Alzheimer's Disease & Anti-Dementia Drugs

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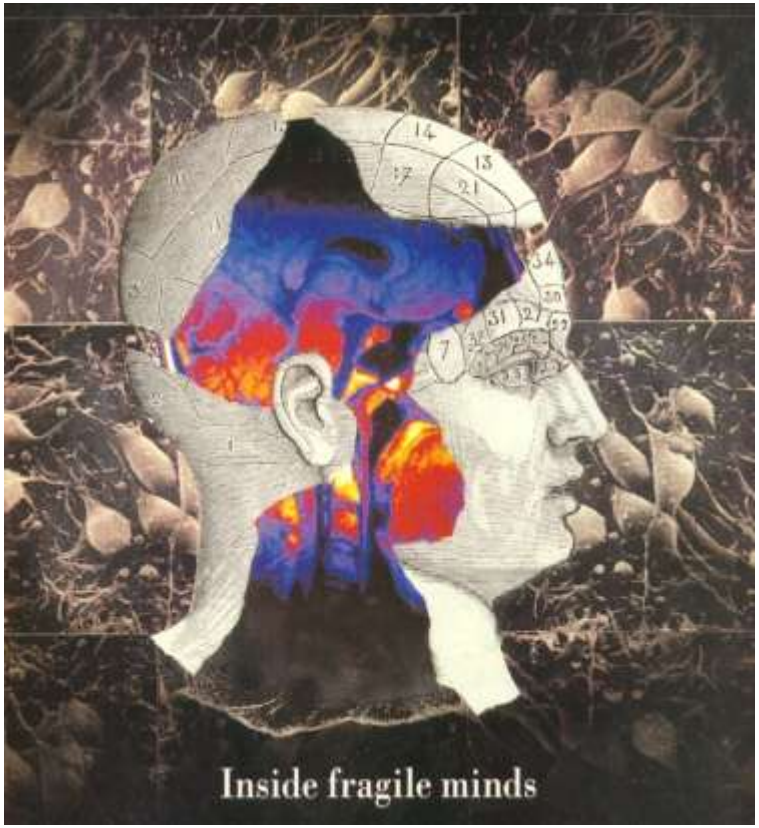


Lecture Outline

- Diagnostic Features of Dementia
- Pathophysiology of AD
- Clinical Pharmacology of Drugs for Alzheimer's

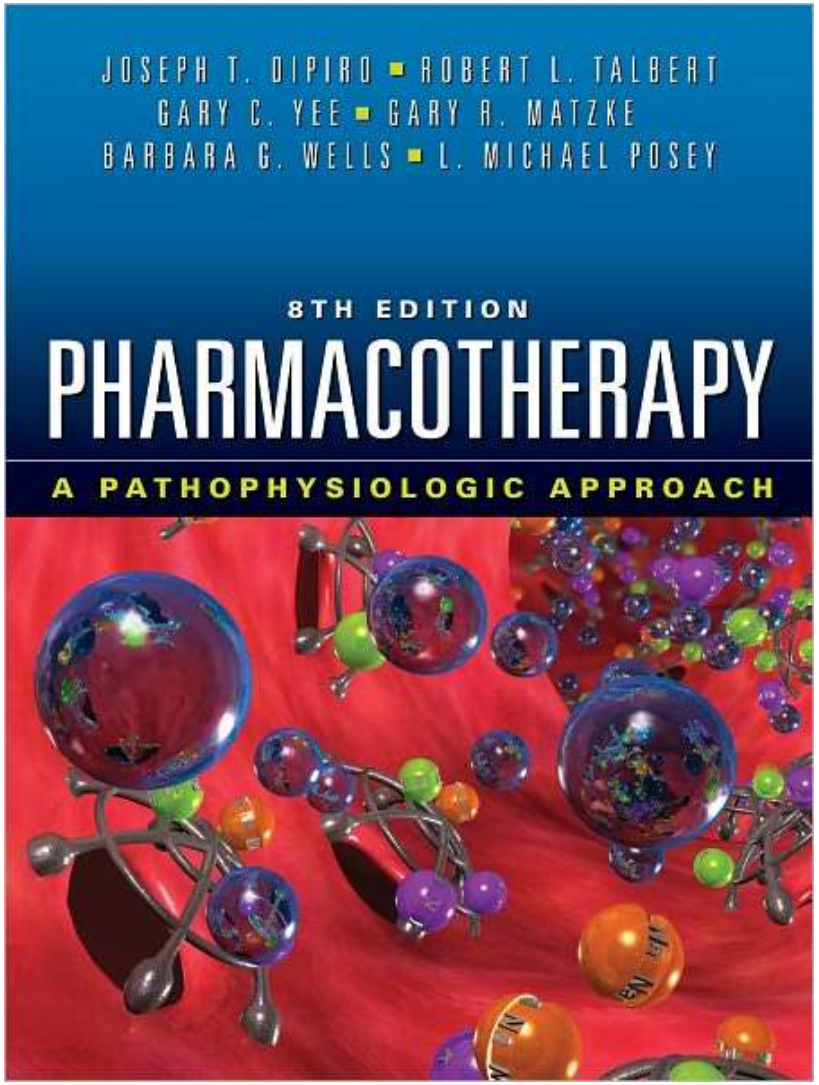
"I now begin the journey that will lead me into the sunset of my life".

Ronald Reagan, 40th President of the United States of America

DiPiro *et al.*,

8th edition (2011)

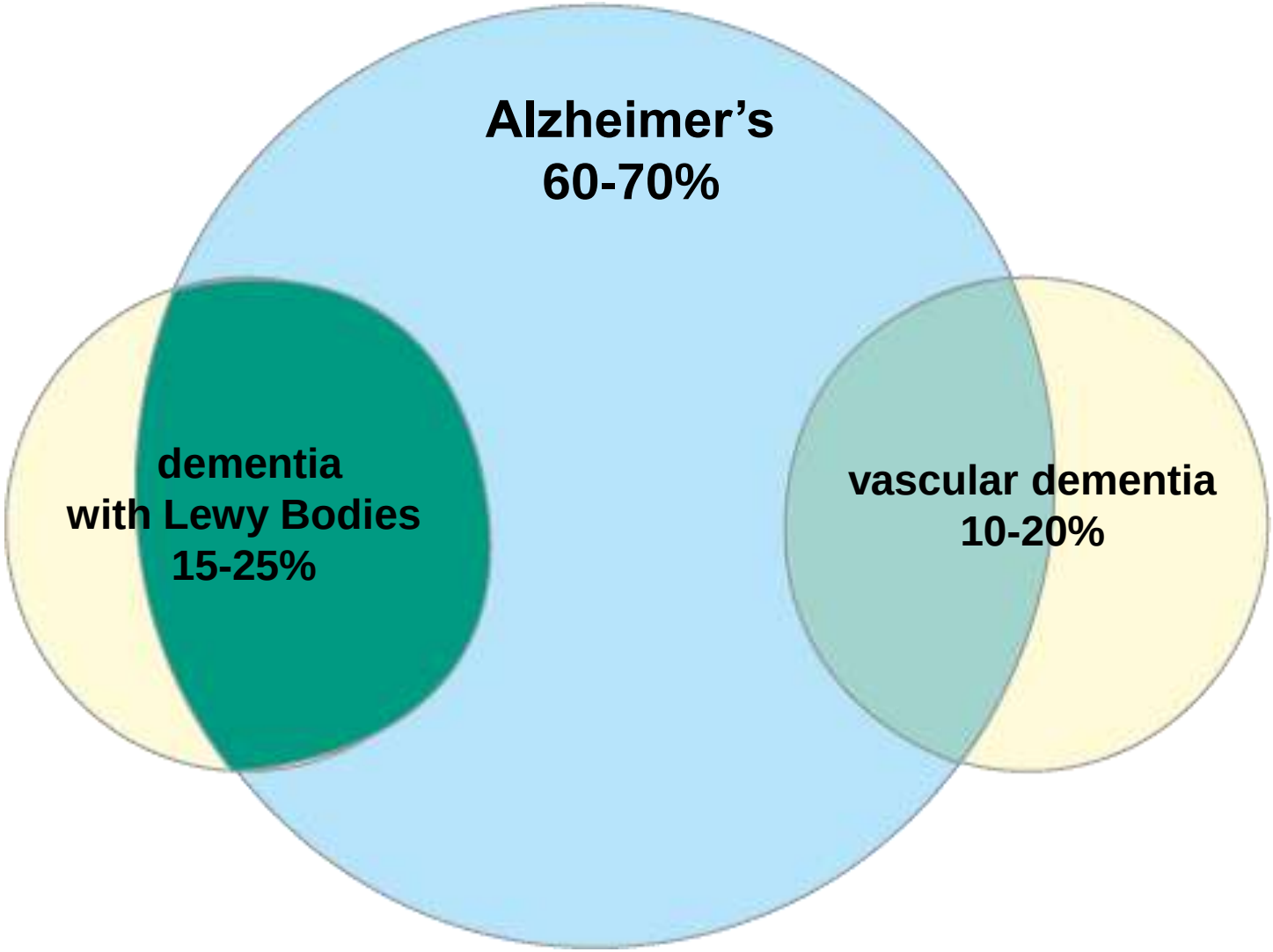
Chapter 63



Some Causes of Memory Loss And Dementia

- Alzheimer's Disease
- Cerebrovascular disease
- Lewy Body Dementia
- Parkinson's Disease
- Fronto-temporal dementia
- Alcoholism *(Korsakoff Syndrome)*
- Infections (AIDS, Syphilis)
- Brain Tumor,
- Vitamin deficiencies *(e.g. Vitamin B12)*
- Stroke
- Trauma

Mixed Dementia: Overlap of AD with Other Dementias



Dr. Alzheimer's Original Description of Dementia*

"A 51-year-old woman demonstrated, as a first conspicuous symptom, ideas of jealousy against her husband. An increasing weakness of memory became noticeable, she was unable to negotiate her way, carried objects in and out, hid them, and sometimes she believed that someone would kill her and began to cry."

Dr Alois Alzheimer (1864-1915)

*Über eine eigenartige Erkrankung der Hirnrinde, *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin*, 64. 1906)

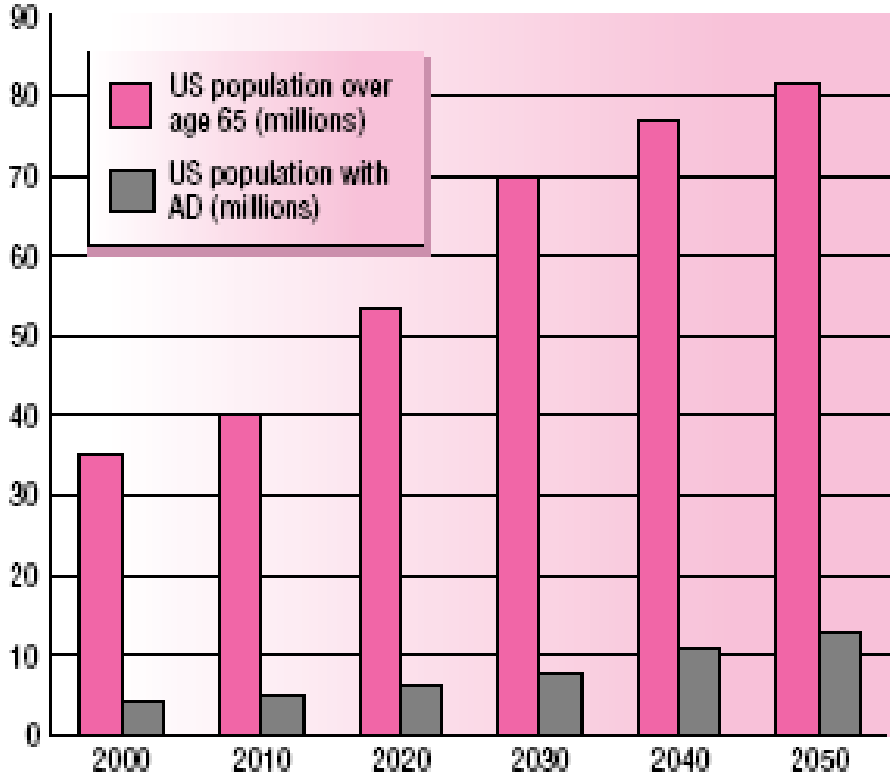
Characteristics of Alzheimer's Disease

- **Senile Dementia**: loss of *memory* in an otherwise alert subject
- Plus impairments in at least one other cognitive function, including:

  language, problem solving, calculation, attention, perception

Prevalence of Alzheimer's Disease

- 7% of people ≥ age 65 yrs.
- 40% of people ≥ aged 80 yrs.
- Currently 5 million AD cases in the USA
- Estimates will be 15 million cases by 2050
- 1st signs develop in 6th or 7th decade of life
- Survival from onset approx 8 years



Risk Factors For Alzheimer's Disease

Obesity

Diabetes

Hypertension

Smoking

Head injury

Infections (AIDS)

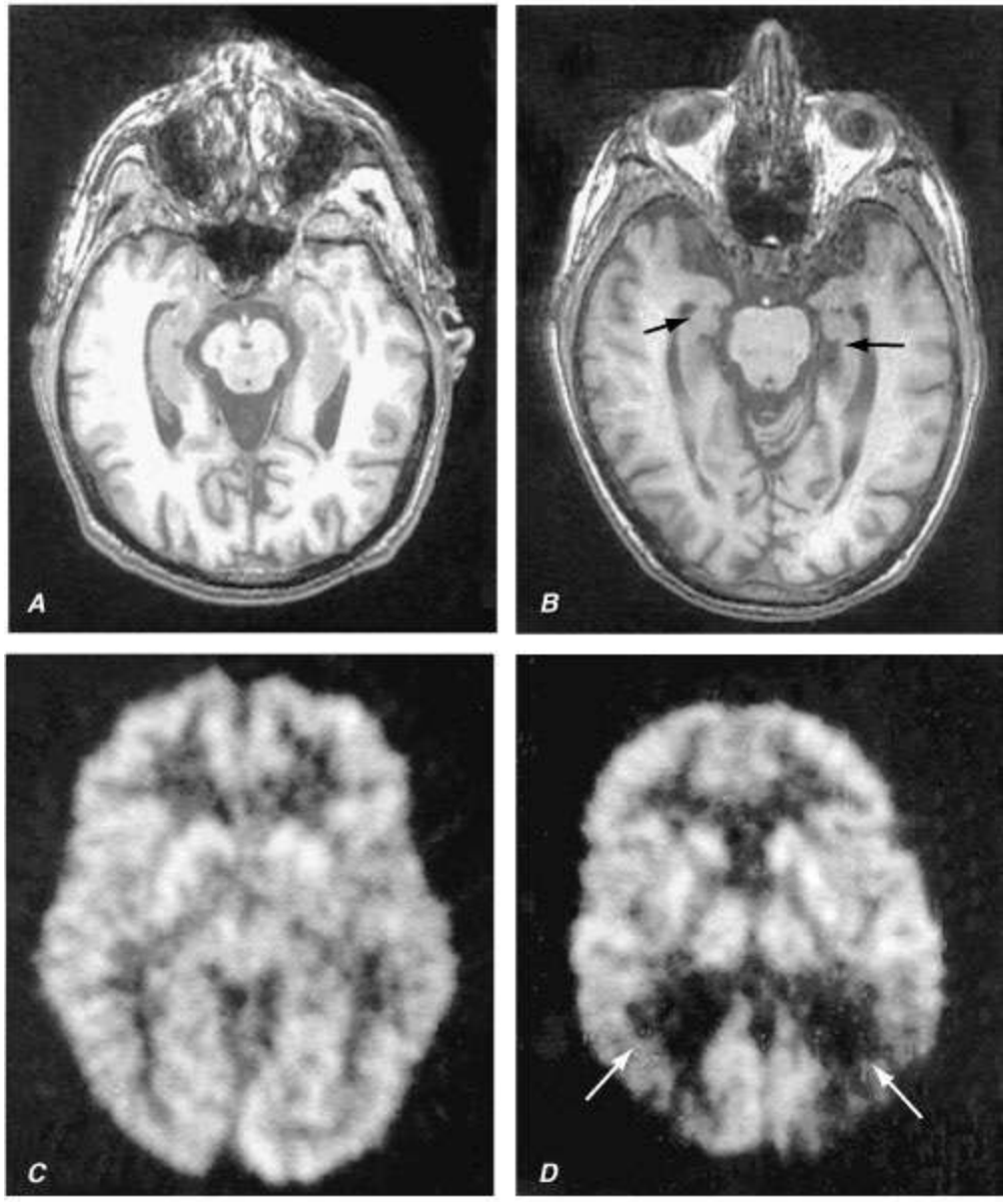
Tumors

Vascular disease

Genetics (e.g. ApoE$_4$ gene)

Neuropathology

A: Axial MRI through midbrain of normal 86 year old athletic individuals brain

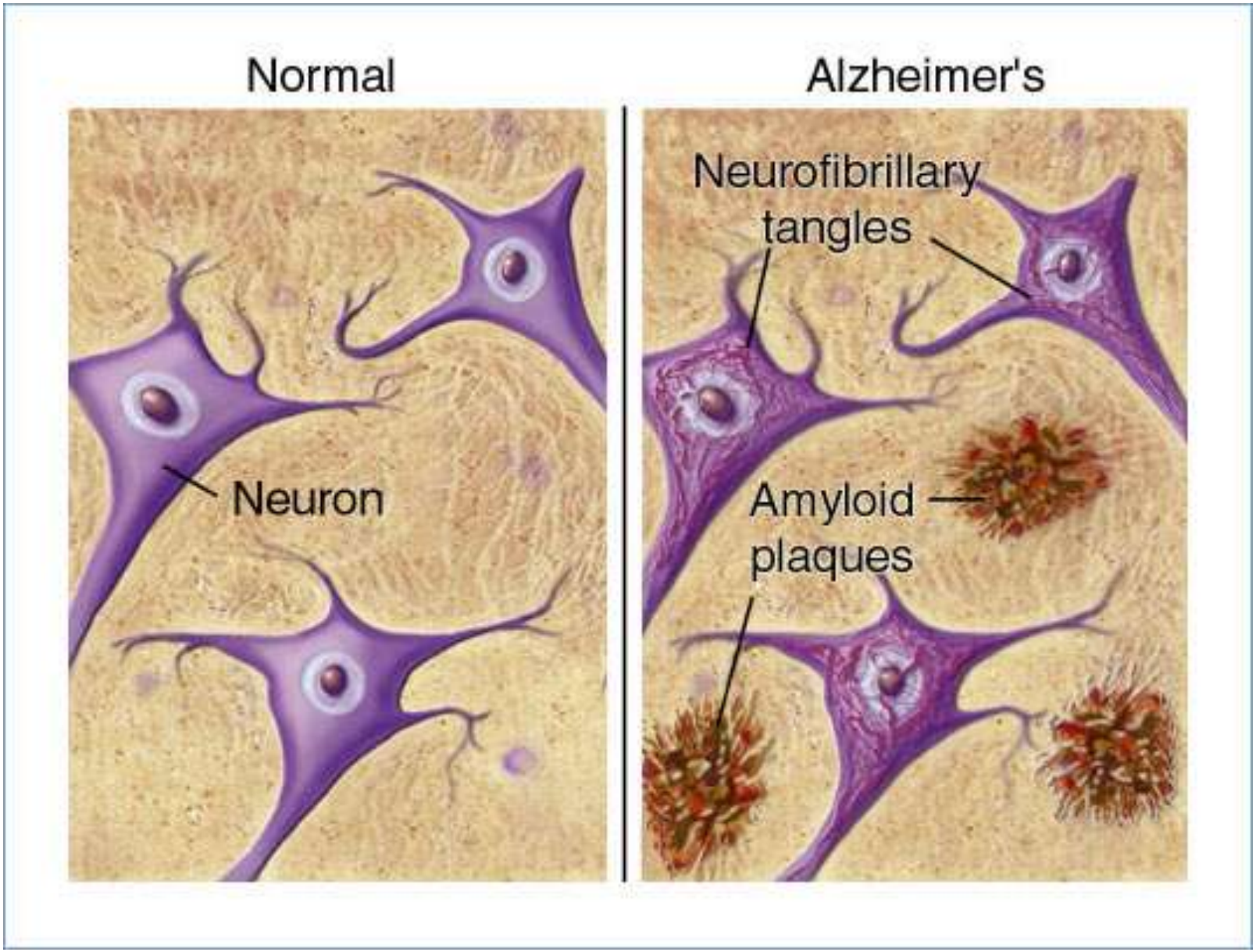


B. Axial MRI through midbrain of 76 year old male with Alzheimer's *(note enlarged sulci and cortical shrinkage)*

C. PET scan of normal control brain

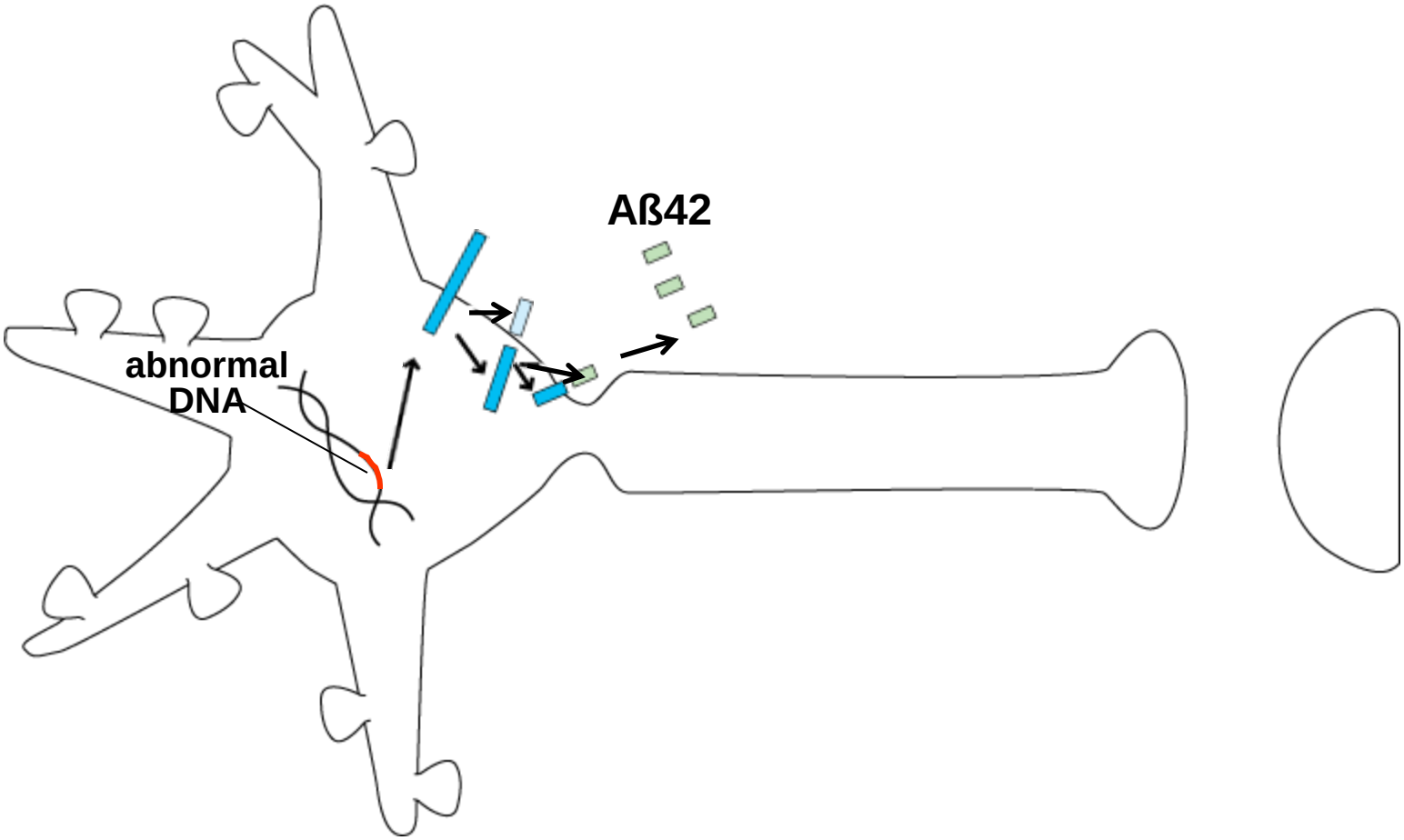
D. PET scan of Alzheimer's brain *(note dark areas indicate low brain activity)*

AMYLOID PLAQUES & NEUROFIBRILLARY TANGLES



Amyloid-Cholinergic Hypothesis of Alzheimer's Disease

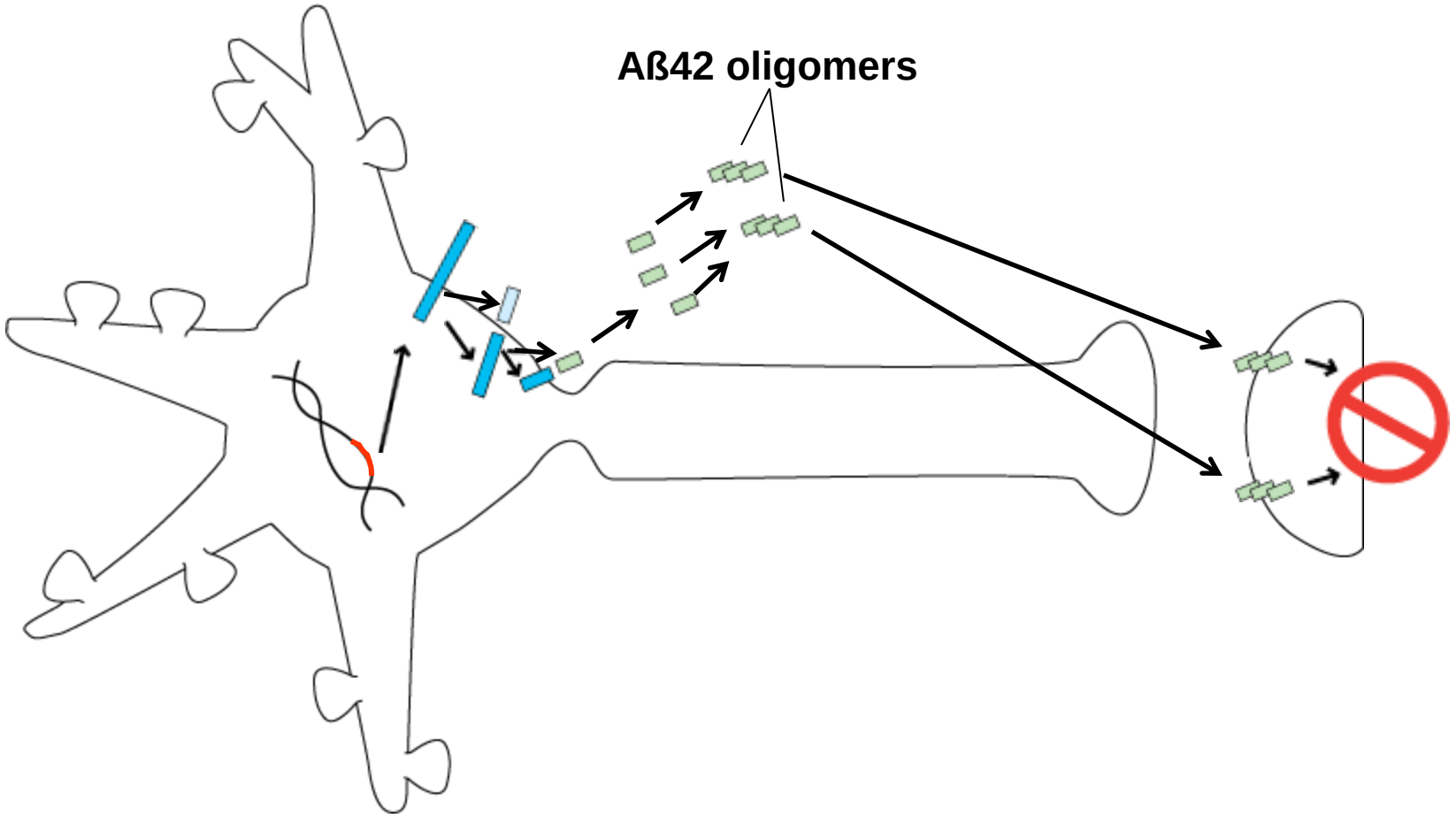
Amyloid Cascade Hypothesis, **Part I:**



Increased Production of Aß42:

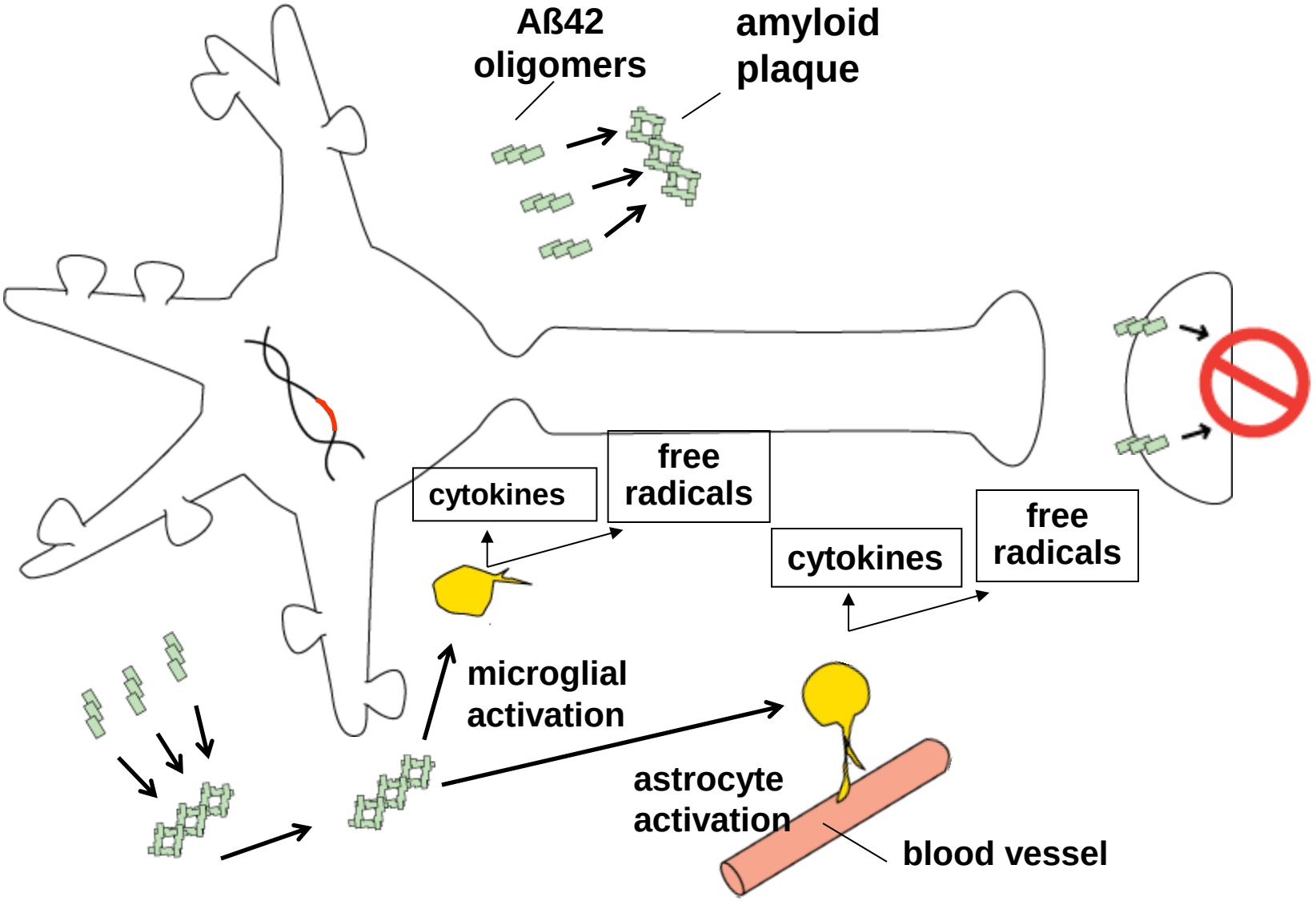
Aß42 is amyloid beta protein, composed of 42 amino acids

Amyloid Cascade Hypothesis, **Part II:**



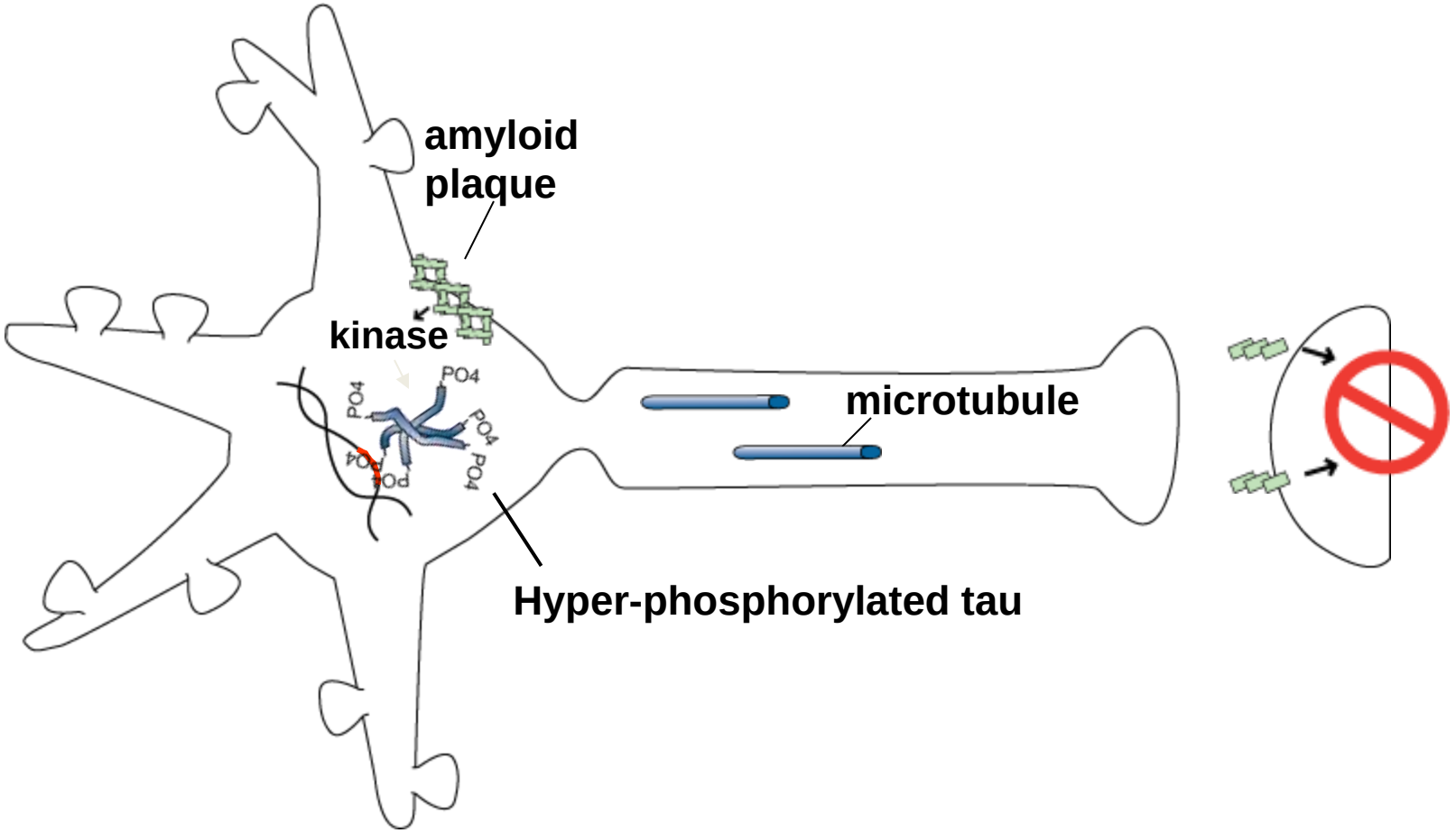
Aß42 Oligomers Form & Interfere with Synaptic Function

Amyloid Cascade Hypothesis, **Part III:**



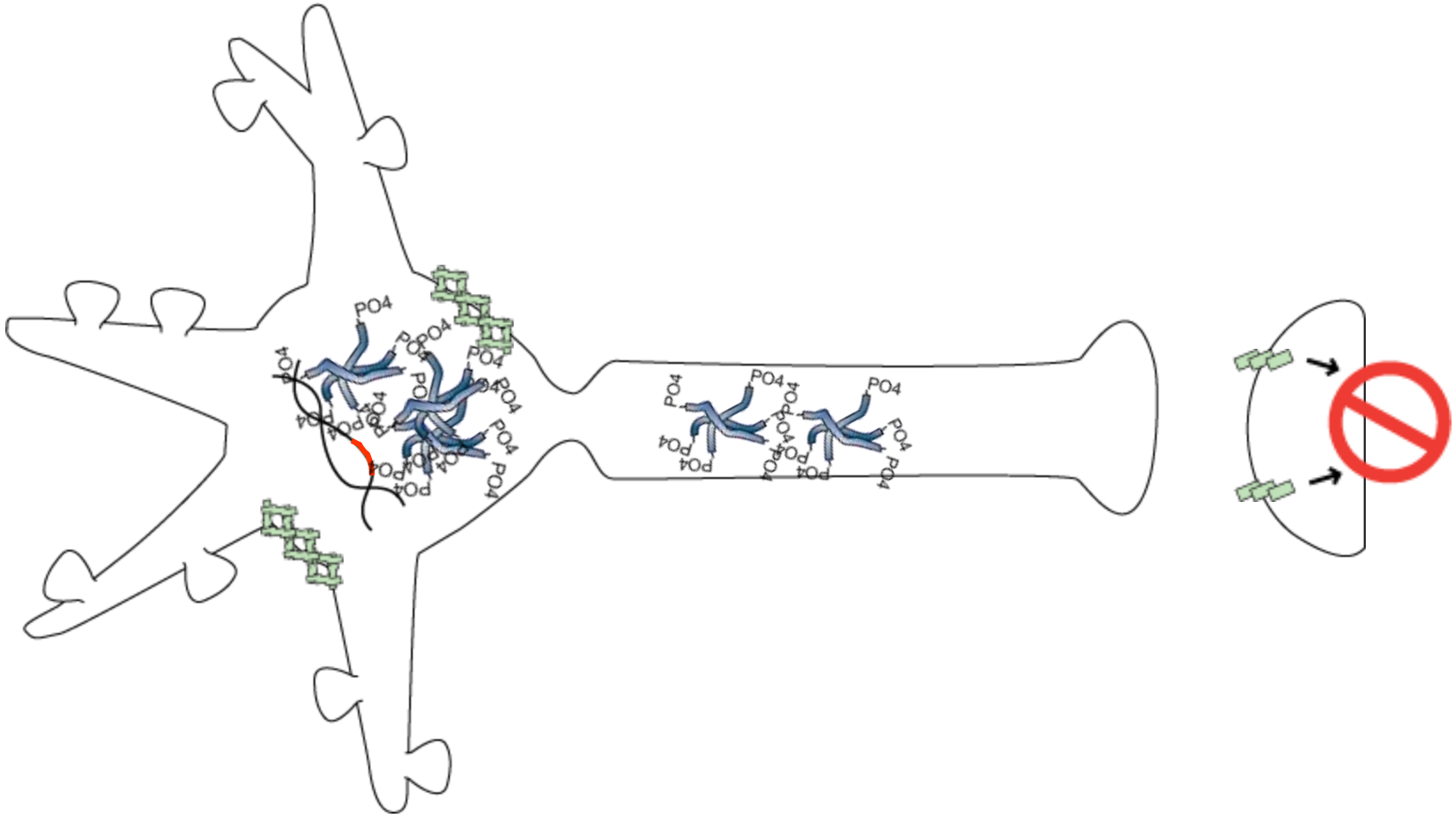
Formation of Amyloid Plaques Causing Inflammation

Amyloid Cascade Hypothesis, **Part IV:**



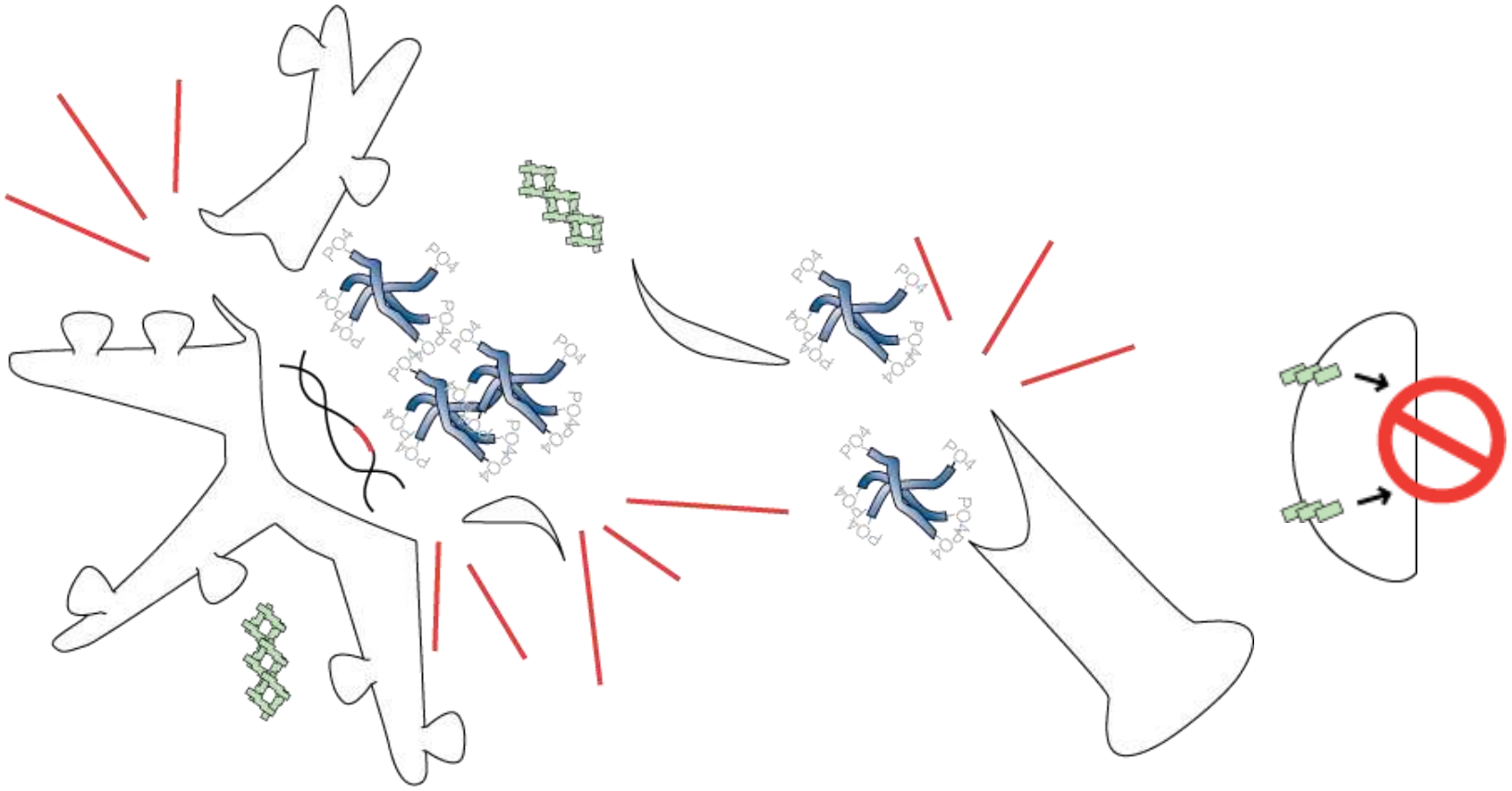
Amyloid Plaque Induces Formation of Tangles: *tangles are hyper-phosphorylated tau protein which is a component of microtubules*

Amyloid Cascade Hypothesis, **Part V:**



Widespread Neuronal & Synaptic Dysfunction, Neurotransmitter Deficits & Neuronal Loss

Amyloid Cascade Hypothesis, **Part VI:**



Widespread Neuronal/Synaptic Dysfunction, Neurotransmitter Deficits and Neuronal Loss

The Brain Cholinergic System

ACh acts on both **muscarinic** (mAChR) & **nicotinic** (nAChR) receptors:

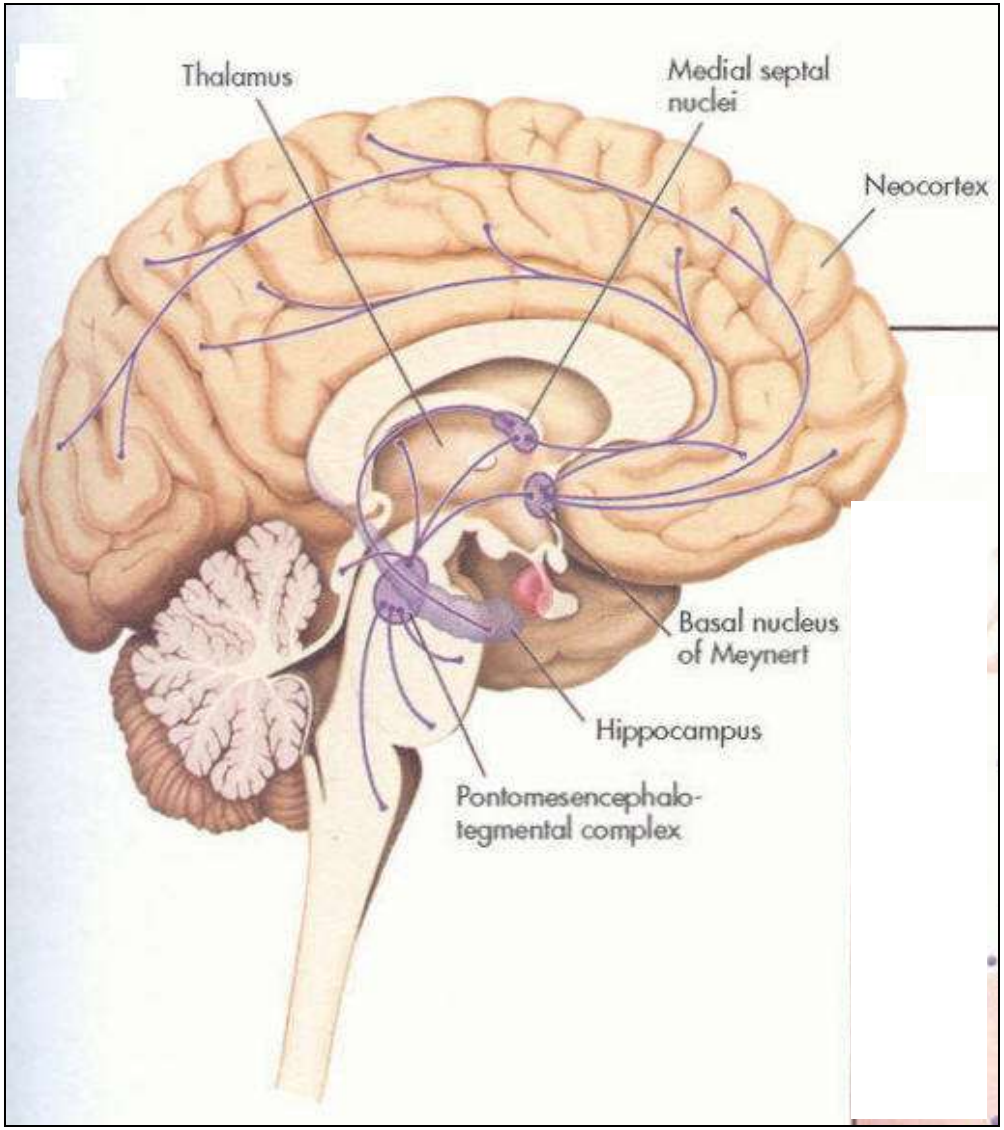
mAChR are GPCR (5 mAChR: M1-M5)
nAChR are LGIC (7 nAChR)

AChR is synthesized from acetate and choline by ChAT

ACh transmission is terminated by its breakdown by AChE

Major cholinergic pathways include:

Septo-hippocampal pathway
Basal forebrain to telencephalon
Pontomesencephalic tegmental system

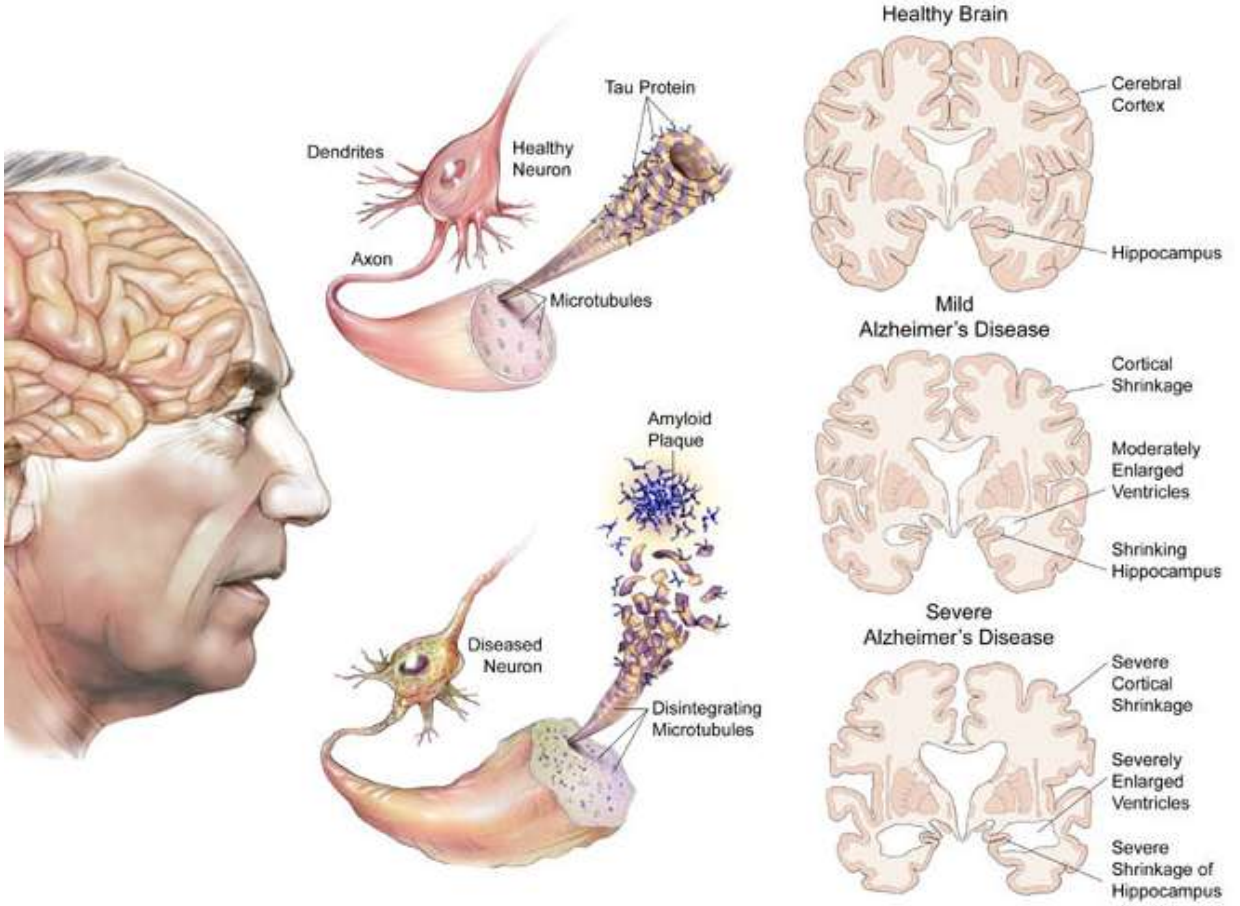


Alzheimer's Disease: Pathophysiology In Summary

Widespread presence of ***neurofibrillary tangles*** & ***senile plaques***

Atrophy of cortical & limbic neurons

Destruction of cholinergic neurons in *n. basalis, septal nucleus* & *Diagonal Band of Broca*



Clinical Diagnosis

Diagnosis

The mini mental state examination

Orientation

Year, month, day, date. season _____/5
Country, county, town, hospital, ward (clinic) _____/5

Registration

Examiner names three objects (for example, apple, pen, and table)
Patient asked to repeat objects, one point for each. _____/3

Attention

Subtract 7 from 100 then repeat from result, stop after five subtractions. (Answers: 93, 86, 79, 72, 65)
Alternatively if patient errs on subtraction get them to spell world backwards: D L R O W
Score best performance on either task. _____/5

Recall

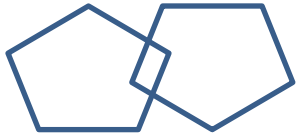
Ask for the names of the objects learned earlier. _____/3

Language

Name a pencil and a watch. _____/2
Repeat: 'No ifs, and or buts.' _____/1
Give a three stage command. Score one for each stage (for example, 'Take this piece of paper in your right hand, fold it in half and place it on the table.' _____/3
Ask patient to read and obey a written command on a piece of paper stating: 'Close your eyes.' _____/1
Ask patient to write a sentence. Score correct if it has a subject and a verb. _____/1

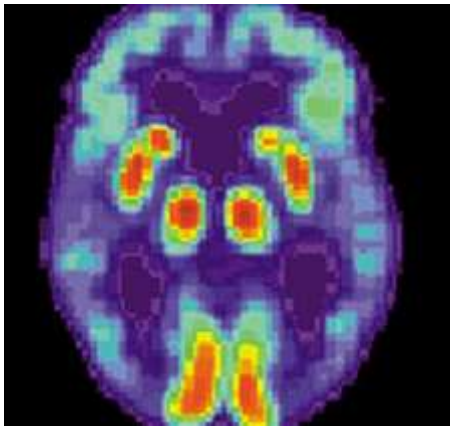
Copying

Ask patient to copy intersecting pentagons.
Score as correct if they overlap and each has five sides. _____/1



Total score: _____/30

Biomarkers



FDA approved 2 diagnostic test for plaques in the brain associated with AD (2012 & 2013).

Florbetapir (***Amyvid***) & **Flutemetamol (*Vizamyl*) bind to amyloid plaques** for use with PET imaging of the brain in adults being evaluated for AD and dementia. Vizamyl is the only PET imaging tracer available that provides brain scans in color rather than in b/w

These will be used to complement current diagnostic criteria.

Aims to strengthen diagnoses - autopsies shown that c. 1/5 patients thought to have AD according to standard criteria have no amyloid plaques (which means diagnosis was mistaken)

Pharmacotherapy for Alzheimer's Disease

AChE Inhibitors:

- Tacrine

(*Cognex*, 1993)

- Donepezil

(*Aricept*, 1996)

- Rivastigmine

(*Exelon*, 2000)

- Galantamine

(*Reminyl / Razadyne*, 2001)

NMDA Receptor Blocker:

- Memantine

(*Namenda*, 2003)

Agents of unproven efficacy:

Estrogens

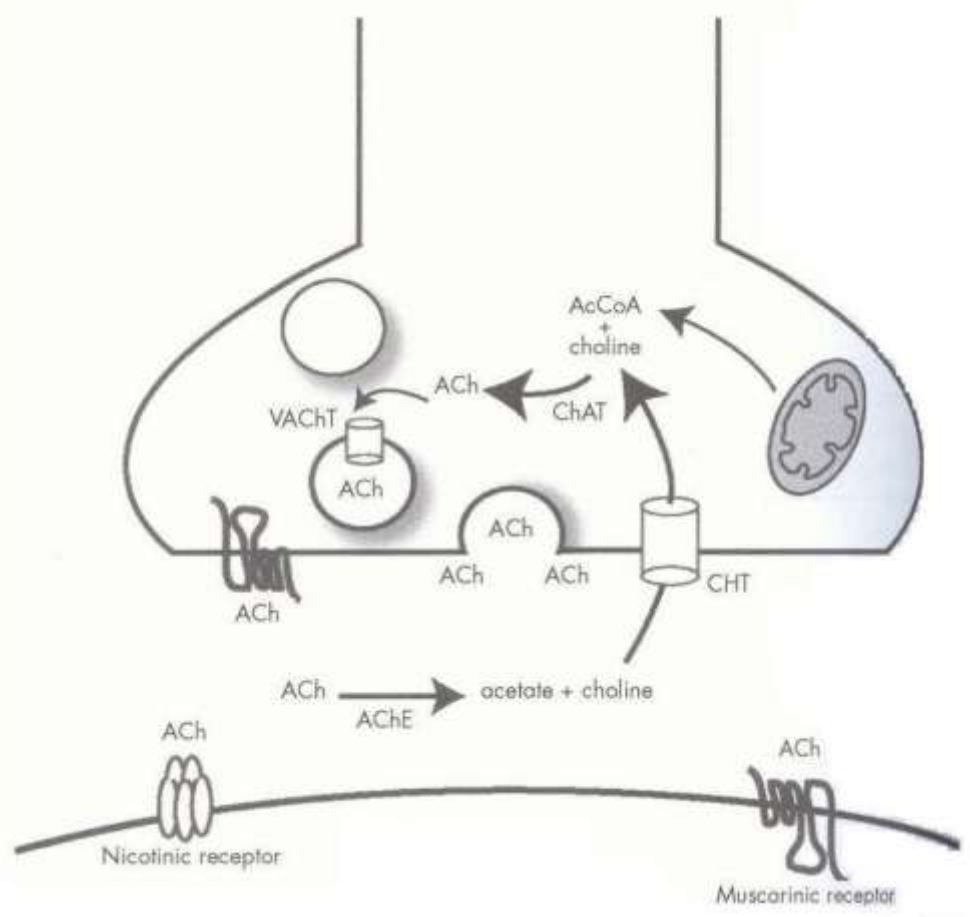
Vitamin E

Gingko biloba

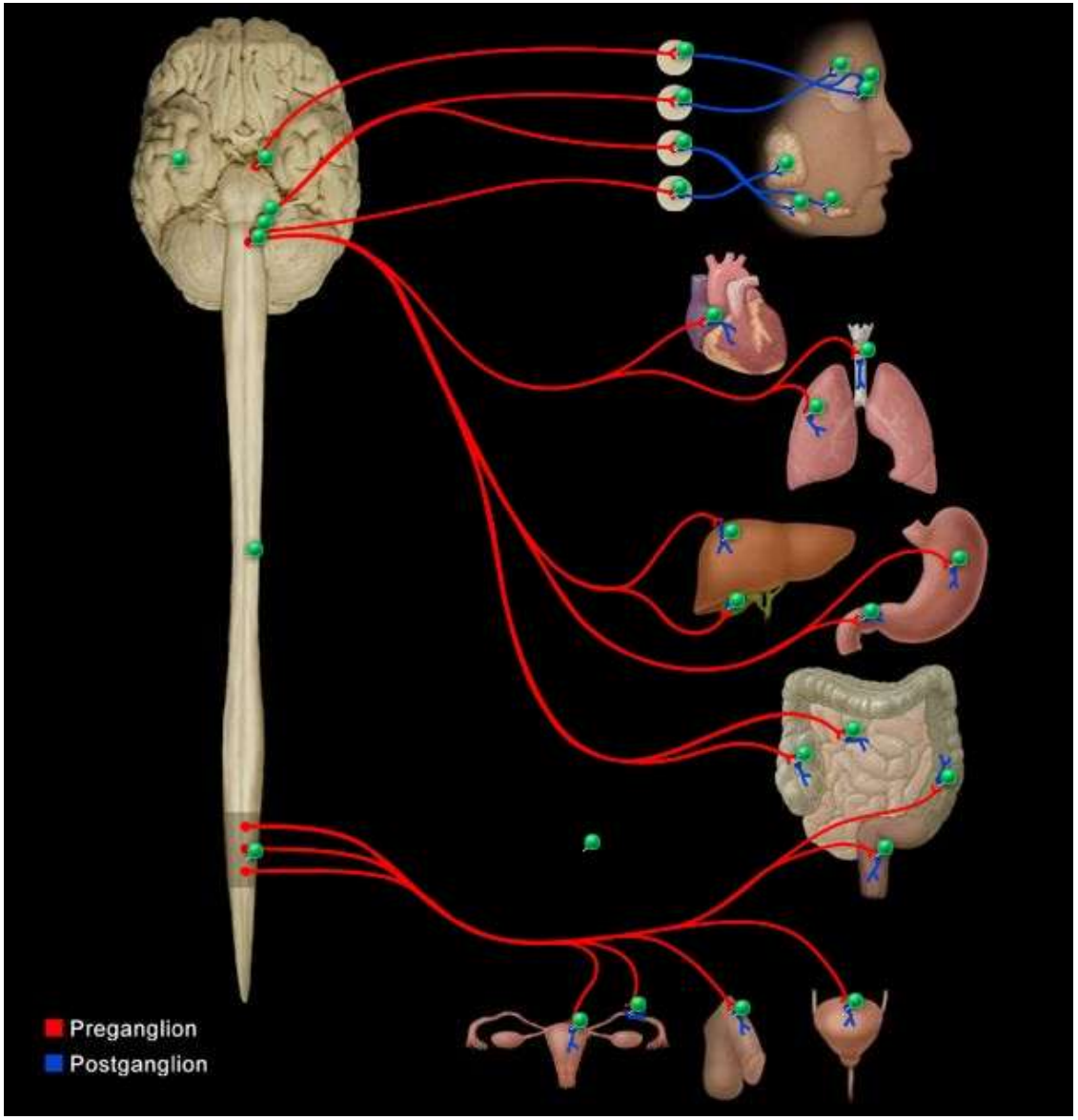
Cholinesterase Inhibitors

Donepezil, Galantamine, Rivastigmine, Tacrine

- Non-selective inhibitors of cholinesterase in CNS (& periphery)
- Leads to enhanced cholinergic transmission
- Modest improvement in MMSE & ADAS-COG



Unwanted Effects of AChE Inhibitors:



Parasympathetic Division of ANS

Blurred vision

Increased salivation

Tongue Edema

Decreased heart rate

Nausea

Airway contraction

Increase GI Tract motility

(nausea, diarrhea

abdominal cramps)

Urinary incontinence

Tremors

Adverse Effects with Cholinesterase Inhibitors

- ***Tacrine***: abdominal cramps, anorexia, nausea, vomiting, diarrhea (1/3 patients); ⇓ HR, myalgia.

- ***Donepezil, Rivastigmine & Galantamine****:* similar adverse effects but less frequent & less severe.

Further Comments on Clinical Pharmacology of Cholinesterase Inhibitors

Memantine (*Namenda*)

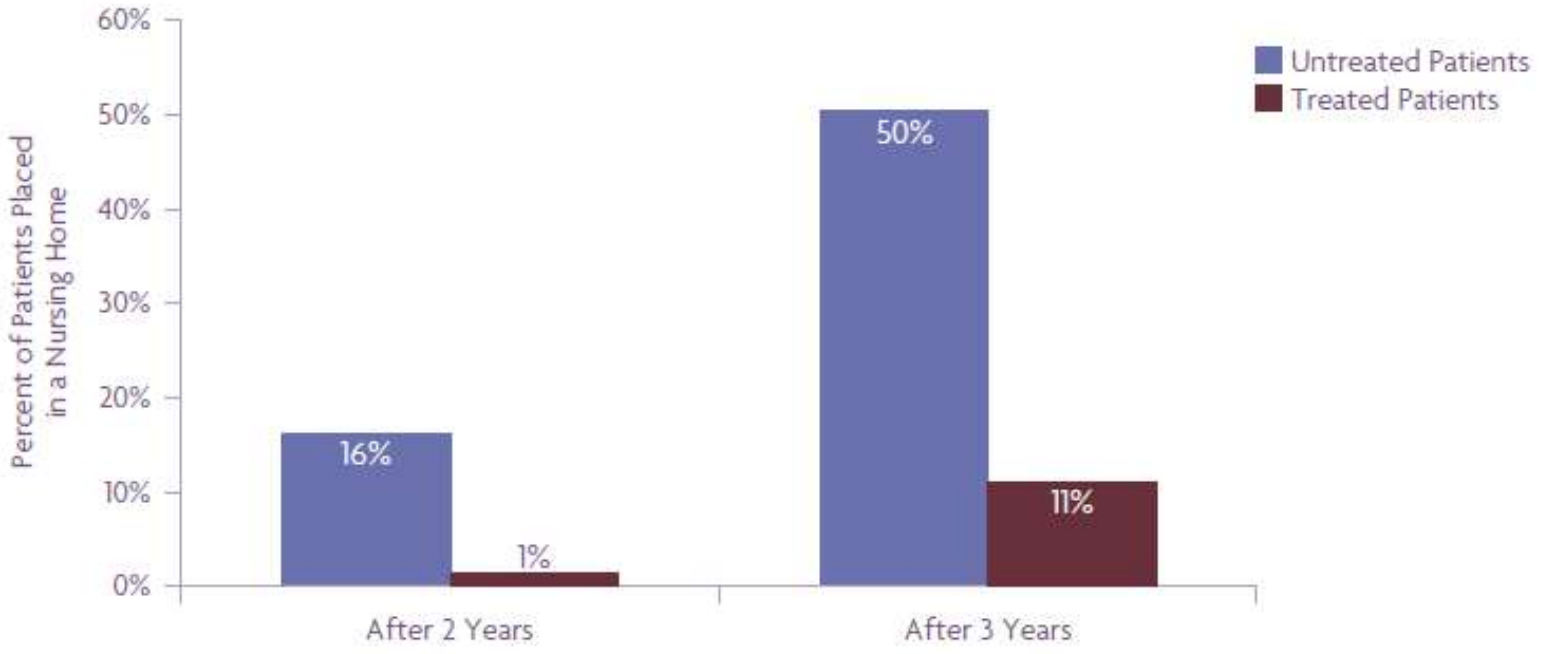
- A N-Methyl-D-Aspartate receptor antagonist
- NMDA Receptors are implicated in learning & memory & excitotoxicity
- Used for moderate-severe AD
- Modest improvements in MMSE
- A Neuroprotective agent which may reduce the rate of deterioration in moderate Alzheimer's disease?
- **Unwanted effects include:** agitation, insomnia & headaches

Precautions & Contraindications With Cholinesterase Inhibitors

Alzheimer's Disease: Delayed Nursing Home Placement

Medicines help delay costly care for Alzheimer's patients.

Nursing-Home Admission of Patients Treated with Alzheimer's Medicine Compared to Untreated Patients[9]



Source: O.L. Lopez et al.[10]

Having completed this lecture we should:

Recognize the cognitive deficits & non-cognitive (behavioral) symptoms of AD

Know the diagnostic criteria for a diagnosis of AD

Describe the major underlying etiologies

Know the pharmacology of the FDA approved drugs used to manage the cognitive & behavioral symptoms of AD

Provide education & counseling to patients & caregivers about AD, the possible benefits & adverse effects of their pharmacotherapy.

Alzheimer's Disease & Drugs for AD: what you should know

- *Clinical diagnostic features of AD*
- *Hallmark underlying pathophysiology*
- *Mechanism of action of anti-dementia drugs and their major side affects*