

V. NEURODEGENERATIVE DISEASES- Alzheimer disease

- Are disorders characterized by the cellular degeneration of subsets of neurons that typically are related by function, rather than by physical location in the brain.

- Many of these disorders are associated with the accumulation of abnormal proteins, which serve as histologic hallmarks of specific disorders
- The clinical manifestations of degenerative diseases are dictated by the pattern of neuronal dysfunction:

- A. Those affect the cortical neurons result in dementia;
- B. Those affect basal ganglia result in movement disorders
- C. Those that affect the cerebellum result in ataxia

I. Alzheimer Disease (AD)

- Is the most common cause of dementia in the elderly population
- It becomes clinically manifest as insidious impairment of higher cognitive functions.
- As it progresses, it leads to memory deficits ,visuspatial orientation, judgment, orientation and language

- Patients rarely become symptomatic before 50 years of age
- The incidence of the disease increases with age,
- The prevalence starts from a level of 1% for the 60- to 64-year-old population and reaching 40% or more for the 85- to 89-year-old.

- About 5% to 10% of cases are familial forms of AD
- While pathologic examination of brain tissue remains necessary for the definitive diagnosis of AD, the combination of clinical assessment and modern radiologic methods allows accurate diagnosis in 80% to 90% of cases as confirmed at autopsy.

Molecular genetics and pathogenesis

- The fundamental abnormality in AD is the accumulation of two proteins in specific brain regions:
 - i. A β amyloid (amyloid plaques)
 - ii. Tau protein (neurofibrillary tangles)
- as a result of excessive production and defective removal

Note:

- Several lines of evidence strongly support a model in which A β generation is the critical initiating event for the development of AD

1. Role of A β

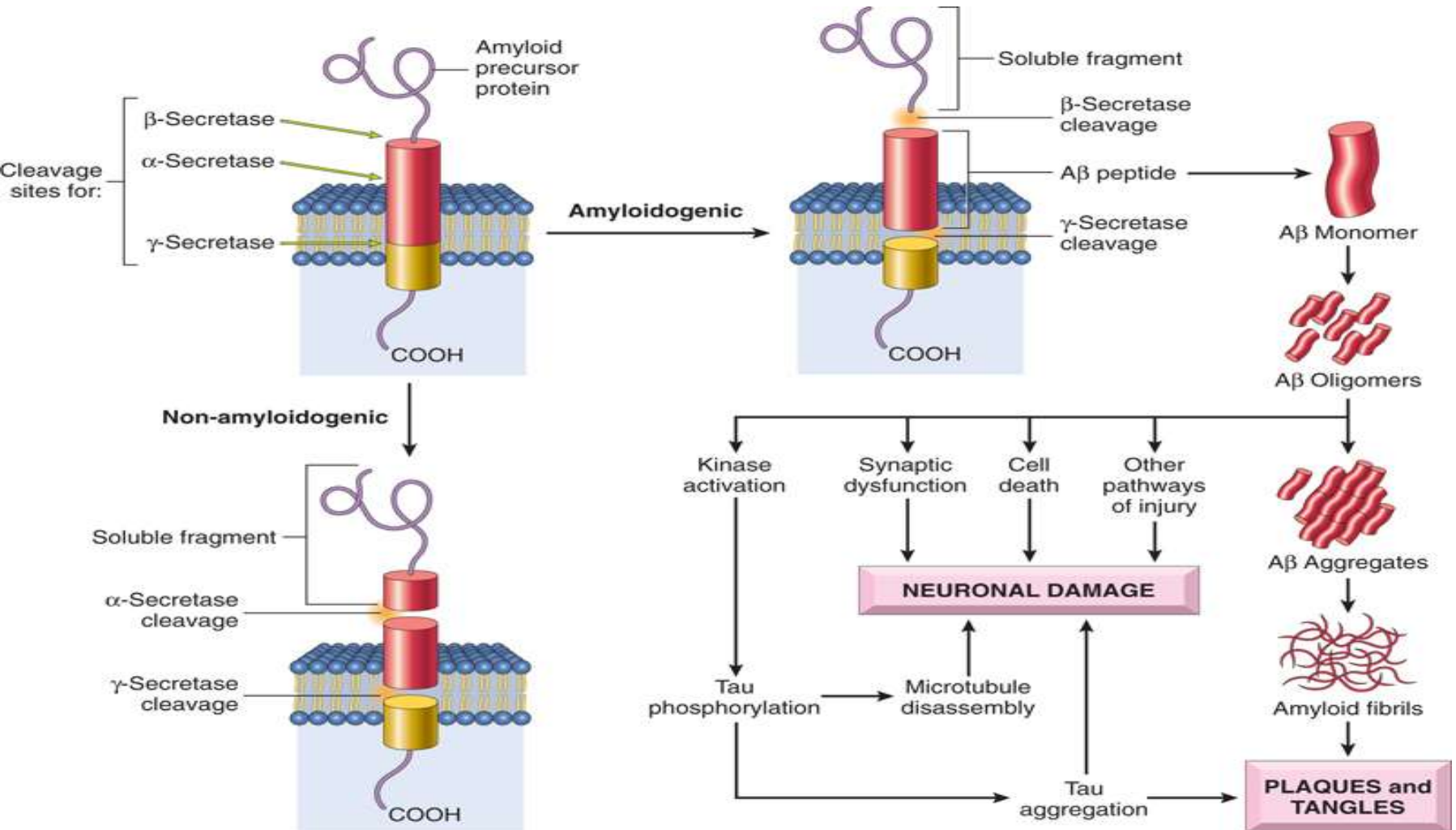
- Amyloid precursor protein is a cell surface protein with a single transmembrane domain that might act as a receptor
- The A β portion of the protein extends from the extracellular region into the transmembrane domain

Normal processing of the APP

1. Begins with cleavage in the extracellular domain
2. Followed by intramembranous cleavage

1. If the first cut occurs at the α -secretase site within the $A\beta$ sequence, then $A\beta$ is not generated (the non-amyloidogenic pathway).
2. Surface APP can also be endocytosed and may undergo cleavage by β -secretase which cuts at the N-terminal region of the $A\beta$ sequence (amyloidogenic pathway)

A β peptide genesis and consequences in AD



- Following cleavage of APP at either of these sites, the γ -secretase complex performs an intramembranous cleavage.
 - a. When paired with a first cut by α -secretase, it produces a soluble fragment,
 - b. but when paired with β -secretase cleavage, it generates $A\beta$.

- Once generated, A β is highly prone to aggregation
 - a. First into small oligomers (which may be the toxic form responsible for neuronal dysfunction),
 - b. and eventually into large aggregates and fibrils.

1. Down syndrome:

- The gene encoding APP, on chromosome 21, lies in the Down syndrome region
- AD pathology is an eventual feature of the cognitive impairment of these individuals.
- Histologic findings appear in the second and third decades followed by neurologic decline about 20 years later.

2. Familial AD

- Localized chromosome 21 duplications that span the APP locus

3. The two loci identified as causes of the majority of early-onset familial AD

Encode the two presenilins (PS1 on ch 14 and PS2 on ch 1).

- These mutations lead to a gain of function, such that the γ -secretase complex generates increased amounts of $A\beta$,.

2. Role of Tau

- Tau is a microtubule –associated protein present in axon
- This tau is shifted to a somatic-dendritic distribution, and becomes hyperphosphorylated ,therefore loses its ability to bind to microtubules

- The mechanism of neurofibrillary tangles (that contain hyperphosphorylated tau) injury in the brain
 - a. The aggregate of tau elicit stress response in neurons
 - b. The microtubule function of Tau is lost

3. Other genetic risk factors;

- a. The genetic locus on chromosome 19 that encodes Apolipoprotein E (APOE) has a strong influence on the risk of developing AD
 - Has three alleles , $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$
 - The dosage of $\epsilon 4$ allele increases the risk of AD and lowers the age of onset of the disease

- This Apo E isoform promotes AB generation and deposition
- The exact pathogenesis is unknown

4. Role of inflammation

- Both small and large aggregates of AB elicit an inflammatory reaction from microglia and astrocytes and this response
 - a. Assists in the clearance of aggregated peptide
 - b. Stimulates the secretion of mediators that cause neuronal damage

- c. May cause hyperphosphorylation of tau
- d. Cause oxidative injury to neurons

Basis for cognitive impairment.

- It is clear that the presence of a large burden of amyloid plaques and tangles is highly associated with severe cognitive dysfunction
- The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of amyloid plaques.

morphology

Gross

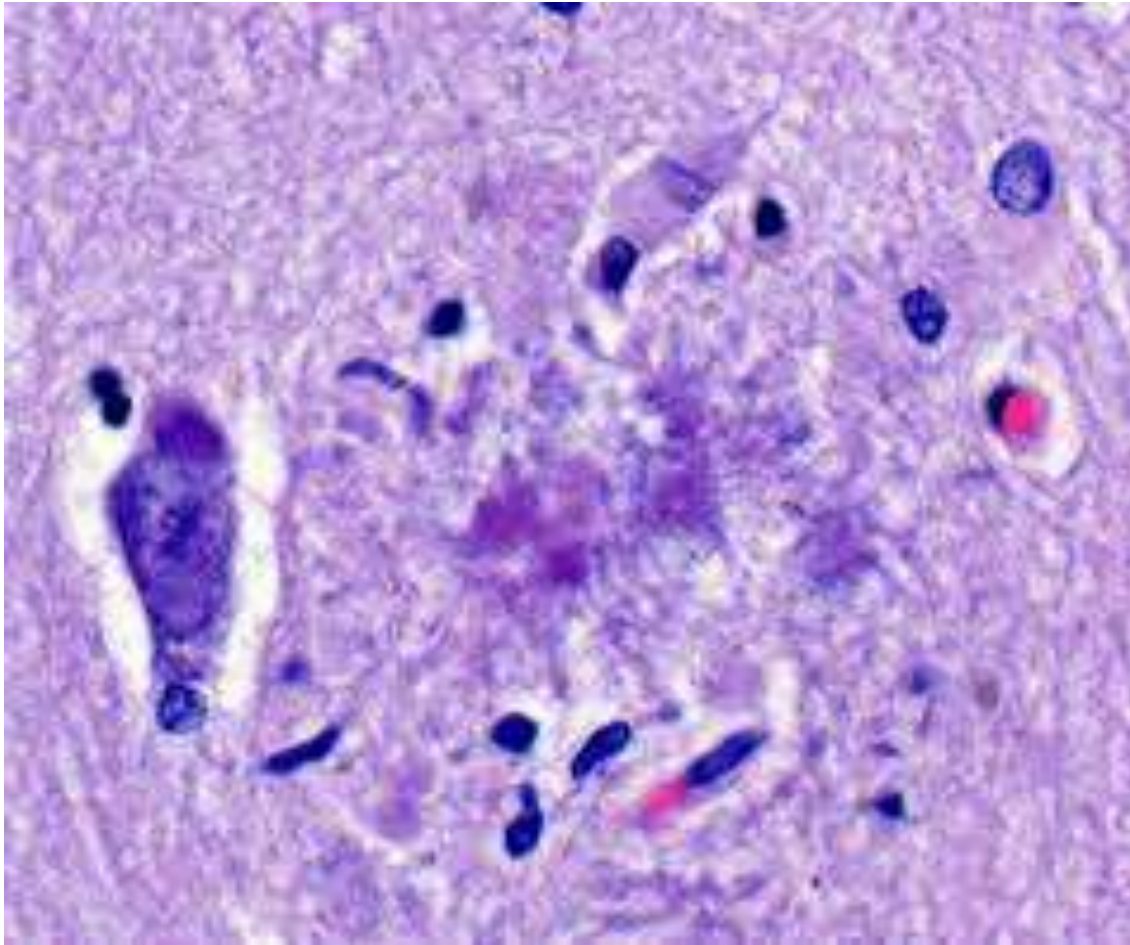
- Variable degree of brain atrophy
- Most prominent in the frontal, temporal and parietal lobes
- Structures of the medial temporal lobe , including the hippocampus, amygdala and entorhinal cortex are involved in the course of the disease and show severe atrophy later on

Microscopic appearance

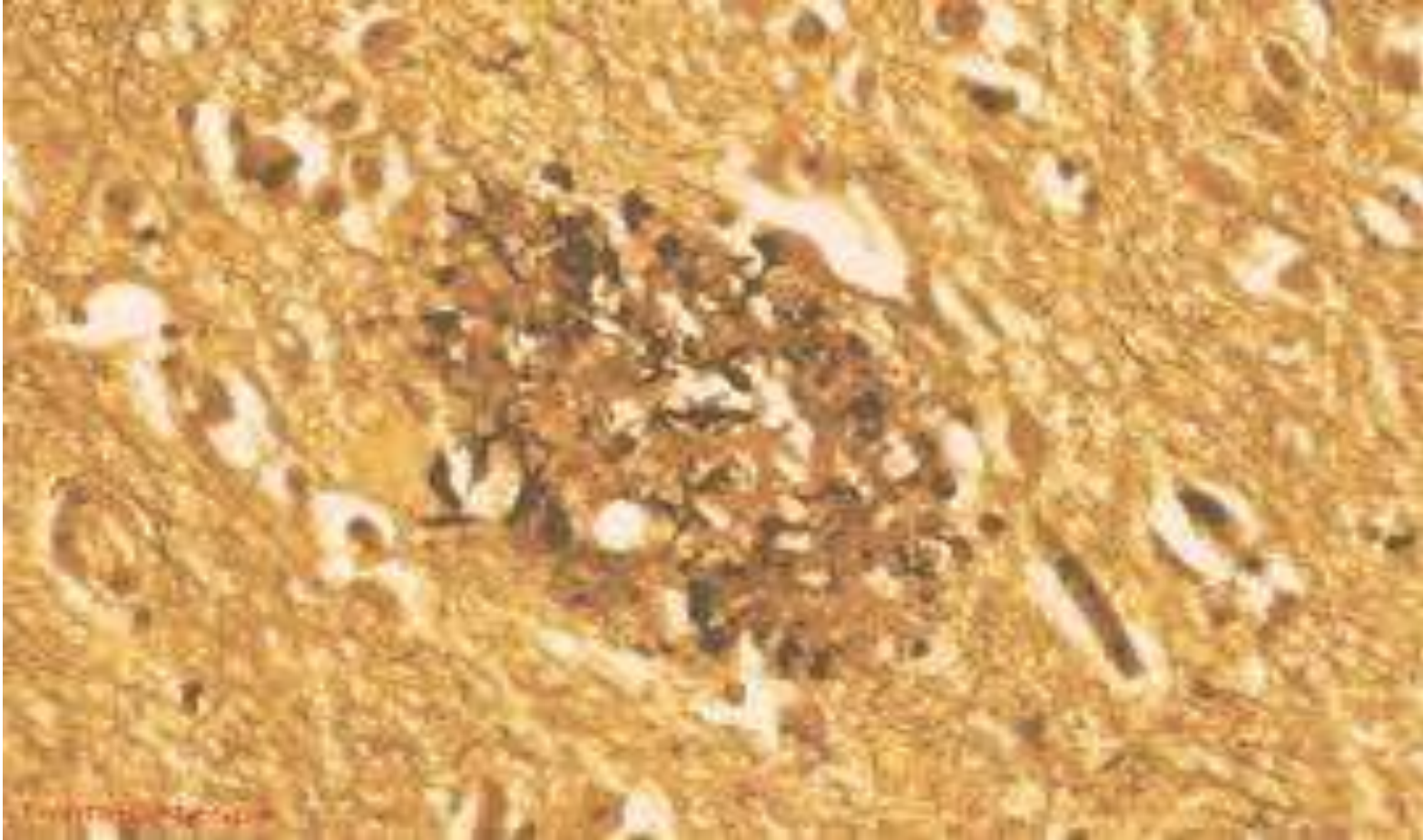
a. Neuritic senile plaques

- Are focal spherical collections of dilated tortuous neuritic processes (dystrophic neurites often around a central amyloid plaque)
- Are found in the hippocampus , amygdala and neocortex
- There is relative sparing of the primary motor and sensory cortices

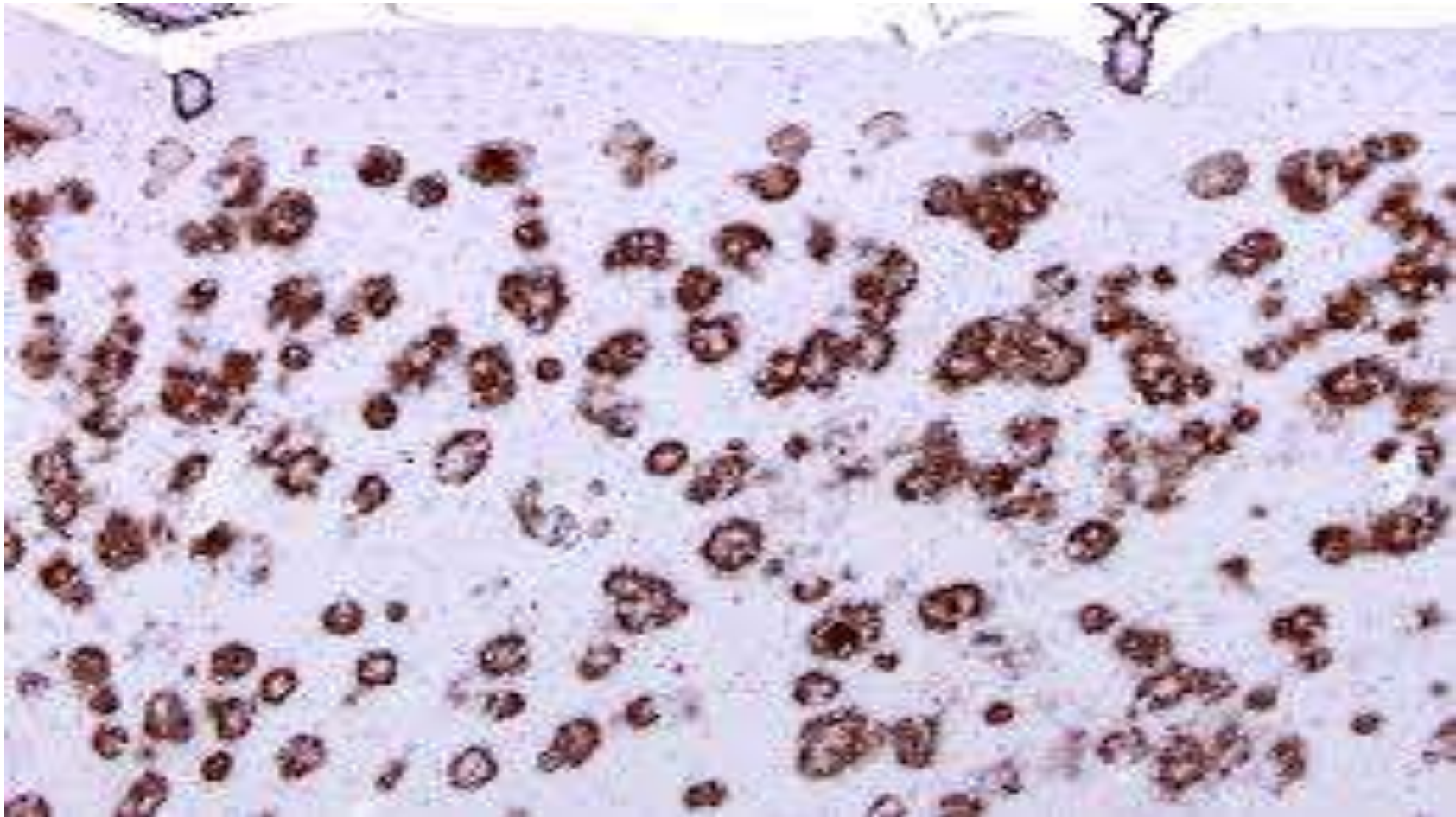
Amyloid plaque



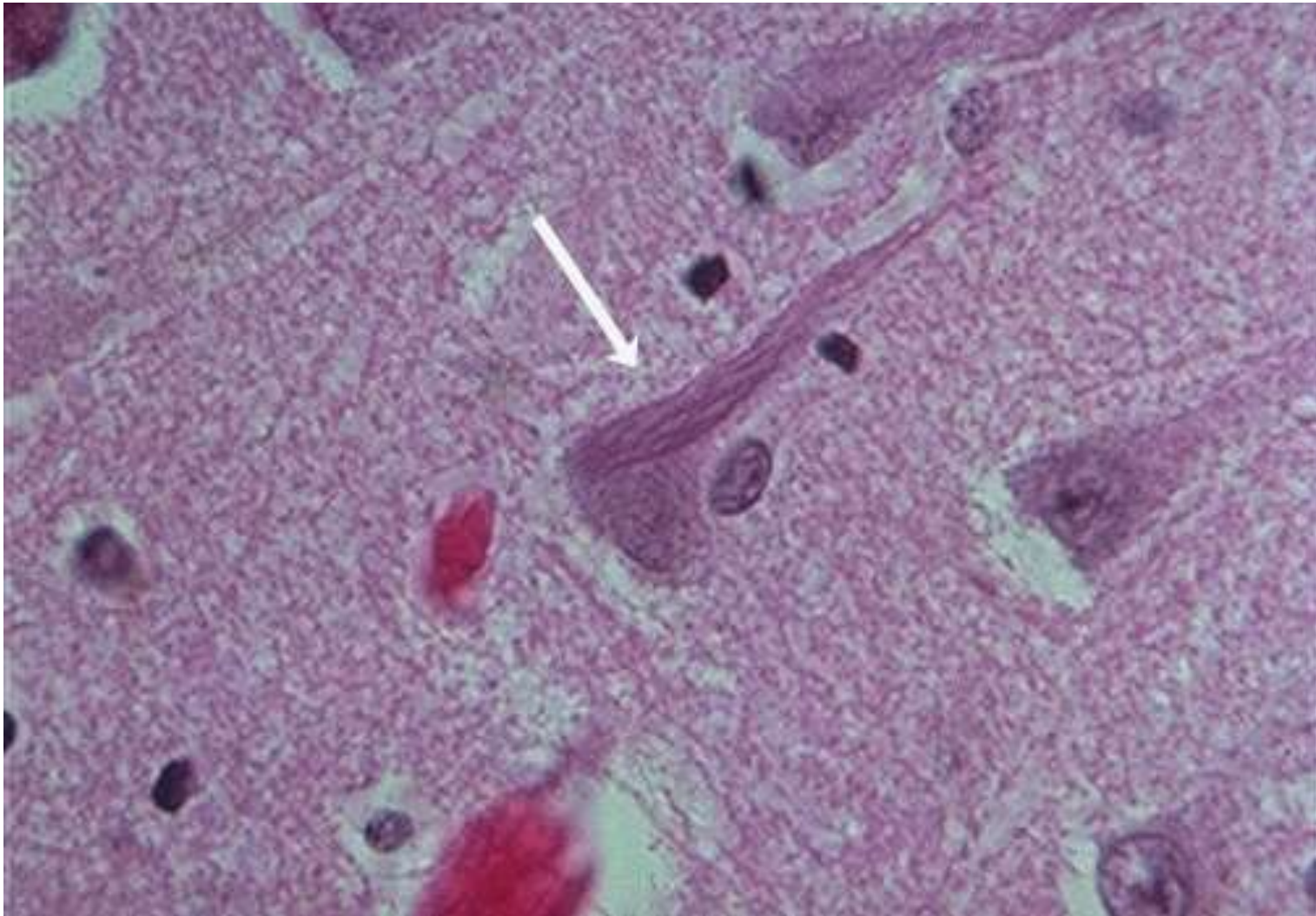
Amyloid immunostain



Amyloid plaques



Neurofibrillary tangle (H&E) stain

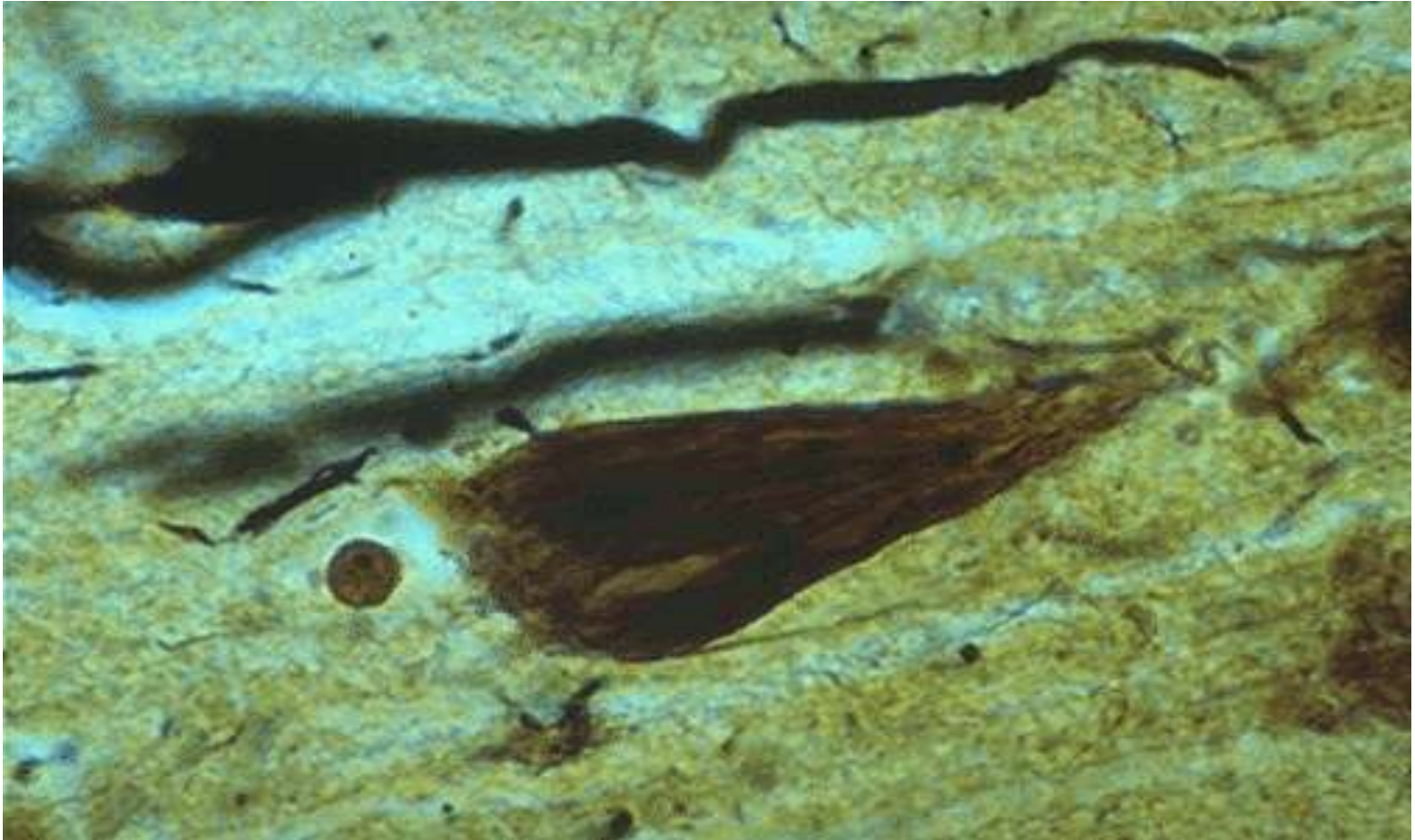


b. Neurofibrillary tangles

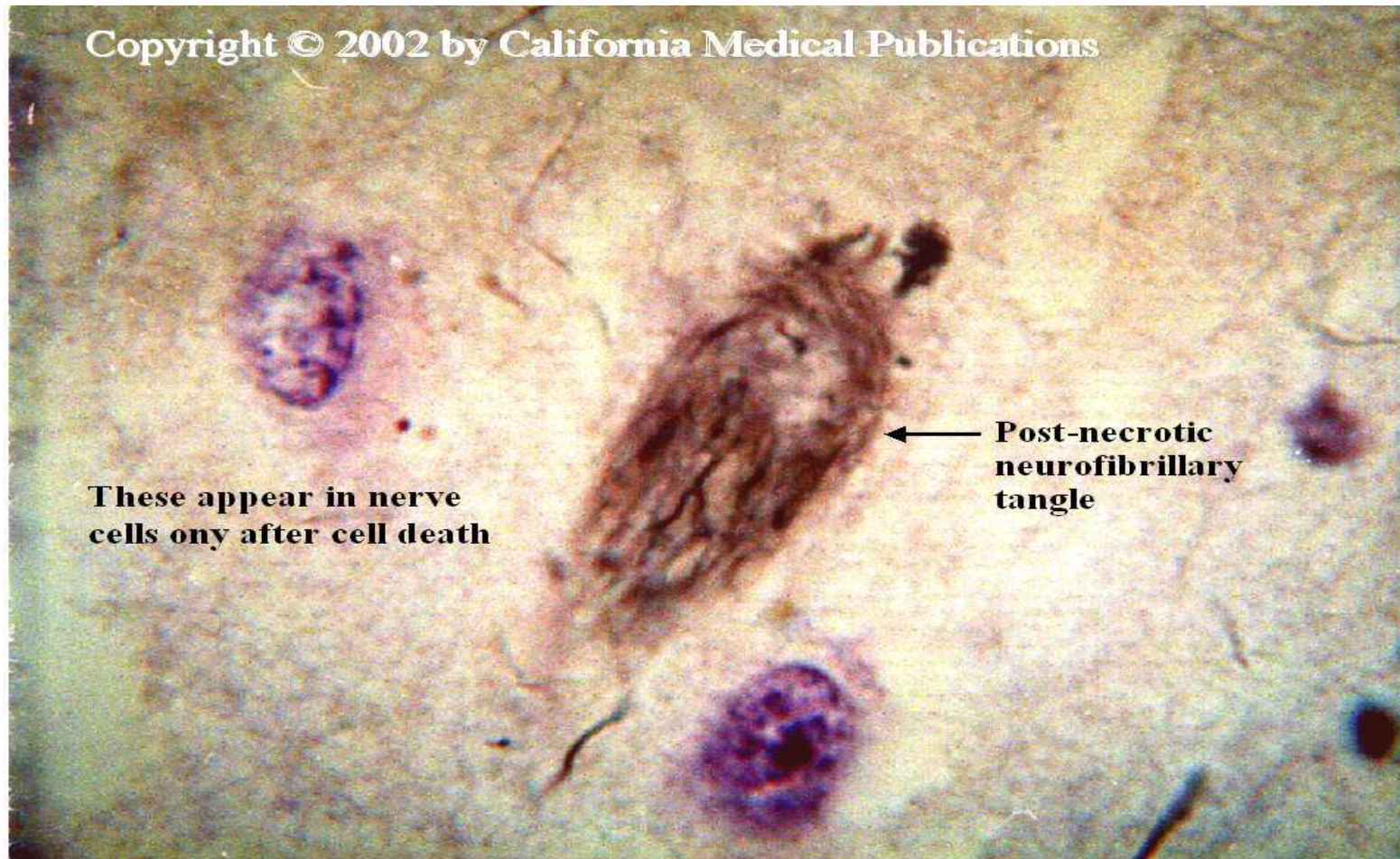
- Are tau-containing bundles of filaments in the cytoplasm of the neurons that displace or encircle the nucleus.
- Are visible as basophilic fibrillary structures with H & E staining but are demonstrated much more clearly by silver staining and with immunohistochemistry directed against tau.

Neurofibrillary tangles

Tau immunostains



Ghost neurofibrillary tangle



- They are commonly found in cortical neurons, especially in the entorhinal cortex, as well as in other sites such as pyramidal cells of the hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.

Note

- Neurofibrillary tangles are insoluble and apparently resistant to clearance in vivo, thus remaining visible in tissue sections as “ghost” tangles long after the death of the parent neuron.
- Tangles are not specific to AD, being found in other diseases as well.

Clinical Features

- The progression of AD is slow with a symptomatic course often running more than 10 years.
- Initial symptoms are forgetfulness and other memory disturbances;
- With progression of the disease other symptoms emerge, including language deficits, loss of mathematical skills, and loss of learned motor skills.

- Intercurrent disease, often pneumonia, is usually the terminal event.
- Current clinical trials are focused on treating subjects in early, preclinical stages of the illness, using strategies that include

- a. clearing A β from the brain through immunologic approaches,
- b. disruption of the generation of A β with pharmacologic agents that target either γ -secretase or β -secretase 1),
- c. Approaches aimed at preventing alterations in tau.