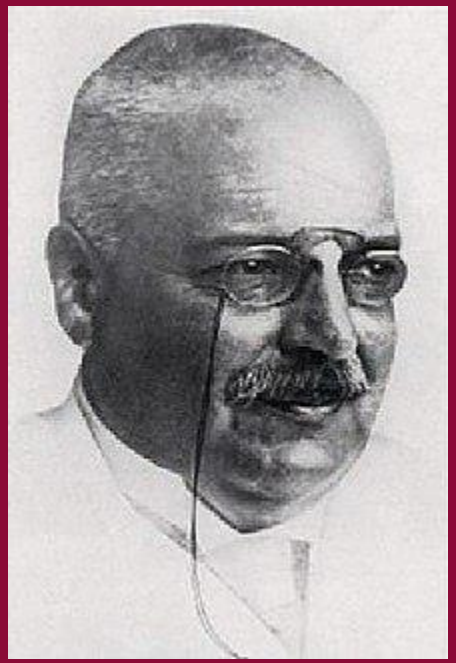


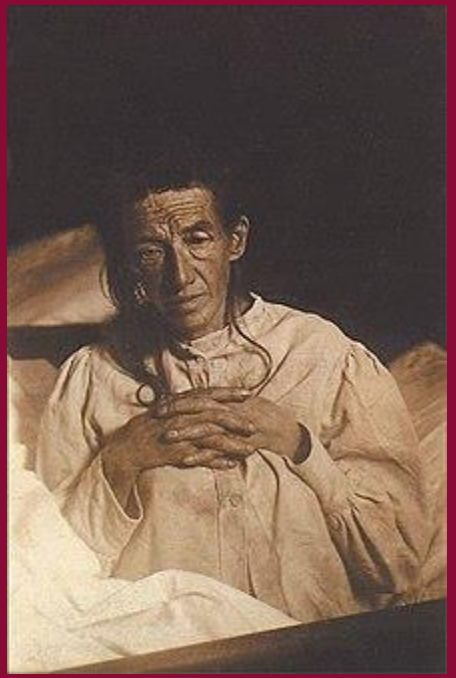
HD
Location: basal ganglia
Macro: neostriatal atrophy
Micro: neuronal loss and astrocytosis



ALS
Location: motor cortex, brainstem, spinal cord
Macro: atrophy of motor neurons and muscles
Micro: inclusions (Bunina bodies, Lewy body–like)

Alzheimer Disease (AD)



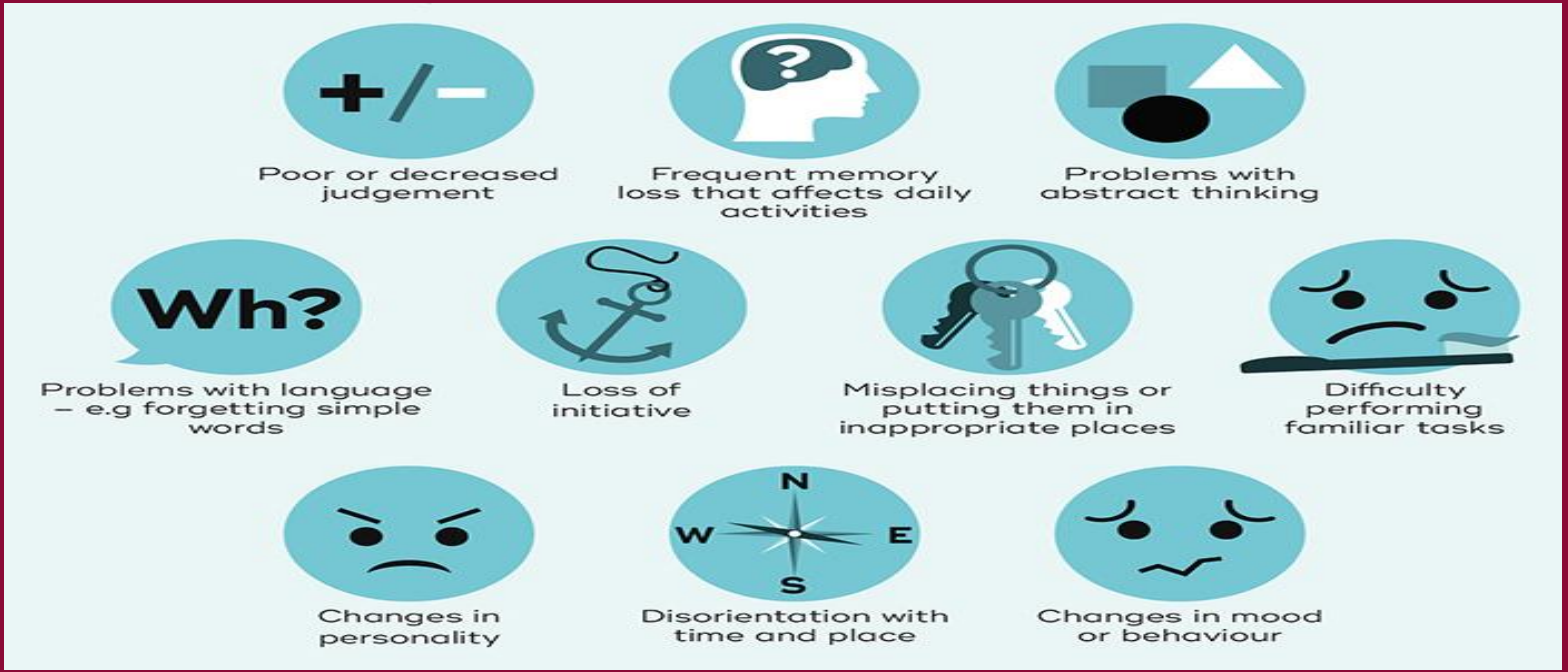


Alzheimer Disease (AD)

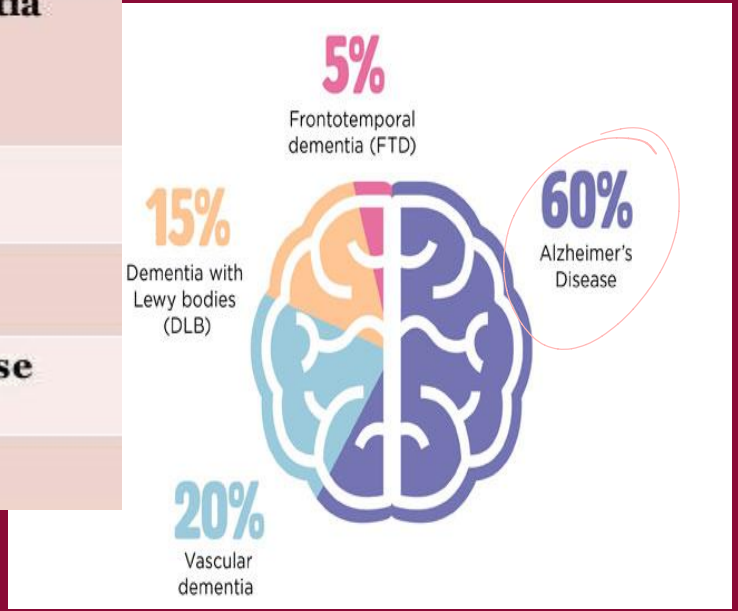
- The most common cause of **dementia** in older adults.
- Rare before 50, incidence increases with age (1% → 60 to 64, reaching 47% in 85 and older).
- Manifests with the insidious onset of impaired higher intellectual function, **memory impairment**, & altered mood and behavior.
- **Aβ** (amyloid β) and ***tau*** proteins accumulation is the fundamental abnormality.
- AD is an eventual feature of the cognitive impairment in trisomy 21 individuals (Down syndrome).

Alzheimer = Dimentia
But Dimensia DOSE N'T mean Alzheimer.

Dementia is a general term for loss of memory and other mental abilities severe enough to interfere with daily life of a conscious patient, is not a specific disease it's an umbrella term.

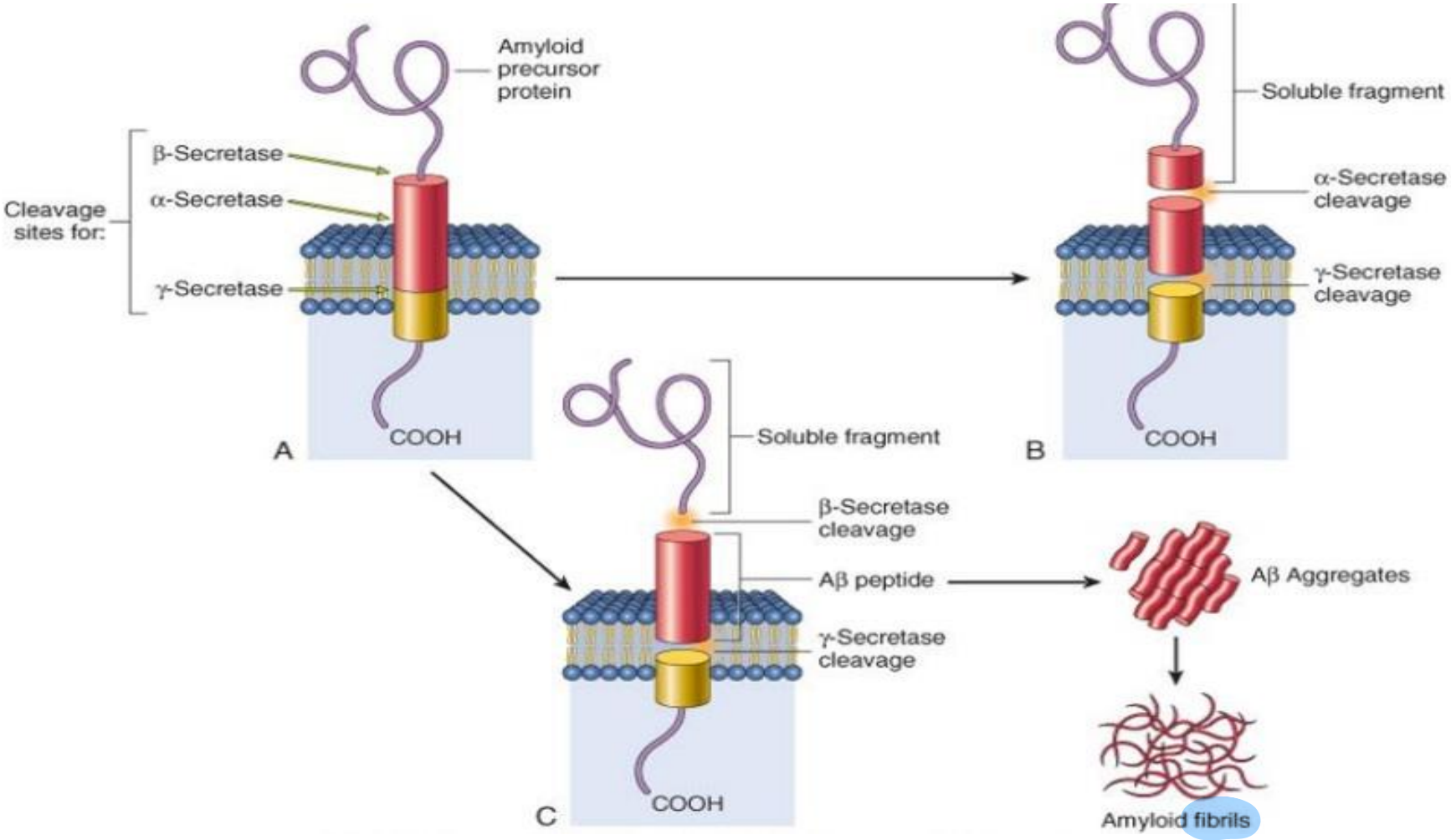


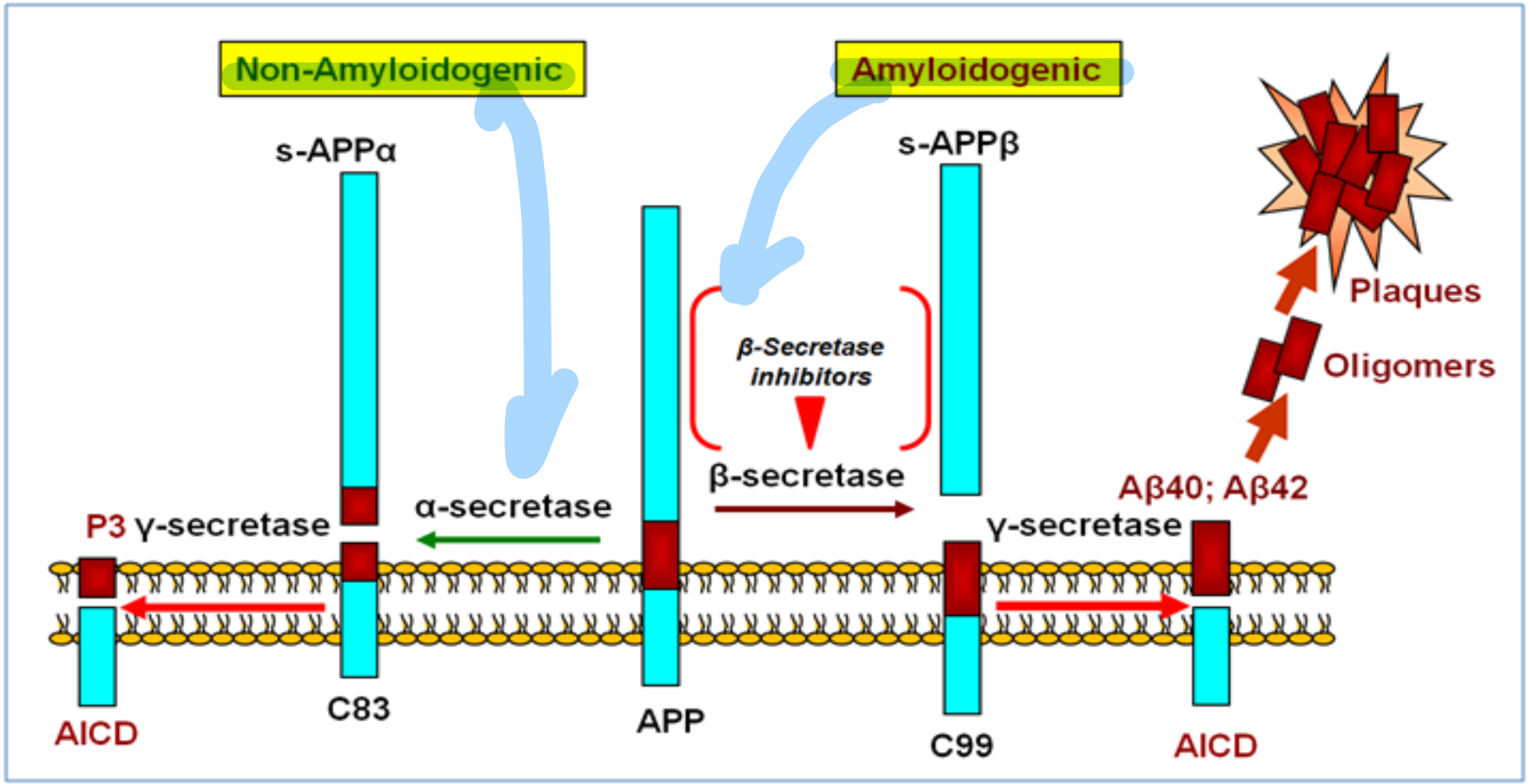
REVERSIBLE DEMENTIA[10-20%]	IRREVERSIBLE DEMENTIA[80-90%]
D= Drugs	Alzheimer
E= Endocrine disorders	Lewy Body dementia
M= Metabolic	Frontotemporal Dementia (Picks disease)
E= Emotional	Parkinson disease
N= Nutritional	Huntington's disease
T = Toxic, Tumor, Trauma	Creutzfeldt-Jakob disease
A= Alcohol	others



AD – Pathogenesis

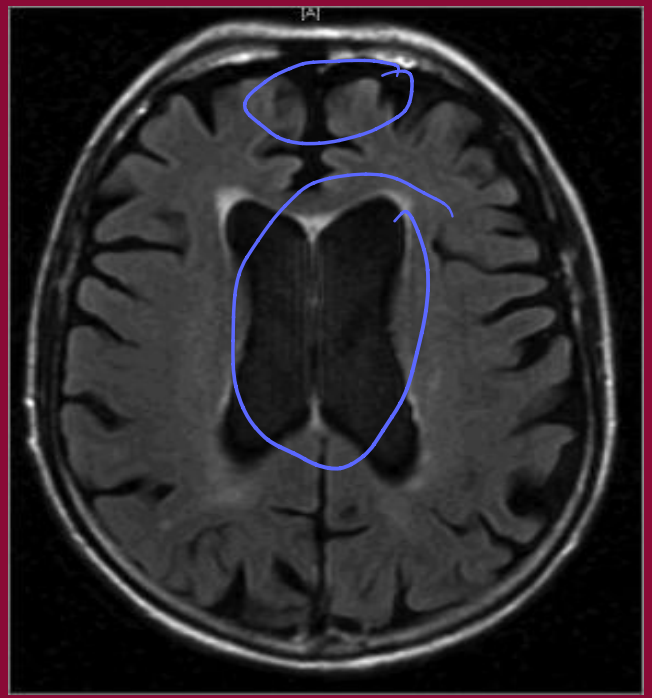
- **Aβ generation → critical initiating event to develop AD**
- **Aβ is** derived from a membrane protein; amyloid precursor protein (APP).
- APP processed in 2 ways pathways:
  (1) Starts with α-secretase (non-amyloidogenic), **no Aβ generation.**
  (2) Starts with β-secretase (amyloidoigenic), **Aβ generation.**
- APP gene located on chromosome 21 (extra copy in Down syndrome).
- Aβ is highly prone to aggregation, causing neural dysfunction, & elicits a local inflammatory response that can result in further cell injury & death

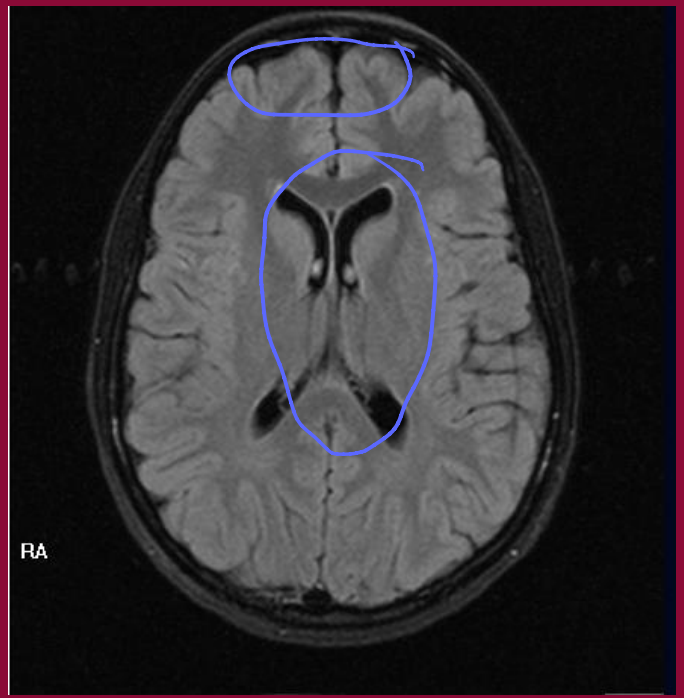

Amyloid precursor protein
Cleavage sites for:
β-Secretase
α-Secretase
γ-Secretase
COOH
A
Soluble fragment
α-Secretase cleavage
γ-Secretase cleavage
COOH
B
Soluble fragment
β-Secretase cleavage
Aβ peptide
γ-Secretase cleavage
COOH
C
Aβ Aggregates
Amyloid fibrils


Non-Amyloidogenic
Amyloidogenic
s-APPα
s-APPβ
β-Secretase inhibitors
β-secretase
α-secretase
P3 γ-secretase
γ-secretase
Aβ40; Aβ42
Plaques
Oligomers
C83
APP
C99
AICD
AICD

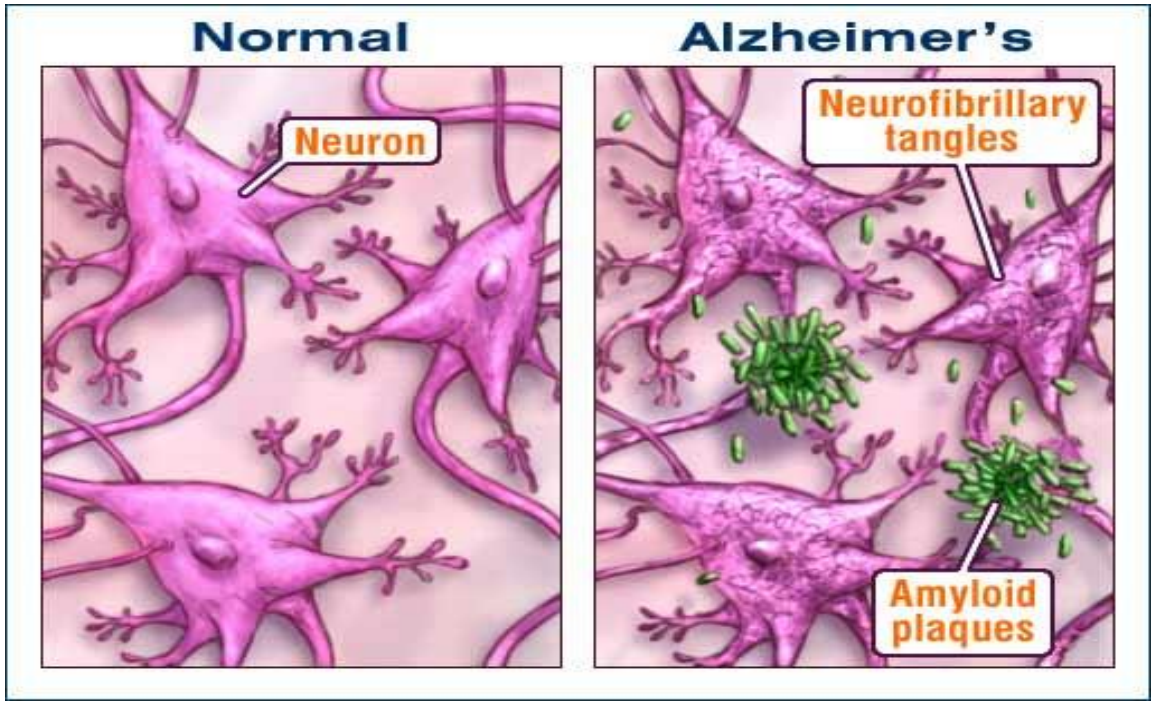
A variable degree of cortical atrophy, resulting in a widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes.

The atrophy produces a compensatory ventricular enlargement (hydrocephalus ex vacuo)

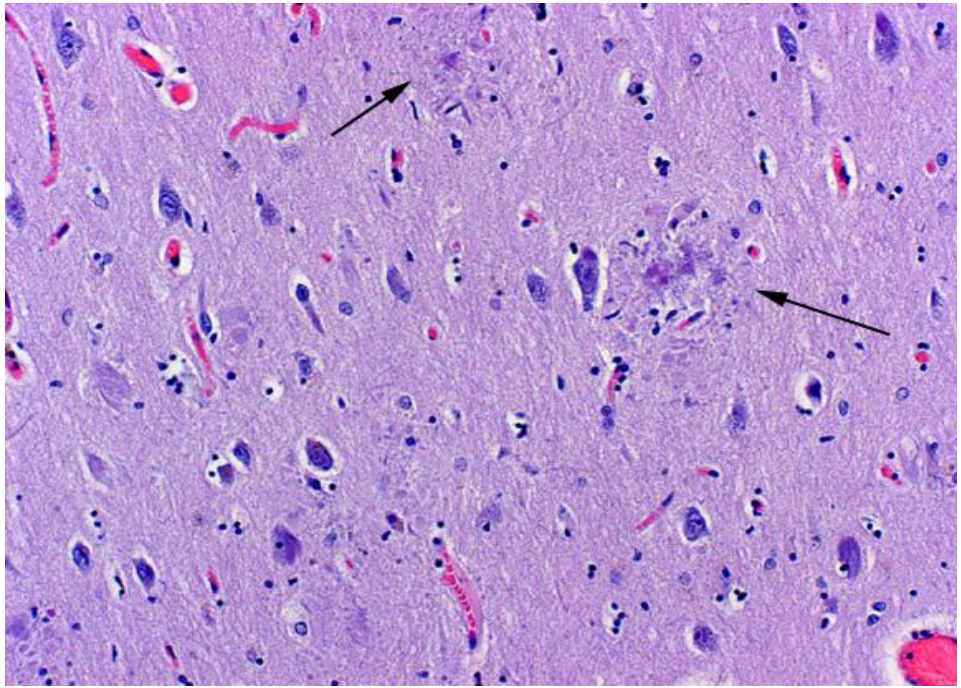


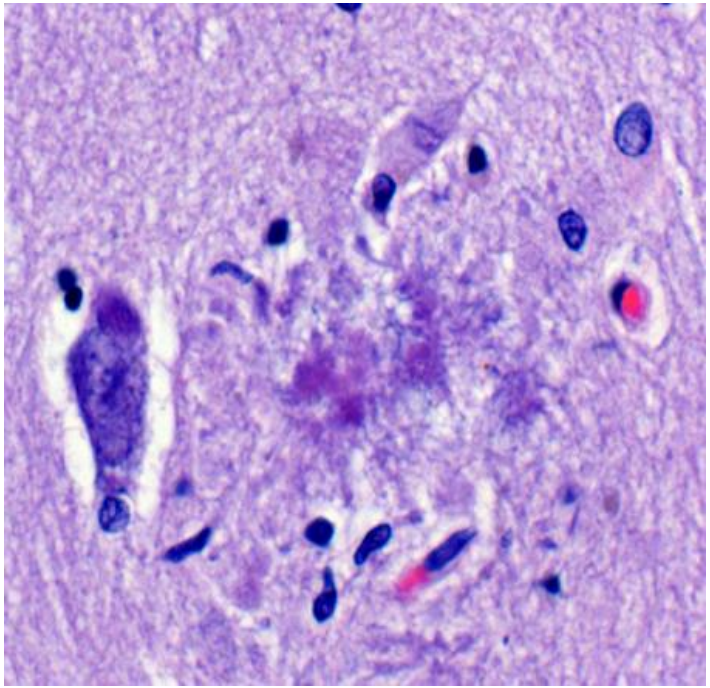


- Microscopy: Amyloid plaques (extracellular - accumulation of Aβ amyloid) and neurofibrillary tangles (intracellular - *Tau* accumulation).



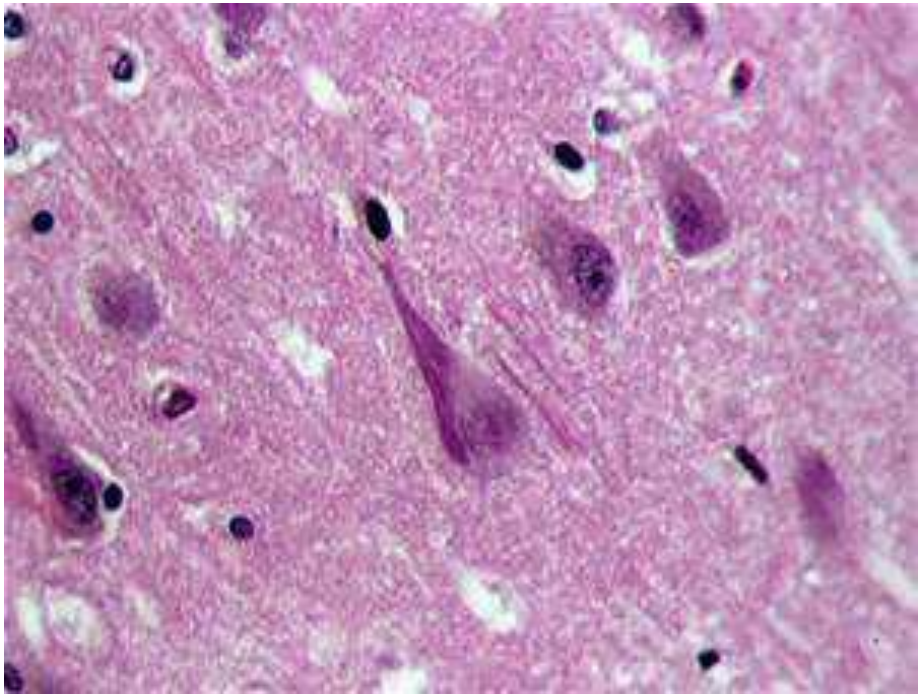
Neuritic plaques are focal, spherical collections of dilated, tortuous, processes of dystrophic neurites around a central amyloid (Aβ) core. Aβ deposition without neurites termed **diffuse plaques.**

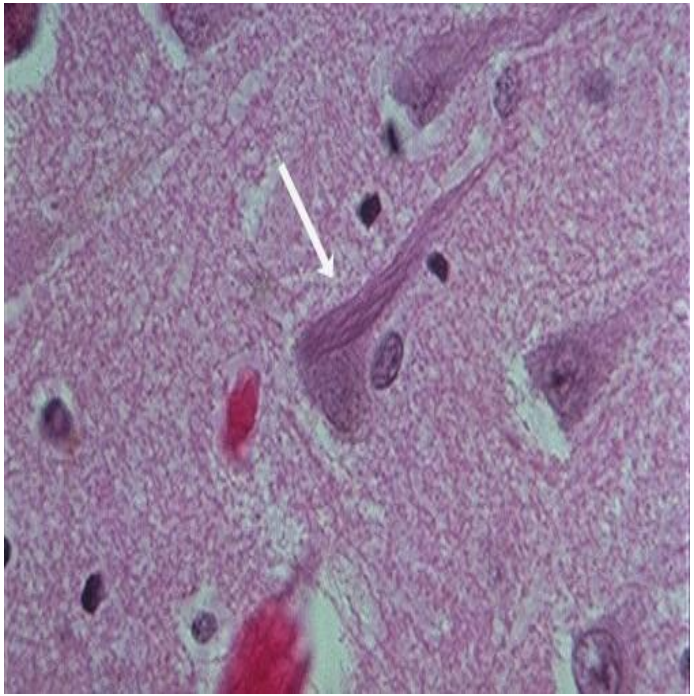




Neurofibrillary tangles: Tau containing bundles of filaments in neurons cytoplasm (encircle the nucleus), <**flame** shapes>

Where ? cortical neurons (entorhinal cortex), & the pyramidal cells of hippocampus, amygdala, basal forebrain, the raphe nuclei.



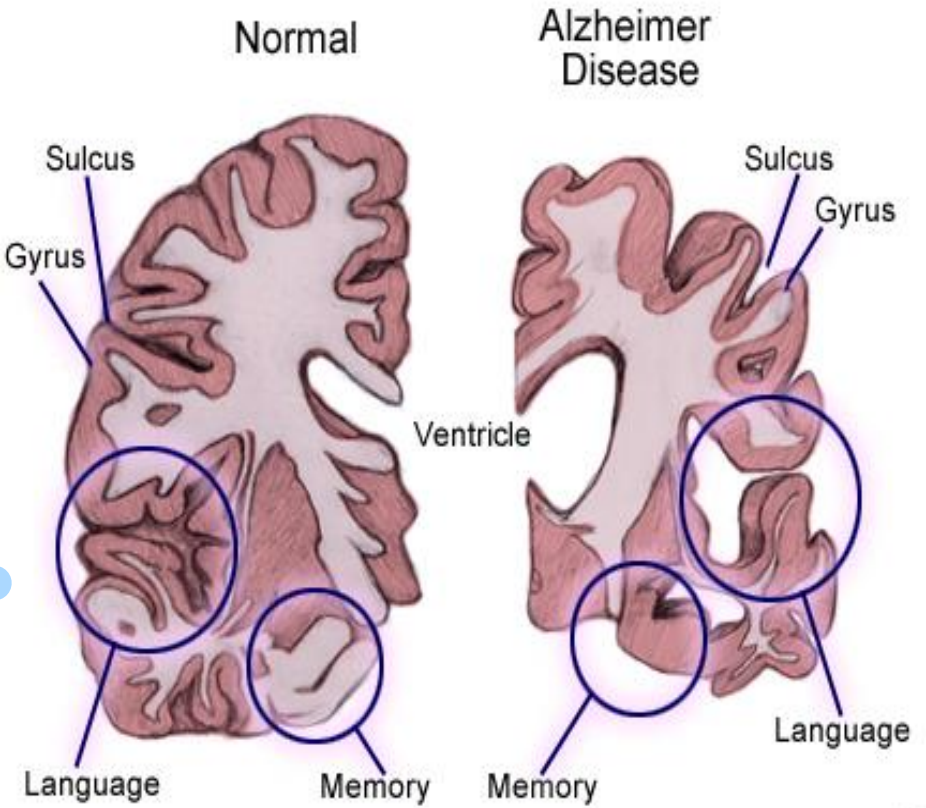


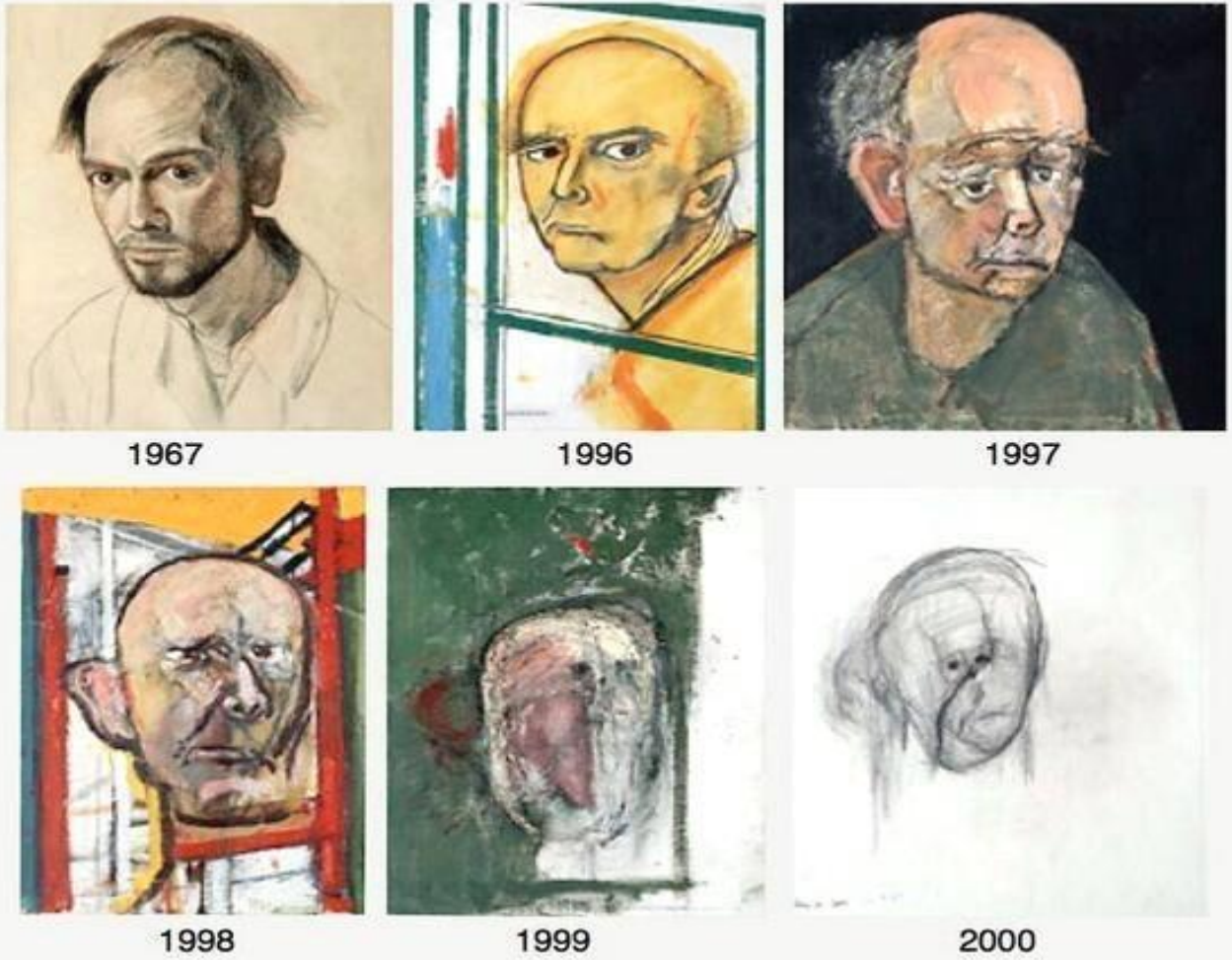
Clinically: Insidious onset of impaired higher intellectual function & memory & altered mood & behavior.

Over time, disorientation & aphasia.

In final stages they are disabled, mute & immobile.

Death → intercurrent pneumonia or other infections.

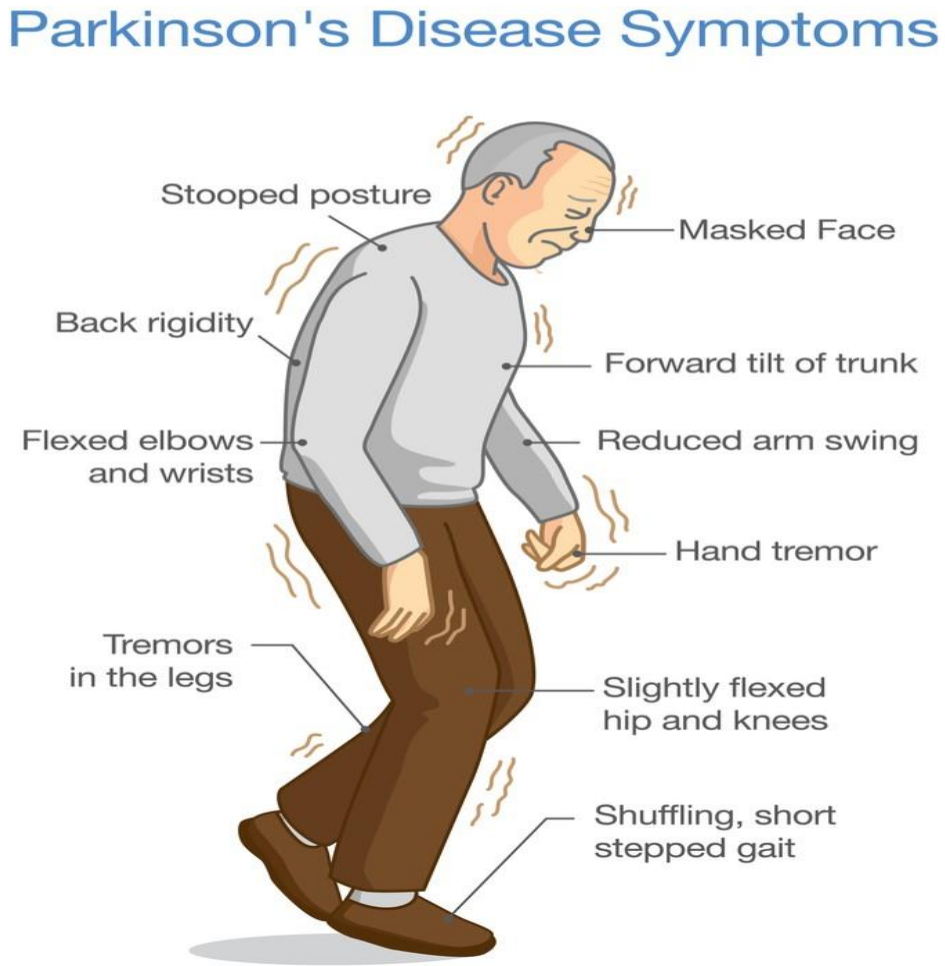




"can the arts ever illuminate a condition that by its very nature resists all understanding?"

William Utermohlen's self-portraits, the first, made in 1967, the rest from 1996 the year following his diagnosis of Alzheimer's disease, to 2000, charting his decline.

Demyelinating & degenerative diseases of CNS



Parkinson Disease (PD)

Parkinson Disease

- A neurodegenerative disease marked by a prominent hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the **substantia nigra.**
- Has characteristic neuronal inclusions containing α-synuclein. **(Lewy bodies)**
- **Parkinsonism**: a clinical syndrome characterized by diminished facial expression (masked facies), stooped posture, slowness of voluntary movement, festinating gait (progressively shortened, accelerated steps), rigidity, & a "pill-rolling" tremor.

Parkinsonism is seen in a range of diseases that damage dopaminergic neurons, which project from the substantia nigra to the striatum (nigrostriatal pathway) and are involved in control of motor activity.