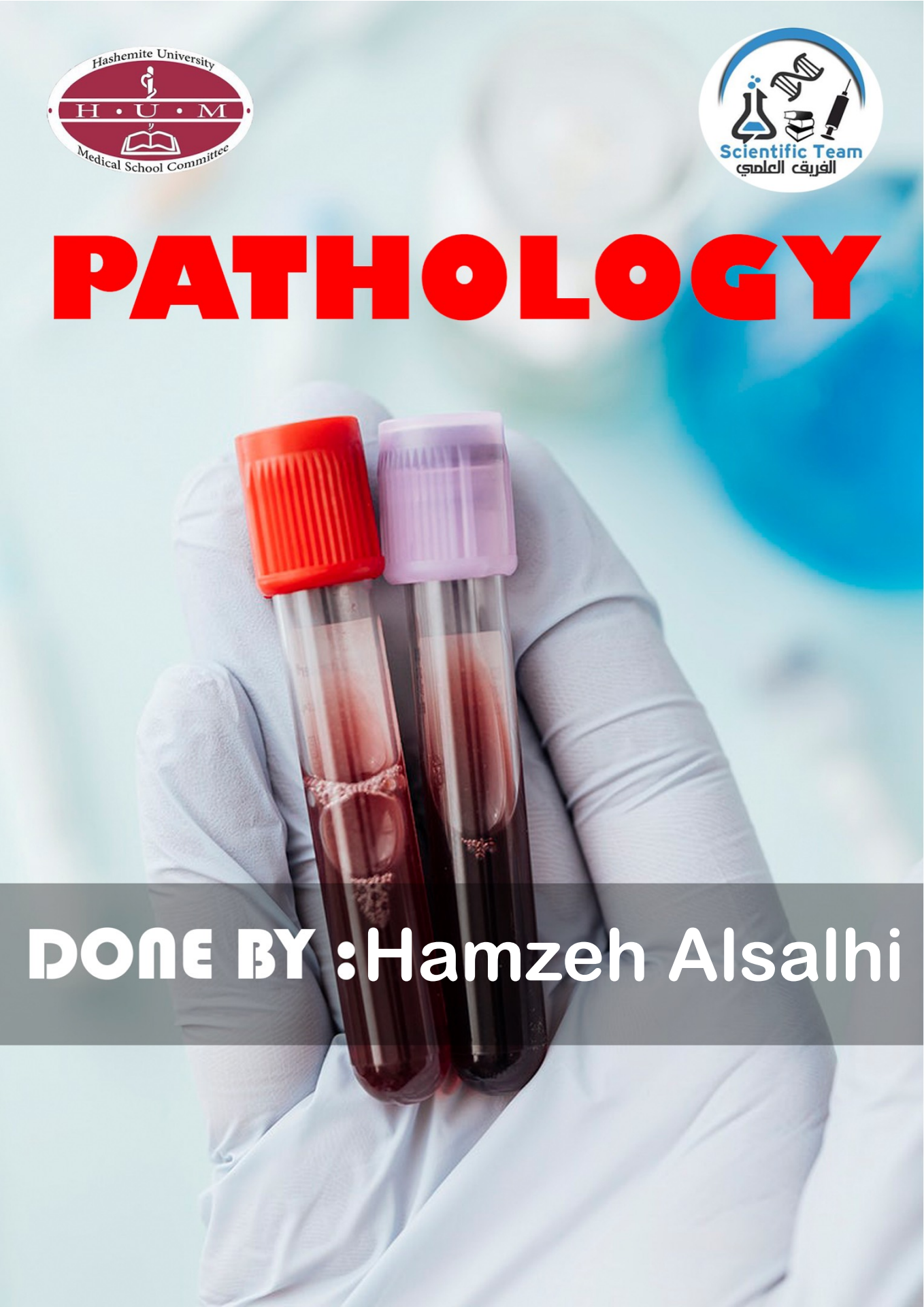
Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY



DONE BY :Hamzeh Alsalhi

▼ *Clinically,* Each disorder of the various leukodystrophies has a characteristic **clinical presentation**, & most can be **diagnosed by genetic or biochemical methods.**

☺ Affected children are normal at birth, ☹ but begin to miss developmental milestones during infancy & childhood.

Diffuse involvement of white matter leads to deterioration in motor skills, spasticity, hypotonia, or ataxia.

LECTURE 2 :-

DEGENERATIVE DISEASES & DEMENTIAS

الخرف

★ **Dementia** is the **development of memory impairment & other cognitive (recognition) deficits, with preservation of a normal level of consciousness**.

✱ It is emerging as one of the most important public health issues in the industrialized world. There are many causes of dementia (Table 23-3); BUT, regardless of etiology; the

هم

★ **Rule: Dementia is not part of normal aging & always represents a pathologic process.**

هي مرض وليست جزء من عملية التقدم بالعمر

Table 23-3 Major Causes of Dementia

★Primary Neurodegenerative Disorders

Alzheimer AD, **Huntington** D, **Motor neuron** D, **Parkinson D** & diffuse Lewy body disease ; **Pick** D & other frontotemporal degenerations, Progressive supranuclear palsy,

★Infections

Prion-associated D: Creutzfeldt-Jakob D, fatal familial insomnia, & others.

(**AIDS** dementia) Human immunodeficiency virus encephalopathy

Progressive multifocal leukoencephalopathy **(PML)**

Miscellaneous forms of viral encephalitis, **Neurosyphilis**, Chronic meningitis

★Vascular & Traumatic Diseases

Multi-infarct dementia & other chronic vascular disorders

Global hypoxic-ischemic brain injury,

Chronic subdural hematomas

★ Nutritional & Metabolic Diseases

Thiamine deficiency (Wernicke-Korsakoff syndrome), Vitamin **B12** deficiency, **Niacin** (pellagra) & Endocrine diseases.

★ Miscellaneous → causes مجموعة متفرقة من الـ

Brain **tumors**, Neuronal **storage** diseases, **Toxic injury** (including mercury, lead, manganese, bromides)

زئبق .

★ While the diseases to be discussed in this section are considered as "degenerative" i.e., reflecting an underlying cellular degeneration of neurons in the brain, …

Not all forms of dementia is degenerative.

الـ degeneration هو سبب الـ dementia لكن مش كل dementia بتكون سببها degeneration.

★ Vascular disorders are an important cause of dementia. Patients who suffer multiple, bilateral, gray & white matter (centrum semiovale) infarcts during months or years develop dementia, called ***vascular (multi-infarct) dementia***.

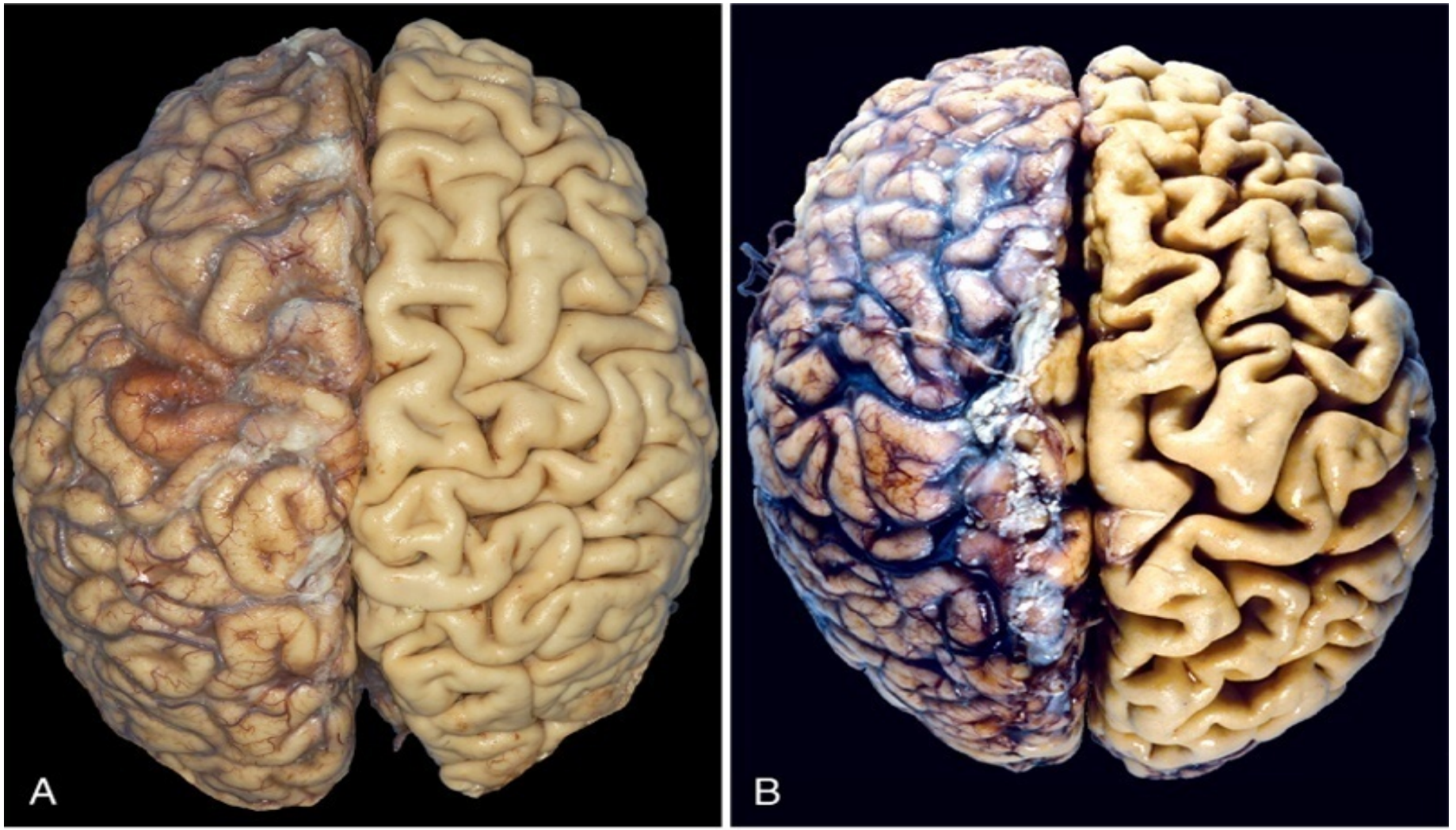
not primary neurodeg.

★ When the pattern of injury preferentially involves large areas of the subcortical white matter with myelin & axon loss, the disorder is referred to as ***Binswanger disease*** ***(F1-4)***.

★ Herewith, we will discuss the main causes of dementia, including Alzheimer, Parkinson, & Huntington diseases.

20, 30, 40 years old.

F1-4: **A, Normal** young adult brain., **B, Atrophy** of the brain in an 82 years-old male with atherosclerotic disease. Note that the loss of the brain substance (due to **aging** & **reduced blood supply**) narrows the gyri & widens the sulci. vascular cause.



Alzheimer Disease (AD)

★ **AD is the most common cause of dementia in the elderly.** The disease usually becomes clinically apparent as insidious impairment of higher intellectual function, with alterations in mood & behavior. Later, progressive disorientation, memory loss, & aphasia indicate severe cortical dysfunction, & over the next 5 to 10 years, the patient becomes profoundly disabled, mute, & immobile.

☠ Death usually occurs from **intercurrent infections.**

★ **AD** incidence is: **3%** (in 65-74 years age group), **19%** (75-84 y), & **47%** (85 years or more).

★ This ↑ incidence with age has given rise to **major medical, social, & economic problems** in some countries.

★ Although **pathologic examination** of brain tissue remains necessary for the **definitive diagnosis of AD**, the combination of **clinical** assessment & modern **radiologic methods** allows accurate diagnosis in 80% to 90% of cases.

★ Most **AD** cases are sporadic, 5% -10% are familial.

★ **AD** patients rarely become symptomatic before 50 years of age, but early onset is seen with some of the heritable forms.

★ Evidence from familial forms of the AD disease indicates that → the **accumulation of a peptide (myloid β, or Aβ) in the brain initiates a chain of events** that result in the morphologic changes of AD & dementia. This peptide is derived from a larger membrane protein known as amyloid precursor protein (APP), which is processed in one of two ways **(F 23-28)**

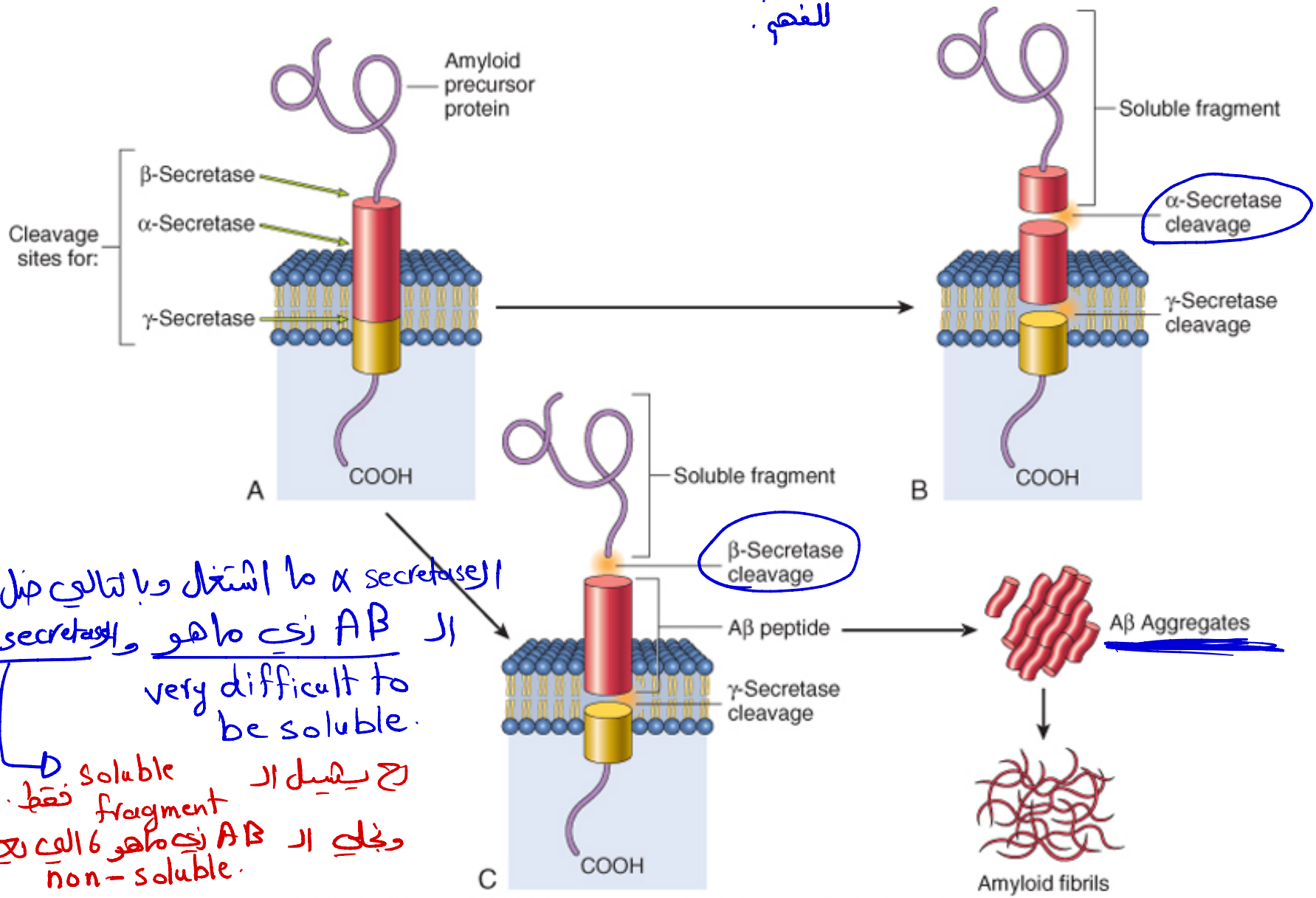
★ **AD** occurs in all patients with trisomy 21 (Down syndrome)- where the gene encoding APP is located - who **survive** beyond 45 years.

☹ Accumulation of **Aβ has several effects:**

- Small Aβ aggregates can alter neurotransmission, & can be → **toxic to neurons** & **synaptic endings**.
- Larger Aβ deposits, in the form of plaques, lead to → **neuronal death, eliciting a → local inflammatory response that can result in further cell injury,** & may cause altered region-to-region communication, through mechanical effects on axons & dendrites.

F23-28: **Accumulation of the peptide (β amyloid, or Aβ) in the brain in Alzheimer disease.**

الصورة مهمة جدا للفهم.



الـ α secretase ما اشتغل وبالتالي ضل الـ Aβ زي ما هو والـ β secretase very difficult to be soluble.

لح يشيل الـ soluble fragment فقط. وبخلي الـ Aβ زي ما هو والي بعتبر non-soluble.

▶**GROSSLY,** the brain is small (often less than 1000g) shows a variable degree of **cortical atrophy,** with **widening of the cerebral sulci** in the frontal, temporal & parietal lobes & **compensatory ventricular enlargement.**

■ **AD** is diagnosed histologically by the presence of **neuritic plaques** (an extracellular lesion); & **neurofibrillary tangles** (an intracellular lesion) **(F 23-29);** both of which are **not specific** because they may also be present to a lesser extent in the brains of elderly nondemented individuals.

▼The current criteria for a diagnosis of AD are based on a combination of clinical & pathologic features.

★ There is a fairly **constant pattern of progression** of involvement of brain regions: pathologic changes (specifically plaques, tangles, & the associated neuronal loss & glial reaction) are evident ⇨earliest in the entorhinal cortex, then ⇨ spread through the hippocampal formation & isocortex, & then ⇨ extend into the neocortex.

Silver staining or immunohistochemistry are extremely helpful in assessing the true burden of these changes in a brain.

★ **Neuritic plaques** are 20 to 200 μm in ∅ with microglial cells & reactive astrocytes, consist of a:

☹ **Neuritic plaques = amyloid core + Surrounding dystrophic neurites: i.e.,**

(I) *Central amyloid core* (contains **accumulation of a peptide (β amyloid, or Aβ,** F 23-29B),

(II) Surrounded by **dystrophic neurites** (F23 -29 & ◘ 4.18) a focal, spherical collections of dilated, tortuous, silver-staining (argyrophilic) neuritic processes present at their periphery.

★ **Neuritic plaques** can be found in the hippocampus & amygdala as well as in the neocortex, although there is usually relative sparing of primary motor & sensory cortices until late in the course of the disease.

★ **Diffuse plaques are Aβ** deposits which can also be found that **lack** any surrounding neuritic reaction these are typically found in superficial portions of cerebral cortex as well as in basal ganglia & cerebellar cortex & may represent an **early stage of plaque development**

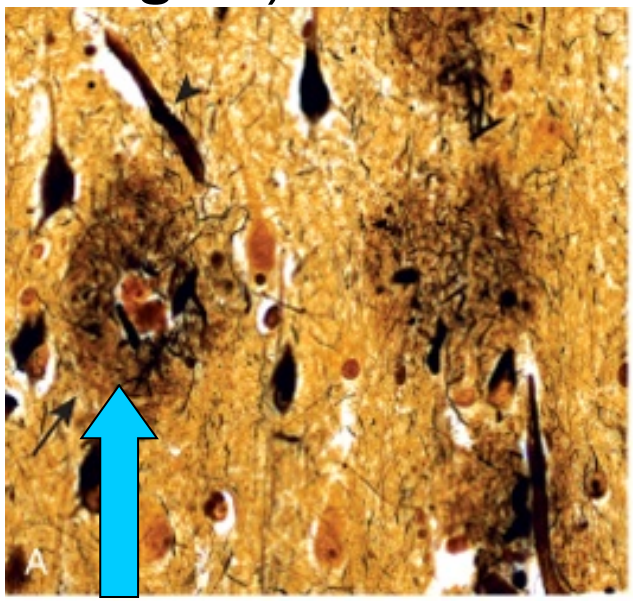
F23-29: **Alzheimer disease. A, Neuritic plaque** {Bielschowsky stain, arrow} is 20 to 200 μm in ∅, focal spherical collections of dilated, tortuous, silver-staining dystrophic neurites & tangles which are filamentous extracellular inclusions, surrounding a central amyloid core,

B, Immunohistochemistry against **Aβ (β amyloid)** shows that the **Aβ** peptide is present in the core of the neuritic plaques & in the surrounding region.

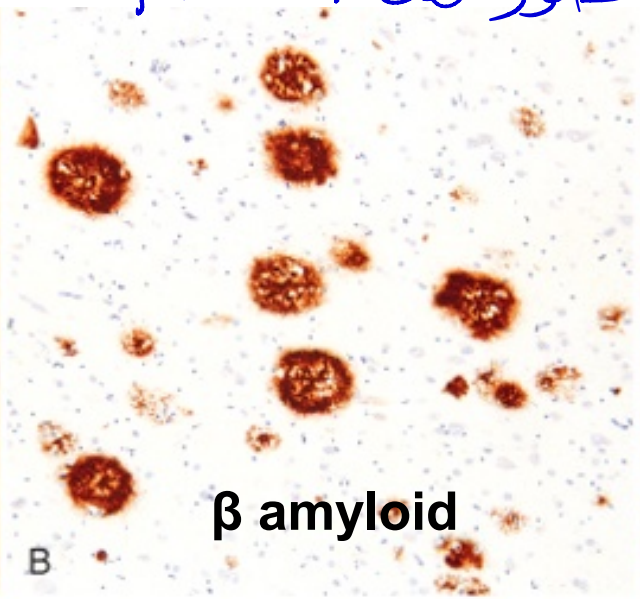
tangles · بكون ملتوي لذلك اسمه

C, Immuno stain for **tau** protein showing neurons containing **tangles**).

for Lab. . الصور مهمة

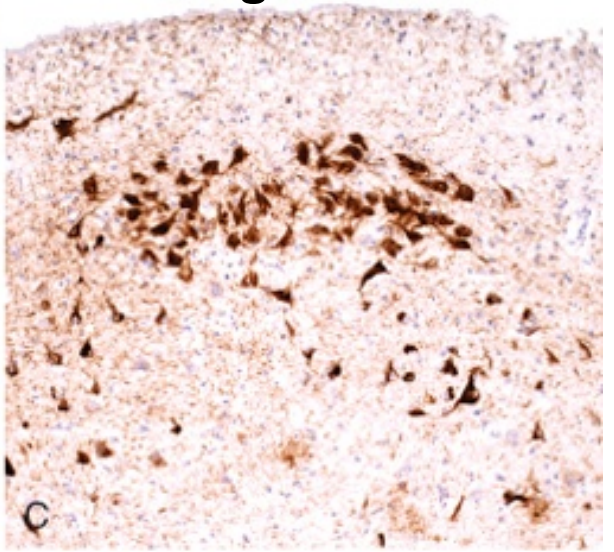


Neuritic plaque



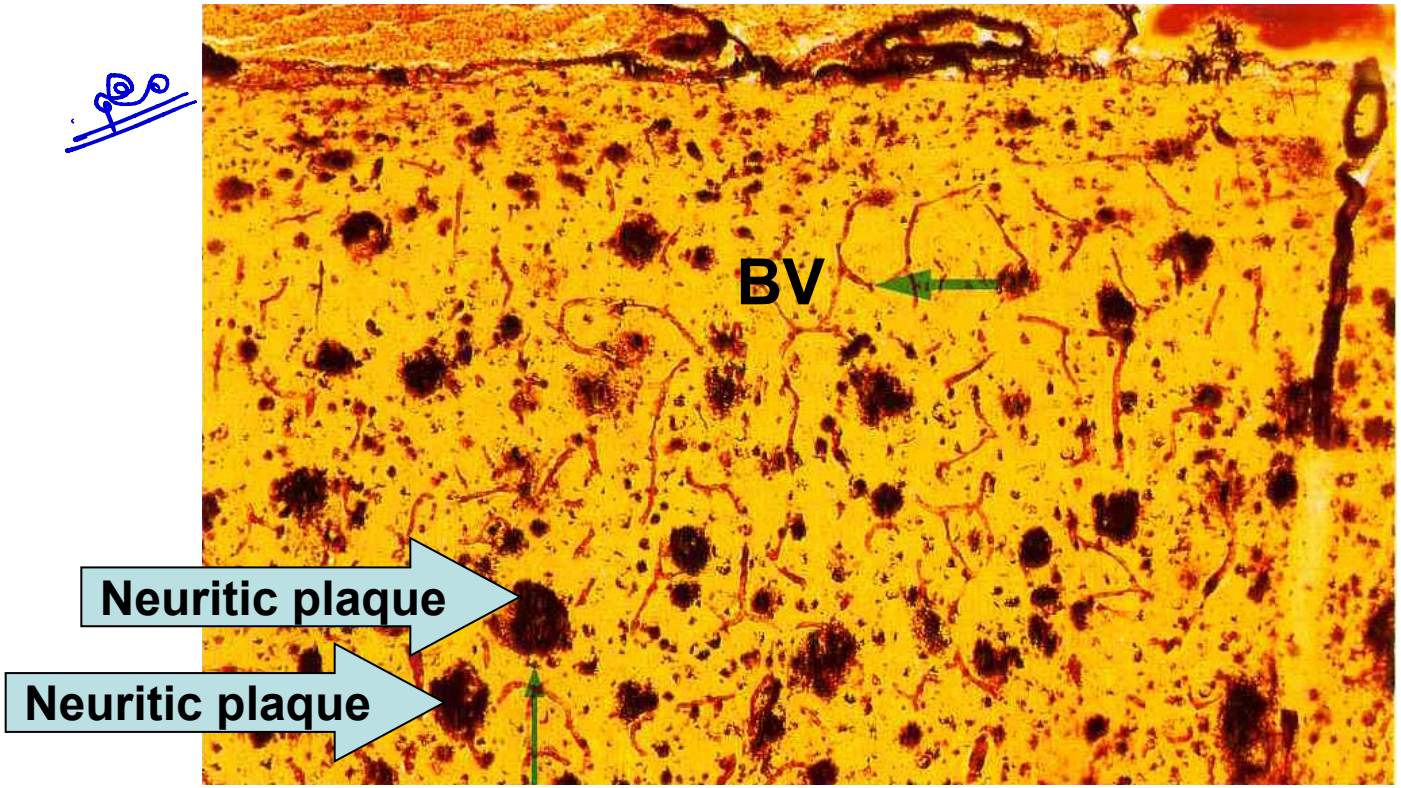
β amyloid

Tangles of tau



◘ 4.18: **Alzheimer disease: Brain X90.** Biopsy specimen from the cortex of a man of 63 stained by periodic acid silver method.

- The subarachnoid space & cortex surface are at top.
- Many rounded & dark **neuritic plaques** (thin A) consisting of (I) *Central amyloid core* (contains **accumulated β amyloid),** (II) Surrounded by **Dystrophic neurites**, spherical collections of extracellular dilated, tortuous, silver-stained (argyrophilic) degenerated neuritic processes



★Neurofibrillary tangles;

Are bundles of paired helical filaments visible as basophilic fibrillary **intracytoplasmic** structures of the neurons, that displace or encircle the nucleus (F23-29C);

Tangles can remain after neurons die, then becoming a form of extracellular pathology.

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, & the raphe nuclei.

A major component of paired helical filaments is abnormally hyperphosphorylated forms of the protein **tau** (F23-29C).

Tangles are not specific to AD, being found in other degenerative diseases as well.

Frontotemporal Dementia

★**Is** another **major** category of disease that results in dementia, some of these dementias are caused by mutations in the gene encoding **tau**, the protein found in tangles.

☹ They shares clinical features (**progressive language deterioration & personality changes**) corresponding to degeneration & atrophy of temporal & frontal lobes. **These symptoms often occur before memory disturbance, &** this difference in presentation can assist in their separation from cases of AD on clinical grounds.

نقد و يفين بيهم من خلال هذا الـ finding.

►**GROSSLY,** the basic finding is **frontal & temporal lobes atrophy.** Different subgroups characterized by specific inclusions, which in some consist of **abnormal** accumulations of **tau.**

Parkinsonism

★Is a clinical syndrome characterized by diminished facial expression **(masked facies), stooped (bended) posture, slowness of voluntary movement, festinating gait** (progressively shortened, accelerated steps), **rigidity,** & a "pill-rolling" **tremor.**

★This **syndrome** of motor disturbance is seen in a number of conditions that share **damage to dopaminergic neurons of the substantia nigra** or to their projection to the striatum, including **post-encephalitic Parkinsonism** (associated with the influenza pandemic), multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, & some cases of HD.

★**Parkinsonism can be induced** by drugs that affect these neurons, particularly **dopamine antagonists & toxins**; one toxin, **MPTP,** has now become an important tool in **animal models** to develop & test new therapies.

Idiopathic Parkinson disease

Is the most common neurodegenerative disease associated with Parkinsonism. Its ▼ **Diagnosis** is made in patients with progressive Parkinsonism in the **absence of a toxic or other known underlying etiology & if they show clinical response to l-dihydroxyphenylalanine (l-DOPA) treatment.**

★Most Parkinson disease cases are sporadic;

★However, there are both autosomal dominant & recessive forms of the Parkinson disease.

★ Genetic analysis has identified specific causal mutations, e.g.; **α-synuclein mutations cause autosomal dominant Parkinson disease,** as can gene duplications & triplications.

★ Even in cases of Parkinson disease not caused by mutations in this gene, the **diagnostic feature of the disease-the Lewy body-is an inclusion containing α-synuclein.** This is a widely expressed neuronal protein that is involved in synaptic transmission & other cellular processes.

★**The presence of α-synuclein in the Lewy bodies** has *suggested that defective degradation of the protein in the proteasome might play a role.*

present in all cases.

► **Grossly,** typically there is **pallor of the substantia nigra (F23-30A & B) & locus ceruleus.**

◘ H, there is (1) loss of the pigmented, catecholaminergic neurons in these regions with gliosis; & (2) **Lewy bodies (F23-30C)** may be found in some of the remaining neurons.

◘ **Lewy bodies** are **single or multiple, round or elongated, eosinophilic intracytoplasmic inclusions that often have a dense core surrounded by a pale halo.**

◘ ◘ Ultrastructurally, Lewy bodies are composed of fine filaments, densely packed in the core but loose at the rim. These filaments are **composed of α-synuclein,** along with other proteins including **neurofilament & ubiquitin.** Lewy bodies may also be found in the cholinergic cells of the basal nucleus of Meynert, & in other brain-stem nuclei.

◘ The presence of **Lewy bodies** in limbic & neocortical structures is associated with cognitive impairment-the disorder recognized as **[Dementia with Lewy bodies]**.

F23-30: **Parkinson disease.**

A, ☺ *Normal substantia nigra.*

B, ☹ ***Depigmented*** substantia nigra in idiopathic Parkinson disease.

C, ***Lewy body*** (arrow) in a neuron from the substantia nigra stains pink. An eosinophilic, round intracytoplasmic inclusion in cytoplasm of neuron. having dense core surrounded by a pale halo.