NEURODEGENERATIVE DISEASES

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Objectives

- Explain the basic pathological concepts of neurodegenerative disease, using Alzheimer's and Parkinson disease as a classical example.
- Know the definition of "dementia" syndrome.
- List the possible causes of dementia.
- Explain the basic pathological concepts of a neurodegenerative disease, using Alzheimer's disease as a classical example.
- Understand the major clinic-pathological features of Alzheimer's disease.
- Hypothesize the possible etiologies of Alzheimer's disease.
- List the causes of Parkinsonism.
- Understand the major clinical and pathological feature of Parkinson disease.
- Hypothesize the possible etiologies of Parkinson disease.

Degenerative Brain Diseases

- Neurodegenerative diseases are characterized by the progressive loss of neurons, typically affecting groups of neurons with functional interconnections, rather than by the physical location in the brain.
- They cause symptoms that depend on the pattern of involvement of the brain.
- Although many degenerative diseases have primary targets, other brain regions are often affected later in the course of the illness.

Degenerative Brain Diseases

- Diseases that involve the cerebral cortical neurons result in cognitive changes, often including disturbances of memory, behavior, and language. With time these progress to dementia, as occurs with Alzheimer disease.
- Diseases that affect the neurons of the basal ganglia result in movement disorders as with Parkinson disease.
- Diseases that affect the cerebellum result in ataxia.
- Diseases that affect the motor neurons result in weakness.

Dementia

- It is defined as the development of memory impairment and other cognitive deficits severe enough to decrease the affected person's capacity to function at the previous level despite a normal level of consciousness.

- It arises during the course of many neurodegenerative diseases; it also can accompany numerous other diseases that injure the cerebral cortex e.g. metabolic disorders, infections or toxins.

- Dementia is an increasing public health concern as the population ages.

What to Expect in Late-Stage Dementia

Loss of facial expression

Bedbound, requires around-the-clock care

Unable to speak

Alzheimer Disease

- It is the most common cause of dementia in the elderly.
- The disease usually manifests with the insidious onset of impaired higher intellectual function, memory impairment, and altered mood and behavior.
- Later, severe cortical dysfunction occurs with progressive disorientation, memory loss and aphasia.
- Over the next 5 to 10 years, the patient becomes profoundly disabled, mute, and immobile.
- Death usually occurs from intercurrent pneumonia or other infections.

Alzheimer Disease

- When considered by age groups, the incidence of Alzheimer disease is:
  - 3% for individuals 65 to 74 years of age.
  - 19% for individuals 75 to 84 years of age.
  - 47% for individuals 85 years or more.
- This increasing incidence with age has given rise to major medical, social, and economic problems in countries with a growing number of elderly.

Alzheimer Disease

- Although the pathologic examination of brain tissue remains necessary for the definitive diagnosis of Alzheimer disease, the combination of clinical assessment and modern radiologic methods allows an accurate diagnosis in 80% to 90% of cases.

Alzheimer Disease

- Most cases are sporadic.
- At least 5% to 10% are familial.
- In general, patients rarely become symptomatic before the age of 50, but early onset can be seen with some of the heritable forms.

Alzheimer Disease Pathogenesis

- The fundamental abnormality in AD is the accumulation of two proteins (Aβ and tau) in specific brain regions, in the forms of plaques and tangles, respectively.

- Plaques are deposits of aggregated Aβ peptides in the neuropil, while tangles are aggregates of the microtubule binding protein tau, which develop intracellularly and then persist extracellularly after neuronal death.

Alzheimer Disease Pathogenesis

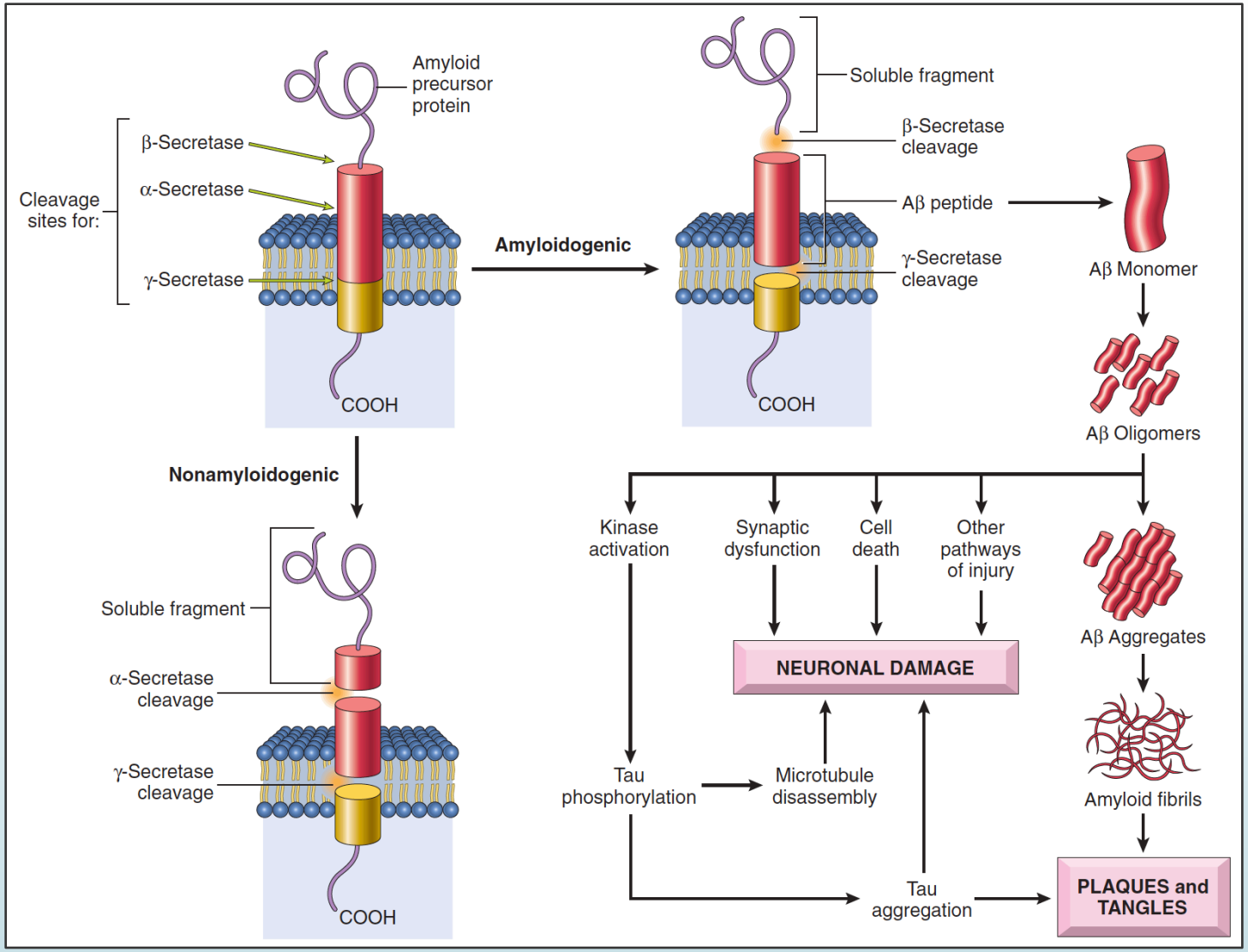
- Aβ generation is the critical initiating event for the development of AD.
- Aβ is created when the transmembrane protein amyloid precursor protein (APP) is sequentially cleaved by the enzymes β-amyloid–converting enzyme (BACE) and γ-secretase.
- APP also can be cleaved by a-secretase and γ-secretase, liberating a different peptide that is nonpathogenic.
- The generation and accumulation of Aβ occur slowly with advancing age.

Alzheimer Disease Pathogenesis

- Mutations in APP or in components of γ-secretase lead to familial (early onset) AD by increasing the rate at which Aβ is generated.

- The APP gene is located on chromosome 21 thus AD occurs in almost all patients with trisomy 21 (Down syndrome) who survive beyond 45 years of age.

Amyloid precursor protein cleavage by a-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme (BACE) and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.



Alzheimer Disease Pathogenesis

- The search for genes associated with typical, sporadic AD is beginning to identify genetic associations that may provide new clues about the pathogenesis of the disease.

Alzheimer Disease Pathogenesis

- An allele of apolipoprotein, called ε4 (ApoE4), is associated with as many as 30% of cases, and it is thought to both increase the risk and lower the age of onset of the disease.

- ApoE4 may contribute to the deposition of Aβ, but how it does so is not known.

Alzheimer Disease Pathogenesis

- Another gene called *SORL1,* has also recently been found to be associated with late-onset Alzheimer disease.

- Deficiency of the SORL1 protein may alter the intracellular trafficking of APP, shuttling it to a compartment where the Aβ peptide is generated by enzymatic cleavage, the net result being increased generation of this pathogenic peptide.

Alzheimer Disease Pathogenesis

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

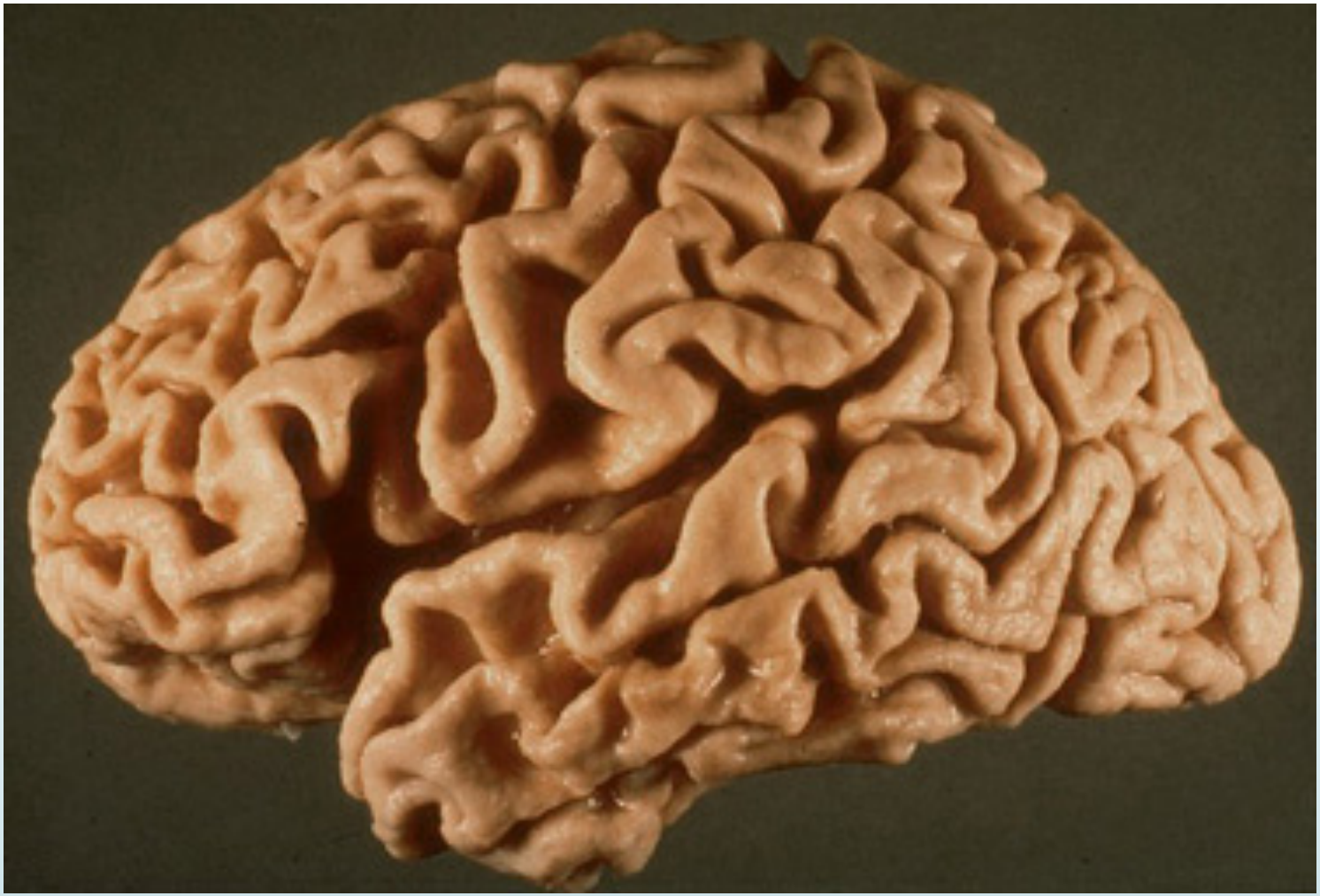
Alzheimer Disease Pathogenesis

- The presence of Aβ also leads neurons to hyperphosphorylate the microtubule binding protein "tau".
  - With this increased level of phosphorylation, tau redistributes within the neuron from the axon into dendrites and cell body and aggregates into tangles.
  - This process also results in neuronal dysfunction and cell death.
  - The anatomic distribution of these changes, which occur roughly in parallel, are responsible for the clinical signs and symptoms; they appear to develop well in advance of clinical presentation.

Alzheimer Disease

- Macroscopic features:
  - A variable degree of cortical atrophy with widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes.
  - With significant atrophy, there is compensatory ventricular enlargement (hydrocephalus ex vacuo).

Alzheimer Disease



Alzheimer Disease

- Microscopic features:
  - **Plaques** (a type of extracellular lesion)
  - **Neurofibrillary tangles** (a type of intracellular lesion)
  - Because these may also be present to a lesser extent in the brains of elderly nondemented individuals, the current criteria for a diagnosis of Alzheimer disease are based on a combination of clinical and pathologic features.

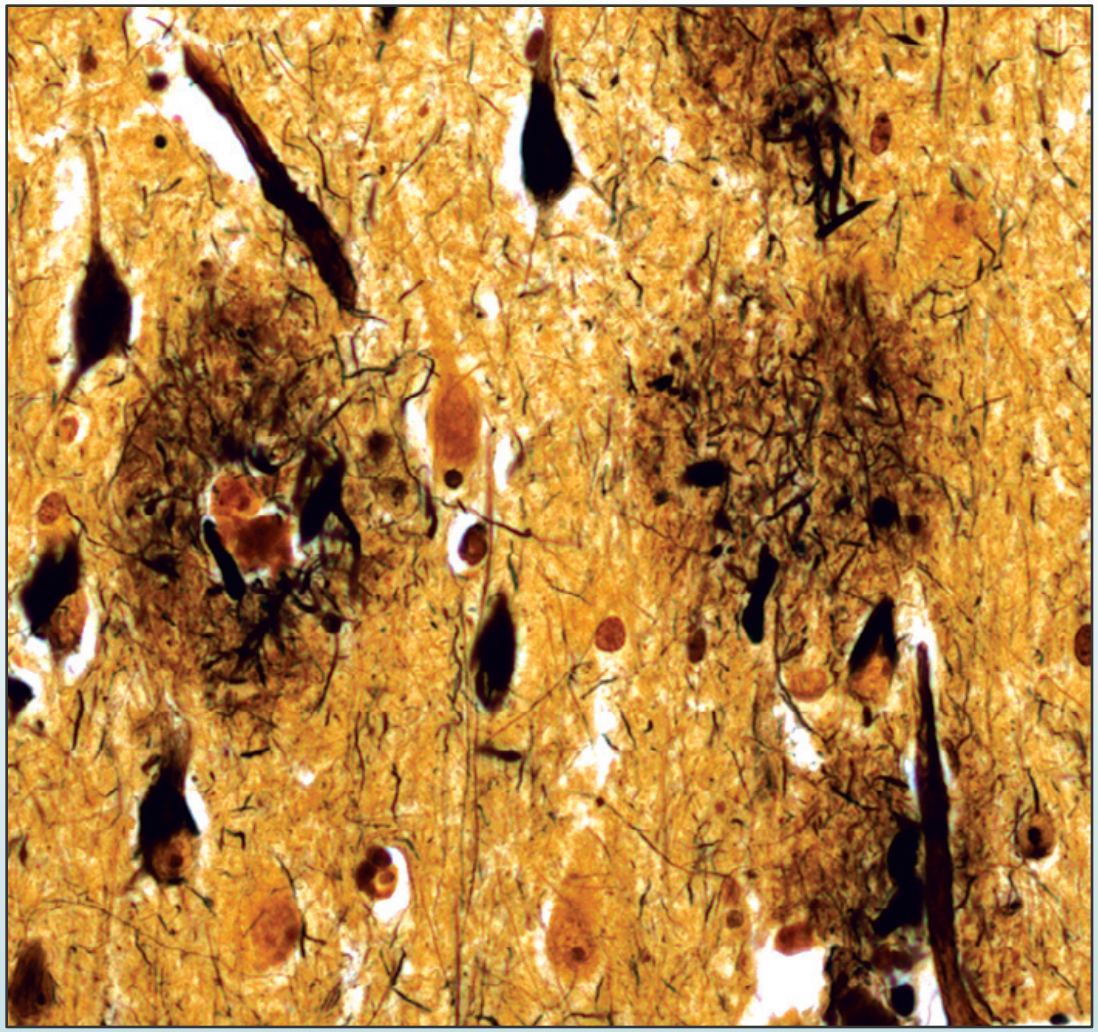
Alzheimer Disease

- There is a fairly constant pattern of progression of involvement of the brain regions pathologic changes:
- The earliest occur in the entorhinal cortex → then spread through the hippocampal formation and isocortex → then extend into the neocortex.
- Silver staining methods or immunohistochemistry are extremely helpful in assessing the true burden of these changes in a brain.

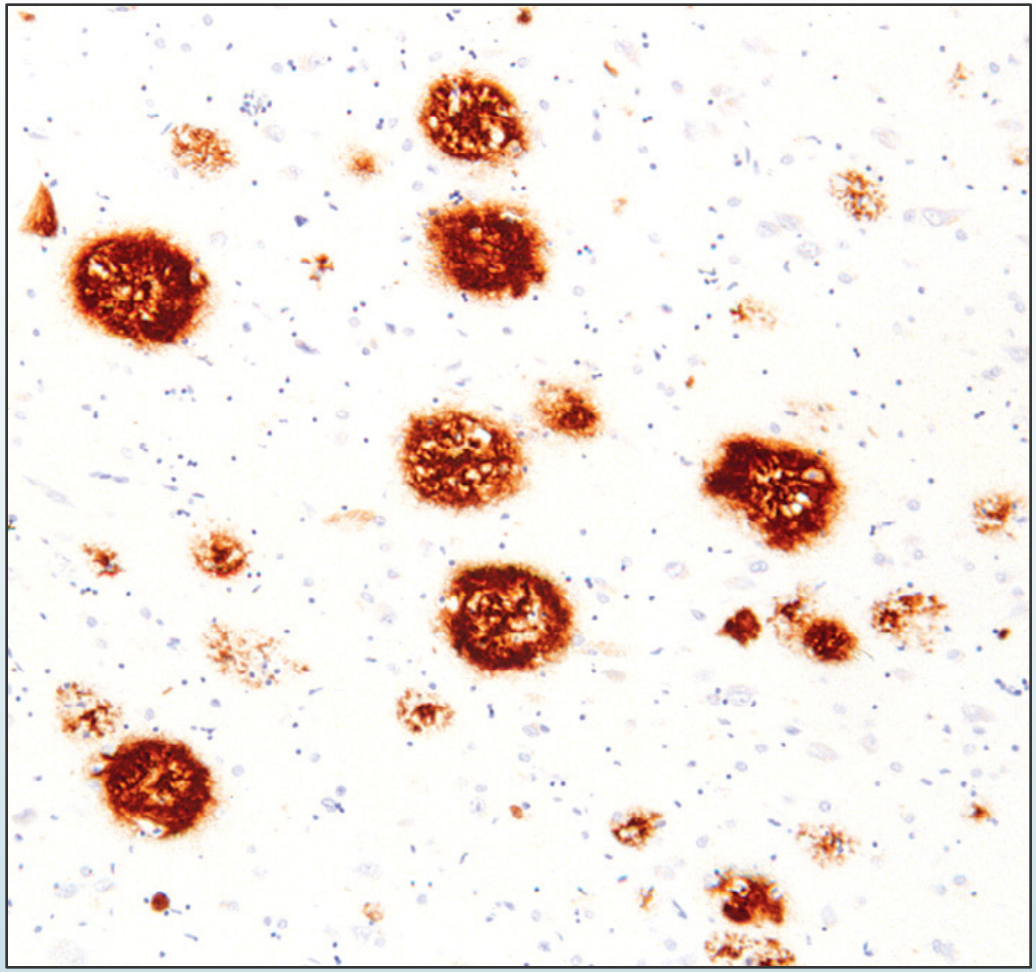
Alzheimer Disease

- **Neuritic plaques**
  - Focal, spherical collections of dilated, tortuous, silver-staining neuritic processes (dystrophic neurites), often around a central amyloid core which contains Aβ.
  - Plaques can be found in the hippocampus and amygdala as well as in the neocortex, although there is usually relative sparing of primary motor and sensory cortices until late in the course of the disease.
  - Aβ deposits can also lack any surrounding neuritic reaction, termed *diffuse plaques*.

Plaques (arrow) contain a central core of amyloid and a surrounding region of dystrophic neurites (Bielschowsky stain)



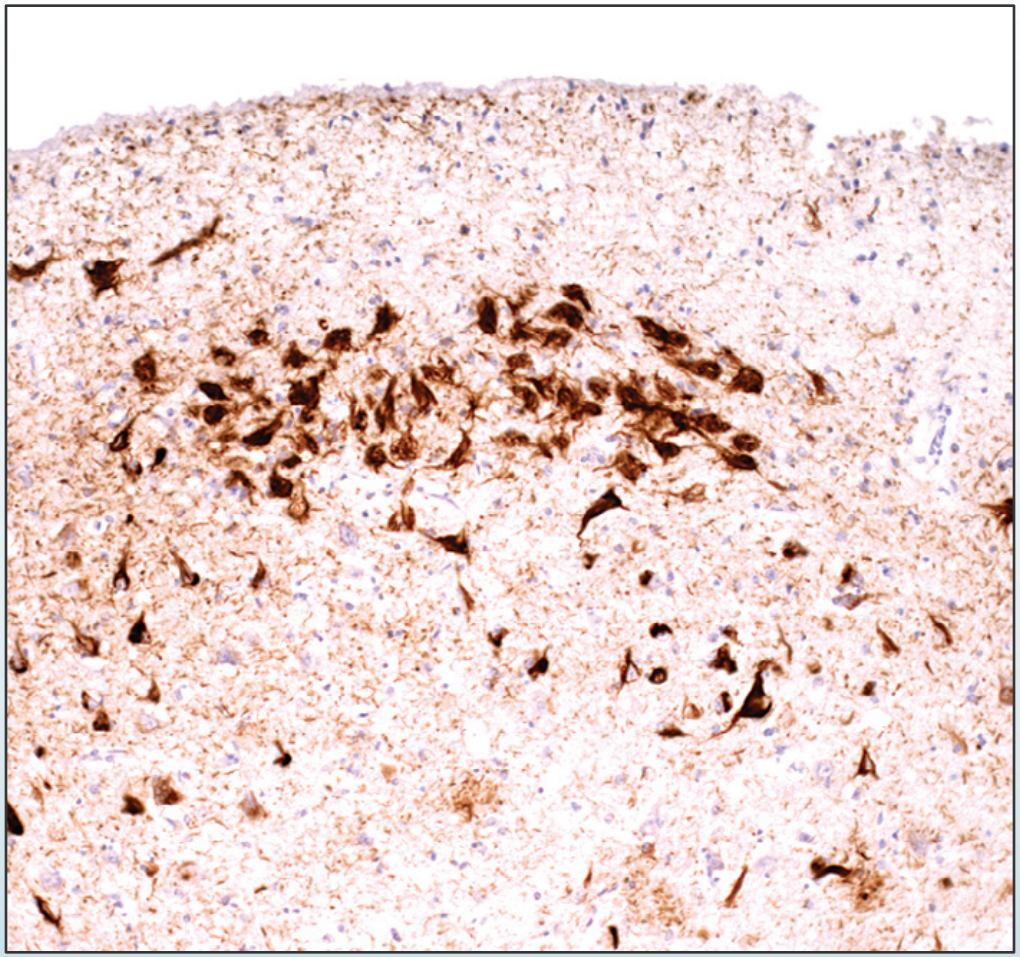
Immunohistochemical stain for Aβ. Peptide is present in the core of the plaques as well as in the surrounding region.



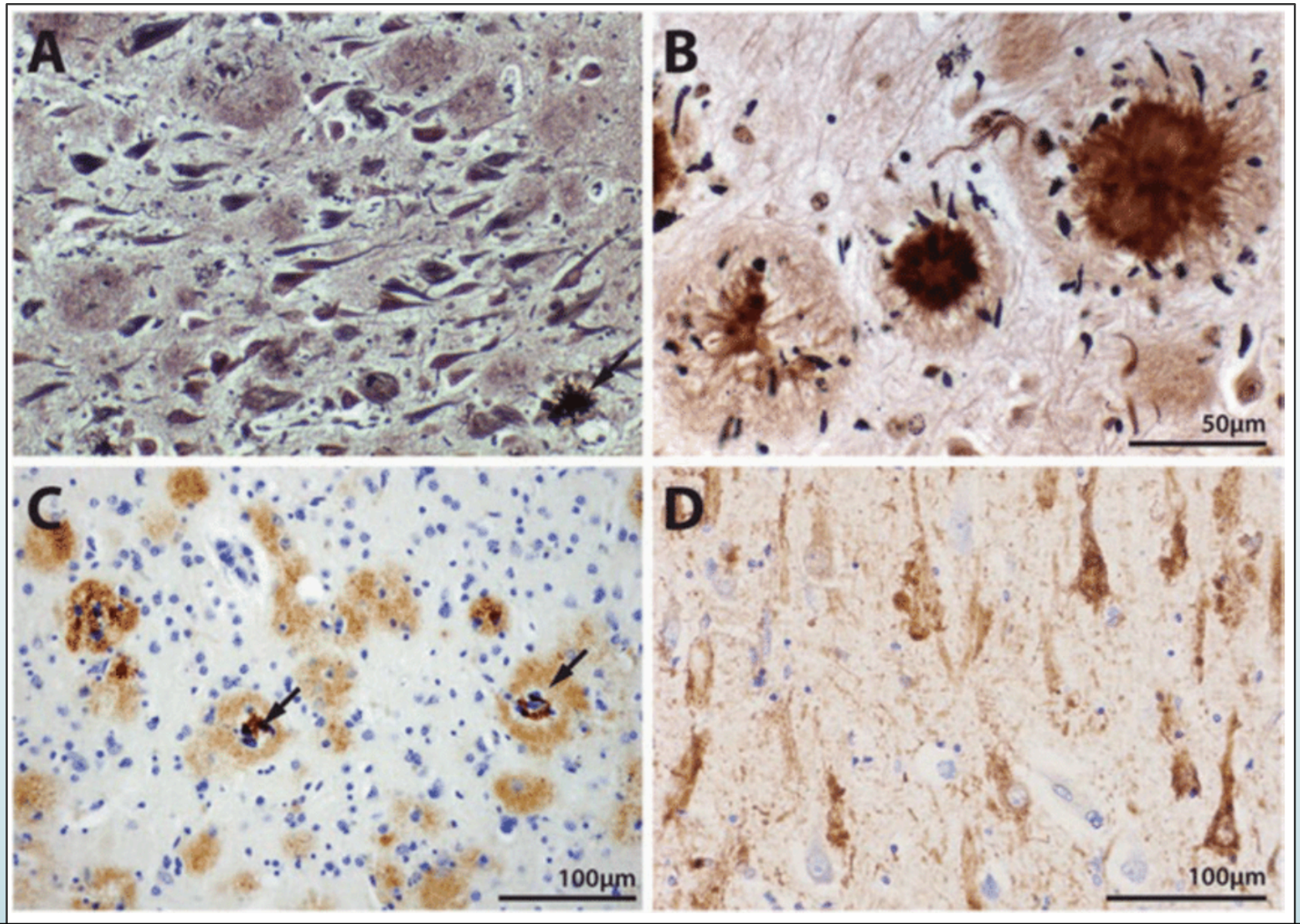
Alzheimer Disease

- **Neurofibrillary tangles**
  - Bundles of paired helical filaments visible as basophilic fibrillary structures in the cytoplasm of the neurons that displace or encircle the nucleus.
  - Tangles can remain after neurons die, becoming a form of an extracellular finding.
  - 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 and the basal forebrain.
  - A major component of paired helical filaments is abnormally hyperphosphorylated forms of the protein **tau.**
  - Tangles are not specific to Alzheimer disease, being found in other degenerative diseases as well.

Neurons containing tangles stained with an antibody specific for tau.



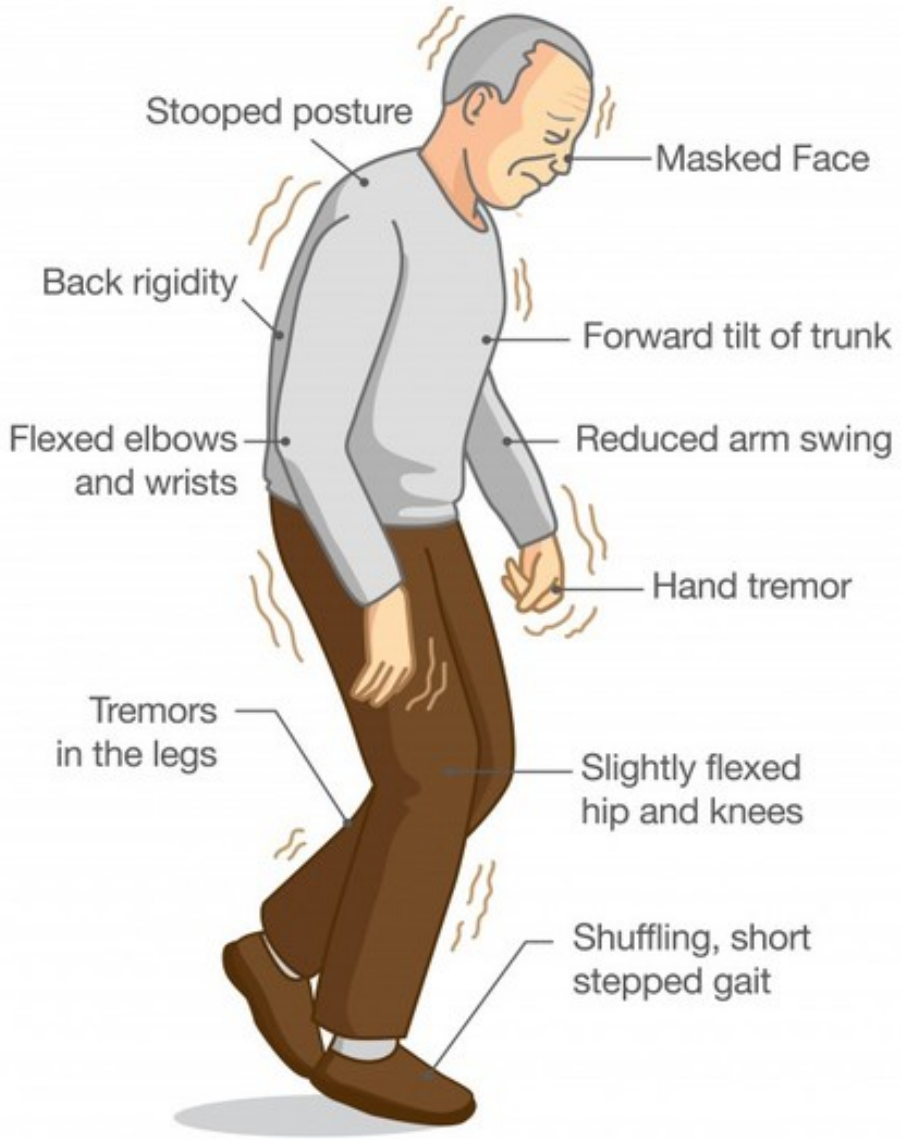
Hallmark pathology of Alzheimer's disease. Silver staining of cortical brain tissue (a) showing plaques and tangles in the cortex and higher power image of silver positive neuritic plaques (b). Amyloid-beta protein in the plaques (c) and hyperphosphorylated tau in tangles (d). Scale in C equivalent to A. Arrows indicate neuritic plaques.



Parkinsonism

- It is a clinical syndrome characterized by:
  - diminished facial expression (masked face)
  - stooped posture
  - slowness of voluntary movement
  - festinating gait (progressively shortened, accelerated steps)
  - Rigidity, bradykinesia and instability.
  - "pill-rolling" tremor

Parkinson's Disease Symptoms



Parkinsonism

- These types of motor disturbances may be seen in a range of diseases that damage dopaminergic neurons in the substantia nigra or their projections to the striatum.

Parkinsonism

- Parkinsonism can be induced by:
  - drugs that affect these neurons, particularly dopamine antagonists and toxins.
  - post-encephalitic parkinsonism (associated with the influenza pandemic).
  - *idiopathic Parkinson disease (the most common neurodegenerative disease associated with parkinsonism)*
  - other neurodegenreative diseases *multiple system atrophy* (MSA), *progressive supranuclear palsy* (PSP) and *corticobasal degeneration* (CBD)
  - *rare: head trauma, stroke*

Parkinson Disease

- Diagnosis
  - progressive parkinsonism
  - absence of a toxic or other known underlying etiology
  - clinical response to L-dihydroxyphenylalanine (L-DOPA) treatment

Parkinson Disease

- It occurs in the 6th to 8th decades.
- It affects more than 2% in North America.
- It affects men more than women.
- The crude prevalence rate in Saudi population if 22/100,000.

Parkinson Disease Pathogenesis

- While most Parkinson disease is sporadic, there are both autosomal dominant and recessive forms of the disease.

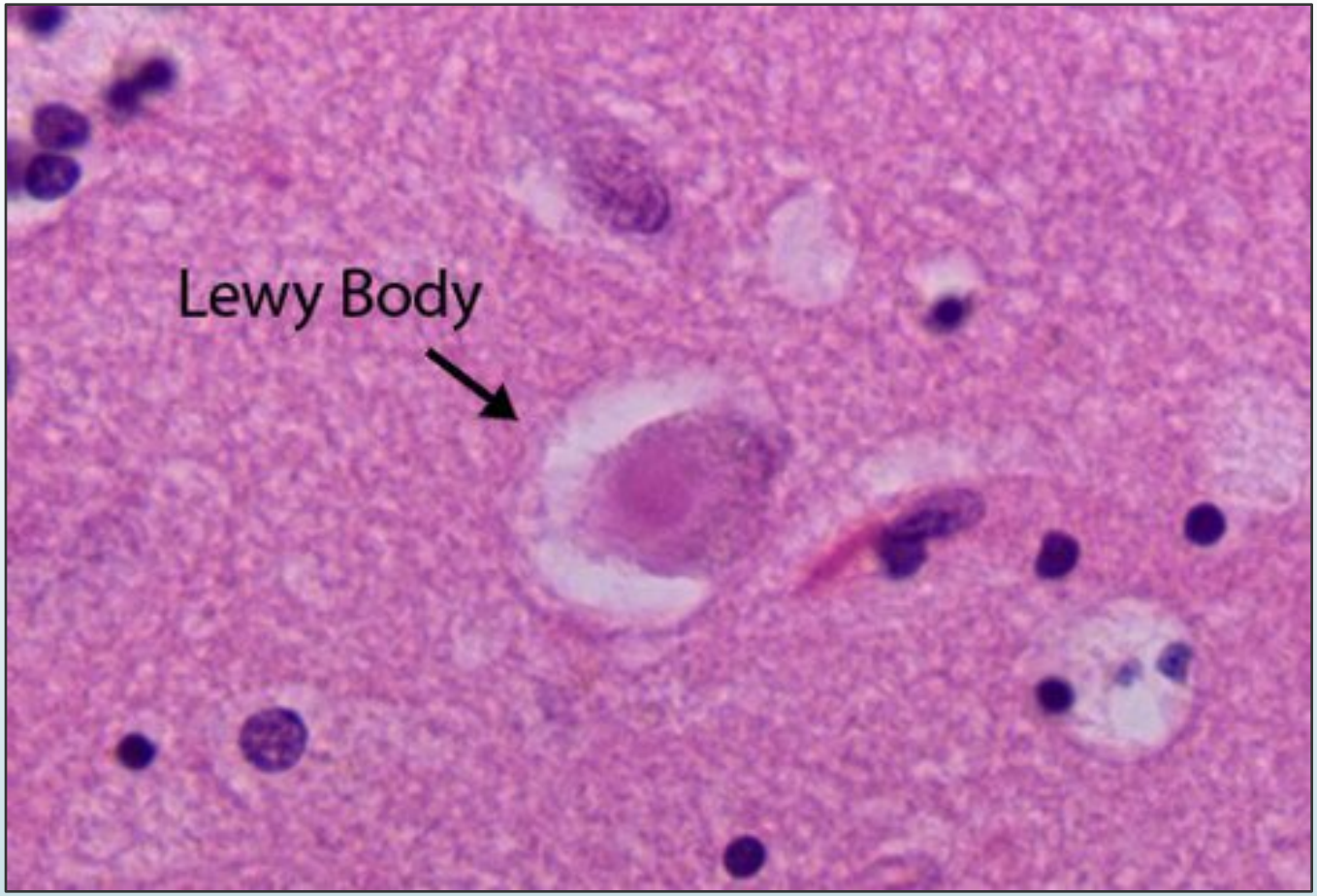
- Point mutations and duplications of the gene encoding a-synuclein, a protein involved in synaptic transmission, cause autosomal dominant PD.

Parkinson Disease Pathogenesis

- Even in cases not caused by mutations in this gene, the diagnostic feature of Parkinson disease, **the Lewy body**, is an inclusion containing a-synuclein.

- This is a widely expressed neuronal protein that is involved in synaptic transmission and other cellular processes.

Parkinson Disease Pathogenesis



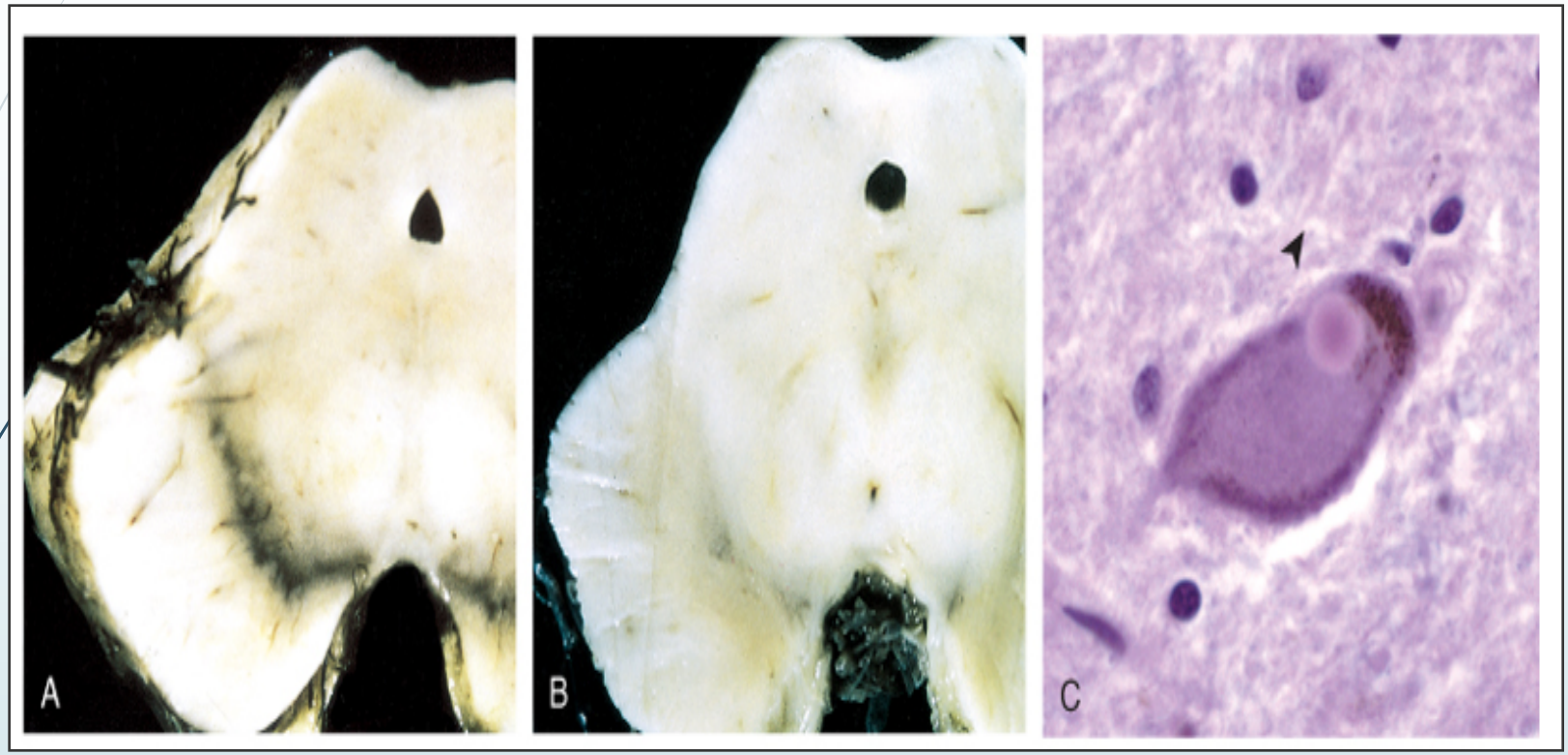
Parkinson Disease Pathogenesis

- How the alterations in sequence or protein levels result in disease is unclear.
- The presence of a-synuclein in Lewy bodies has suggested that defective degradation of the protein in the proteasome might play a role.
- This is supported by the identification of two other genetic loci for Parkinson disease:
  - Loci which involve genes encoding parkin (an E3 ubiquitin ligase)
  - UCHL-1 (an enzyme involved in recovery of ubiquitin from proteins targeted to the proteasome)

Parkinson disease

- Macroscopic features:
  - Pallor of the substantia nigra and locus ceruleus
- Microscopic features:
  - loss of the pigmented neurons in these regions
  - gliosis
  - **Lewy bodies** may be found in some of the remaining neurons

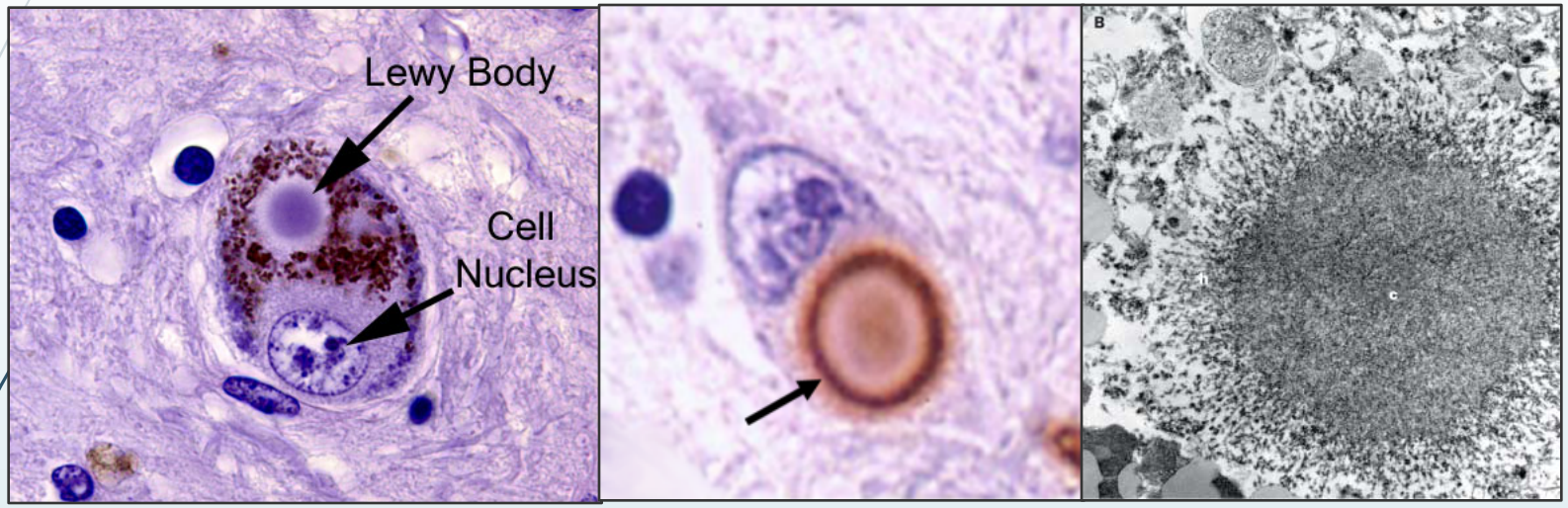
Parkinson disease. (A) Normal substantia nigra. (B) Depigmented substantia nigra in idiopathic Parkinson disease. (C) Lewy body in a neuron from the substantia nigra stains pink.



Parkinson disease

- **Lewy Body**
  - Single or multiple, intracytoplasmic, eosinophilic, round to elongated 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 a-synuclein, along with other proteins, including neurofilaments and ubiquitin.
  - The other major histologic finding is **Lewy neurites**, dystrophic neurites that also contain abnormally aggregated a-synuclein.

Parkinson disease



Parkinson disease

- Clinical features:
  - L-DOPA therapy is often extremely effective in symptomatic treatment, but it does not significantly alter the progressive nature of the disease.
  - Over time, L-DOPA becomes less effective at providing the patient with symptomatic relief and begins to cause fluctuations in motor function on its own.

Parkinson disease

- It usually progresses over 10 to 15 years.
- There is an eventual severe motor slowing to the point of near immobility.
- Death is usually the result of intercurrent infection or trauma from frequent falls caused by postural instability.

Parkinson disease

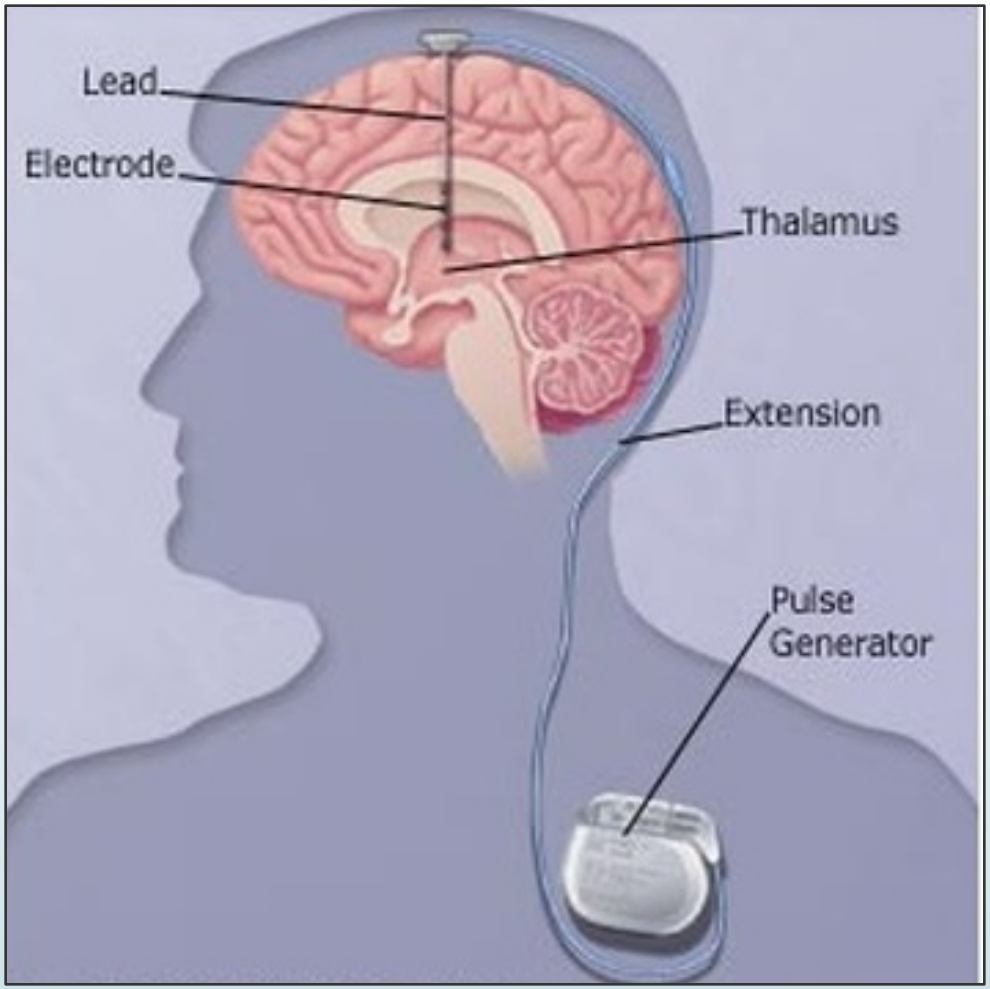
- About 10% to 15% of individuals with Parkinson disease develop dementia, with the incidence increasing with advancing age.
- The characteristic feature of this disorder includes a fluctuating course and hallucinations.
- While many affected individuals also have pathologic evidence of Alzheimer disease, the dementia in other Parkinson disease patients is attributed to widely disseminated Lewy bodies in the cerebral cortex.
- When dementia arises within 1 year of the onset of motor symptoms, it is referred to *Lewy body dementia*.

Parkinson disease

- Parkinson disease has been targeted for many novel therapeutic approaches.

- Current neurosurgical approaches to Parkinson disease include the placement of lesions in the extrapyramidal system to compensate for the loss of nigrostriatal function or placement of stimulating electrodes - deep brain stimulation.

Parkinson disease



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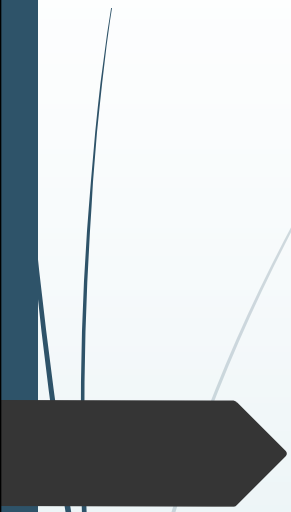

Thank You

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