

# Alzheimer's Disease



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# Differential Diagnosis

Source: Alzheimer's Association 1995

## ALZHEIMER'S DISEASE

- Gradual onset
- Relentless progression
- Underlying vascular disorder not always present
- Degeneration in a broad range of intellectual abilities

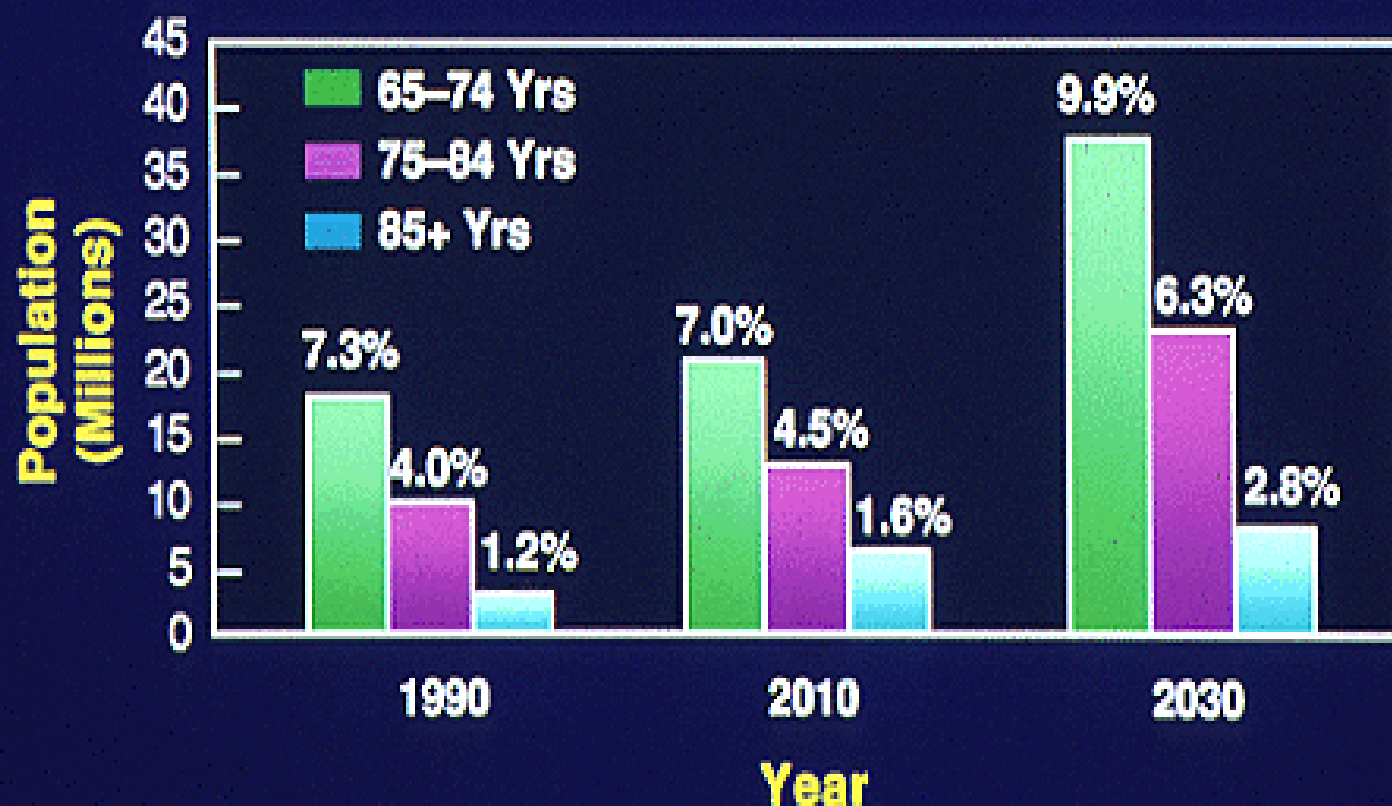
## VASCULAR DEMENTIA

- Abrupt onset
- Underlying vascular disorder present (eg. HTN or Heart Disease)
- Early impairment in motor skills
- Brain scans shows evidence of strokes or stroke-related changes

# Alzheimer's Disease Prevalence

- According to projections by the US Census Bureau, the number of AD patients is now estimated at 4.5 million.
- By 2030, it is estimated that the number will double to approximately 9 million Americans.
- By 2050 it is estimated that 14 million Americans will suffer from Alzheimer's disease.

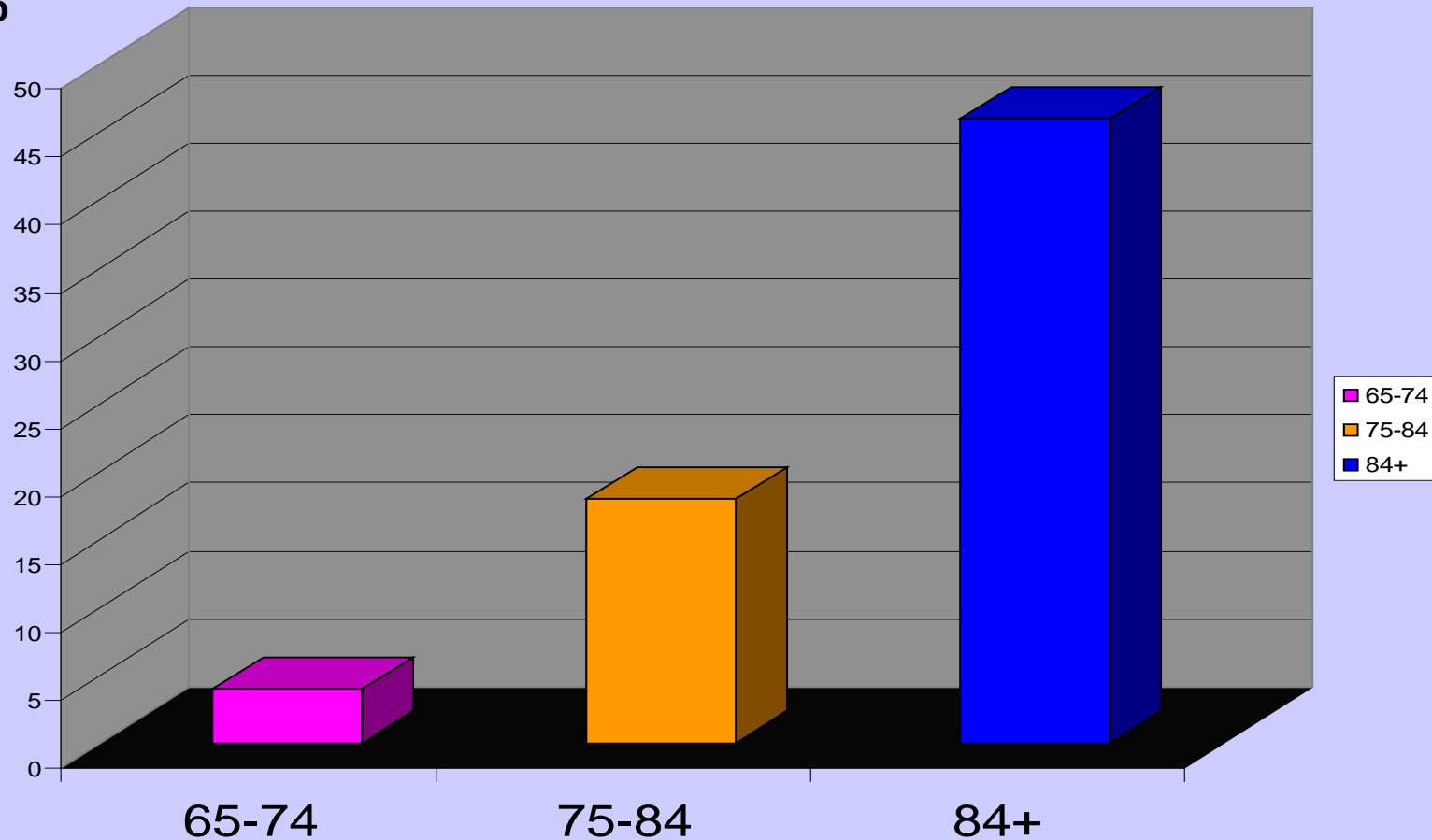
# Elderly Population in the United States Projected Growth and Distribution



Source: US Bureau of the Census. Current Population Reports, Special Studies, P23-190, *65+ in the United States*. Washington, DC: US Government Printing Office; 1996.

# Alzheimer's Disease Prevalence

**% Prevalance of  
AD**



# Causes of Dementia

DEMENTIA

```
graph TD; DEMENTIA --> Alzheimer's_Dementia[Alzheimer's Dementia (>60%)]; DEMENTIA --> Vascular_Dementia[Vascular Dementia]; DEMENTIA --> Others_Dementias[Others Dementias(Rare)  
eg.AIDS related;  
Parkinsonian  
Alcohol Induced];
```

Alzheimer's  
Dementia  
(>60%)

Vascular  
Dementia

Others Dementias(Rare)  
eg.AIDS related;  
Parkinsonian  
Alcohol Induced

# Relative Frequency of Dementia D/O in Old Age

- Dementia- Alzheimer type (DAT) 52%
- Multi-Infarct Dementia (MID) 17%
- Combination of DAT & MID 14%
- Brain Tumors (& rare neurological disease  
ie Huntington's, Picks,etc) 7%
- Parkinson's Disease 2%
- Psychiatric Conditions 1%
- Unknown Causes 7%

# Dementia Pugilistica

## Repeated Blows



# Summary of Prevalence & Economic Impact of AD

- Approximately 4.5 million Americans currently have AD
- > 100,000 people die from AD annually
- Estimated that 14 million Americans will have AD by 2050
- Cost of healthcare \$90 billion annually
- AD is the 3rd most expensive disease to treat in US following cancer and heart disease

# Estimated Annual Pt Costs

Total Yearly Costs to American Society

\$90 billion

## TYPE OF CARE

## ESTIMATED ANNUAL COSTS PER CASE


Nursing Home Care

\$ 36,000

Home Care

\$ 18,000

# Reversible Causes of Dementia

- Adverse drug reaction
  - Depression
  - Metabolic changes
  - Nutritional deficiencies
  - Head injuries
- 

# Head Injuries



# Common Syndromes of Subcortical Dementia

## ➤ Degenerative

- Parkinson's Disease
- Huntington's Disease
- Progressive Supranuclear palsy

## ➤ Vascular

- Lacunar state
- Thalamic infarction

## ➤ Other

- Multiple sclerosis
- HIV associated dementias
- Normal pressure hydrocephalus
- Lewy Body Dementia

# Folstein MMSE

## (Mini Mental Status Exam)

- Orientation
  - Year ,Season, Date, Day & Month (1 pt for each)
  - Country, state, county, city, present location (1pt for each)
- Attention and Calculation-(subtract serially 7's from 100 (93,86,79,72,65]- 1 pt each OR  
Spell" WORLD" backwards (DLROW) 1 pt each
- Recall (3 objects (apple, book ,coat) -1pt each

# Folstein MMSE

## Possible Score 30/30

### ➤ Language

- Identify 2 objects (pencil, watch) 1 pt each
- Repeat-"No ifs, ands, or buts" - 1 pt
- 3 step command - 1 point each
  - 1) Take this piece of paper in your right hand
  - 2) Fold it in half
  - 3) put it on the floor
- Read and obey: Close your eyes - 1 pt
- Write a complete sentence 1 pt
- Copy this design- (2 intersecting pentagons)

# Risk Factors for AD

## ESTABLISHED

- Age
- Family History
- Down's Syndrome

## POSSIBLE

- Previous head trauma
- Environmental factors
- Infectious agents

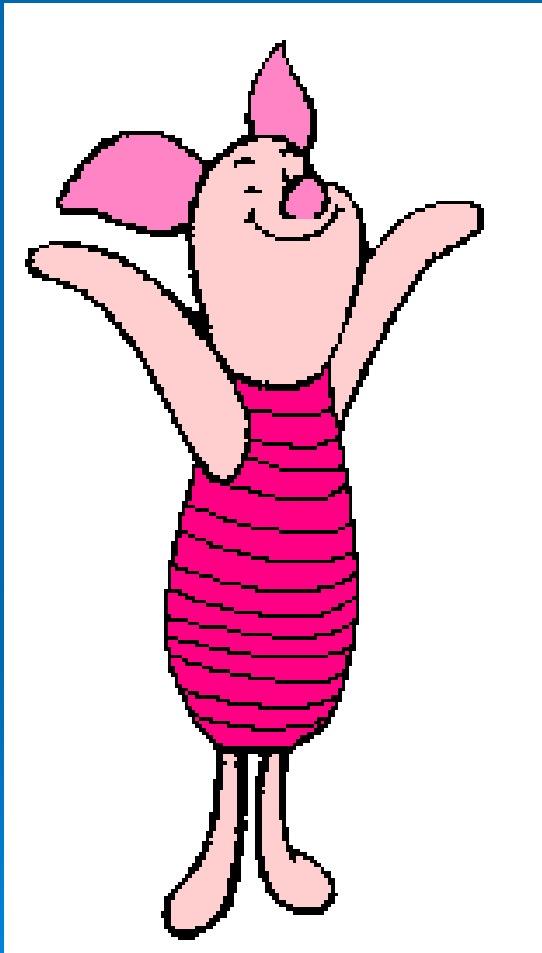
Source: Costa PT et al 11/96

# You've Got a Hard Head

## Charlie Brown



# Risk Factor: Head Size



# Warning Signs of AD

- Difficulty learning and retaining new information
- Difficulty performing complex tasks
- Diminished reasoning ability
- Problems w/spatial orientation
- Language problems
- Changes in personality , mood, or behavior

Source: Agency for Health Care Policy and Research  
Guideline 19 Overview;1996



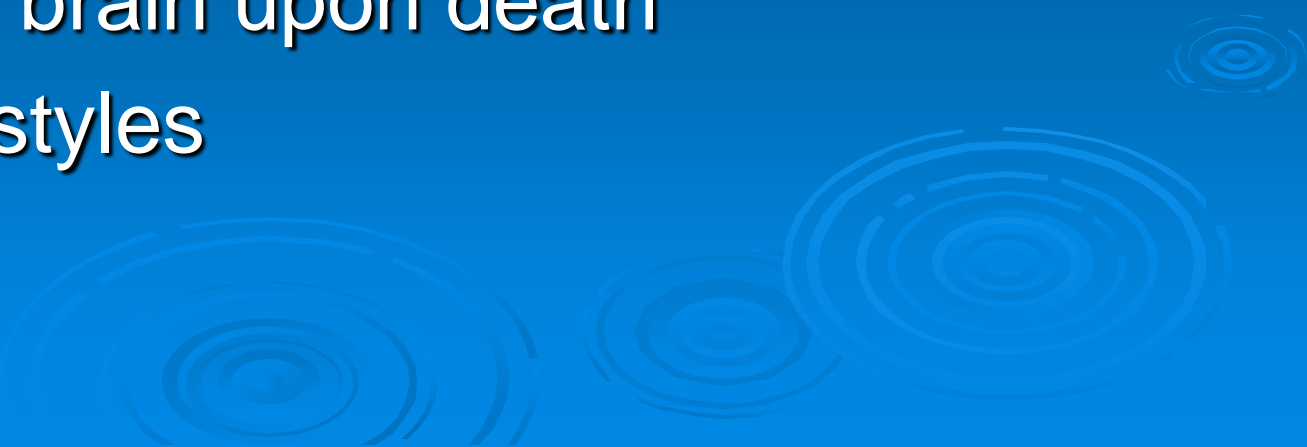
# **GIFT OF LOVE**

A group of nuns  
are donating their  
brains to science  
to help fight  
**ALZHEIMER'S DISEASE**

## **The Nun Study**

# Sisters of Notre Dame

## NIMH study - Dr. David Snowdon

- 678 Catholic sisters studied
  - Ages 75-103
  - Longitudinal study beginning in 1991
  - Annual assessments of cognitive and physical functioning
  - Autopsy of brain upon death
  - Similar lifestyles
- 

# Neuronal Degeneration

The pathobiology of Alzheimer's disease is characterized by:

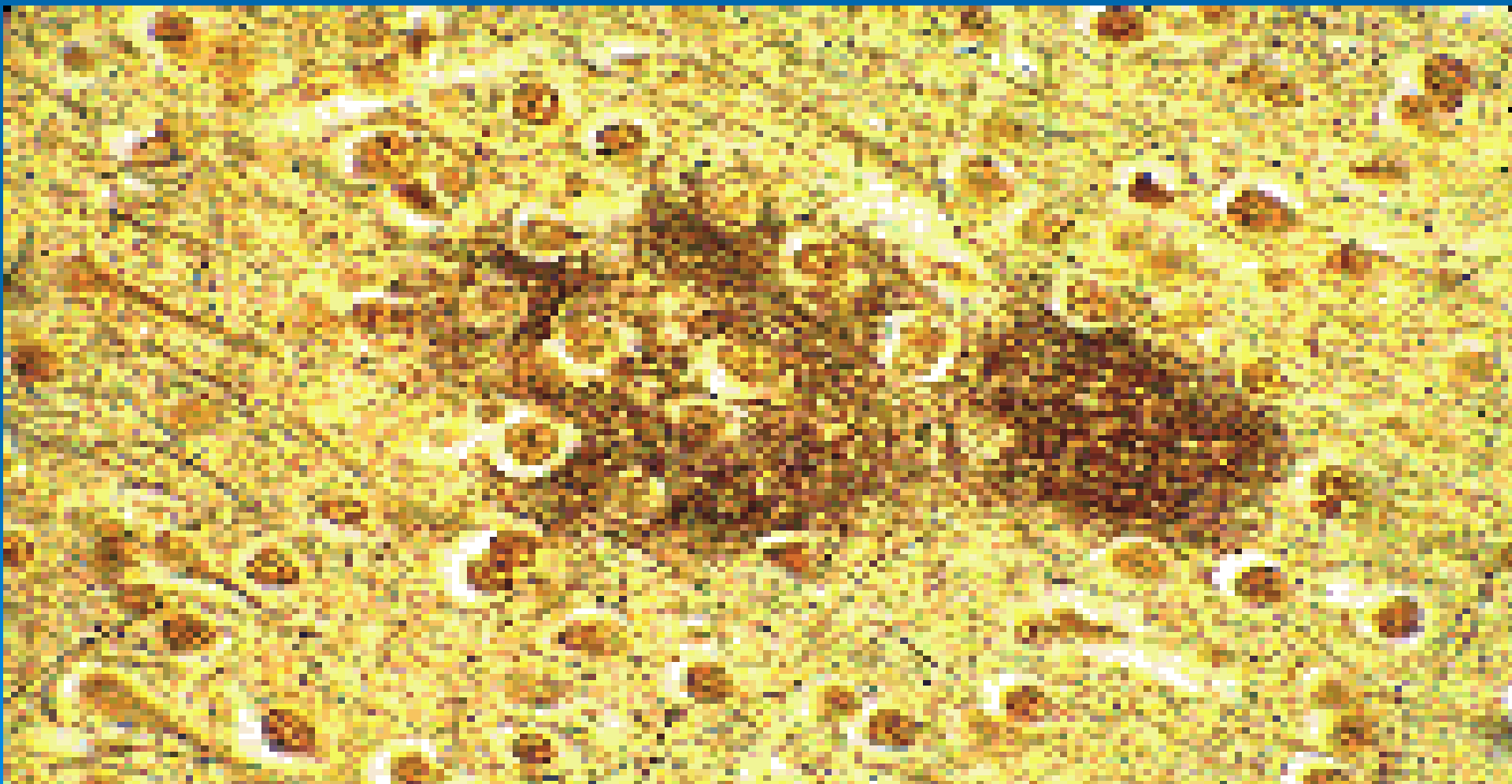
- Amyloid plaques
- Neurofibrillary tangles



# Amyloid Plaques

- Plaques are extracellular structures that are more prevalent in the Alzheimer's patient's brain, particularly in the hippocampus and neocortex
- Amyloid (neuritic) plaques in Alzheimer's disease are dense and insoluble structures
- Plaques consist of a central core of beta-amyloid protein surrounded by abnormal axons and dendrites

# Amyloid Plaques



# The Amyloid Hypothesis

## Amyloid Deposits

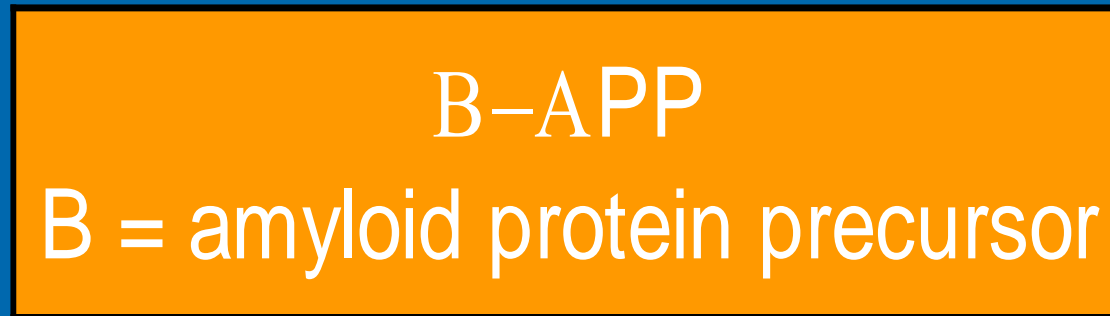
- Correlate with AD pathology and reduced cognitive function
- Accumulate with advancing age

Accumulate in neuritic plaques over span of 30 years

Composed of  $\beta$ -A4 protein

Selkoe, DJ *N Eng J Med* 1989

# Formation of B-A 4



B-APP<sub>770</sub>

B-APP<sub>751</sub>

B-APP<sub>714</sub>

B-APP<sub>695</sub>

B-A4

# B - amyloid

- B -amyloid is normally cleared by  $\alpha$  - secretase into fragments largely cleared from the brain. Gene mutations cause cleavage by B - secretase and  $\delta$  -secretase, producing B -amyloid (1-42 ). This aggregates into B -pleated sheets which make up characteristic amyloid plaques.

# Amyloid Plaques & Neurofibrillary Tangles



# Neurofibrillary Tangles

- Intra cellular inclusion bodies consisting of paired helical filaments that appear in a characteristic double-helix shape
- Filaments appear to be composed of a hyperphosphorylated microtubule - associated protein called *tau*.
- Remains of damaged neuronal microtubules.

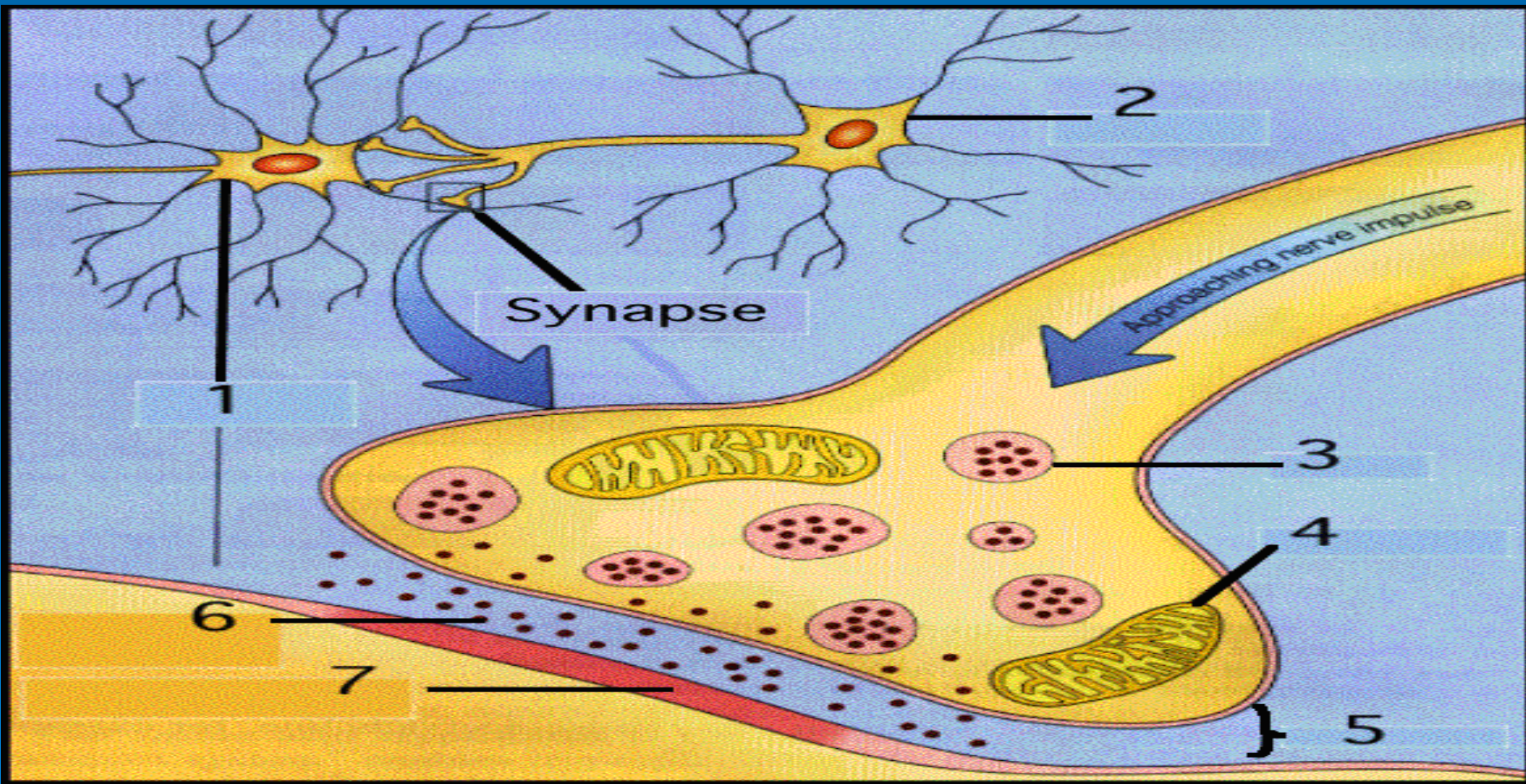
# The Protective Value of Multiple Pathways



# Cognitive Dysfunction Syndrome



# Pathogenesis: The Cholinergic Synapse



# Current Aspects of Alzheimer's Disease Research

- Cholinergic dysfunction
- Noncholinergic deficits
- Genetics
- Treatment-Cholinesterase Inhibitors
  - Cognex- Tacrine Hydrochloride
  - Aricept- Donepezil HCL
  - Exelon- Rivastigmine tartrate

# Genetic Research

- Research has produced evidence of a link between Alzheimer's Disease and chromosomes 1,14,19 and 21.
- Chromosomes 1,14 and 21 have been linked with early-onset Alzheimer's disease, an extremely rare form of the disease.
- ApoE4 gene located on chromosome 19 has been associated with late-onset Alzheimer's disease, the most common form of the disease.

# Importance of Social Relations

- Individuals living alone, with poor social relations and with limited family contacts, have an increased risk of dementia (both vascular and Alzheimer's Disease) by 60%
- > Fratiglioni et al. 2000

# Impact of Estrogen upon the Disease Progression

- Estrogen replacement for one year did not slow disease progression in mild to moderate Alzheimer's patients

▪  
(MMSI 12-28)

• Mulhard et al. 2000

# 3 Key Domains of Global Functioning

- Cognition
- Behavioral
- Activities of Daily Living (ADLs)

The acetylcholinesterase inhibitors target these areas of functioning.

The background of the slide features several faint, concentric circles in a lighter shade of blue, resembling ripples in water, located primarily in the lower right and bottom center areas.

# Possible Drugs for Preventing or Treating AD

DRUG	ACTIVITY	MECHANISM
Cognex Aricept Exelon Ampakines	Acetylcholinesterase inhibitor  Enhance activity of AMPA receptor	Compensate loss of cholinergic neurons  Improve memory by enhancing long-term potentiation
Ibuprofen, Other NSAIDS Vitamin E	Anti-inflammatory  Antioxidant	Prevent inflammatory damage to neurons Protects against the Radical damage
Premarin	Female hormone	Promotes neuronal survival

# Possible Drugs for Preventing or Treating AD

DRUG	ACTIVITY	MECHANISM
Nerve growth factor	Maintain cholinergic neurons in brain	Promotes neuronal survival
Calcium channel blockers	Inhibit calcium ion entry into neurons	Reduce calcium toxicity
Cholesterol lowering drugs	Lower apoE4 concentration	Prevent apoE4 toxicity to neurons
Protease inhibitors	Block B-amyloid production	Prevent neuronal loss to B-amyloid toxicity

# Donepezil HCL (Aricept)

- Reversible acetylcholinesterase inhibitor
- Chemically unrelated to tacrine
- Enhances cognitive function
- Once daily dosing
- 5 mg to 10 mg does are clinically effective
- No Liver function testing required

# Donepezil HCL (Aricept) Dosing

- One tablet daily at bedtime
- May be taken with or without food
- Both the 5 mg and 10 mg daily doses are clinically effective
- Some patients might derive additional benefit by dosage escalation to 10 mg daily after 4-6 weeks of 5 mg therapy

# Rivastigmine Tartrate (Exelon)

- Reversible acetylcholinesterase inhibitor
- Enhances cognitive function
- Twice a day dosing
- Recommended with food (breakfast and supper)

# Rivastigmine Tartrate (Exelon)

- 1.5; 3.0; 4.5 and 6.0 mg capsules
- 6-12 mg target dosing range
- Not metabolized via C-450 pathway
- No liver function testing required

# Galantamine (Reminyl)

- Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain.
- 4mg –BID (8mg/day) Increase by 8mg/day after 4 weeks to 8mg, BID (16mg/day). After another 4 weeks, increase to 12mg, BID (24mg/day), if well tolerated.
- Possible Side effects: Nausea, vomiting, diarrhea, weight loss

# AD Drugs under Development

## ➤ Acetylcholinesterase inhibitors

- Eptastigmine (Mediolanum)
- Metrifonate (Bayer)
- Physostigmine (Forest)

## ➤ Acetylcholine precursors

- Acetyl-1-carbarnitine (sigma-Tau Pharmaceuticals)

## ➤ Muscarinic agonists

- Af-102B (Forest/TEVA/Snow Brand)
- Milameline (Warner Lambert/Hoechst Marion Rossel)
- SB 202026 (SmithKline Beecham)
- SR 46559 (Sanofi)

# Most Common Adverse Events Acetylcholinesterase Inhibitors

- The most common adverse events associated with ARICEPT, EXELON and REMINYL treatment includes nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.
- These adverse events were often of mild intensity and transient, resolving during continued treatment without the need for dose modification.

# AD Drugs under Development

## ➤ Metabolic Enhancers

- Nicergoline (Pharmacia)
- Xanomeline (Eli Lilly)
- Propentofyline (Hoechst Marion Roussel)

## ➤ Others

- Corticotrophin releasing factor (Neuocrine Biosciences)
- Sabeluzole (Johnson and Johnson)

Sources: The Genesis Report/Rx 1995

Pharmaceutical Research and Manufacturers of America  
Survey 1995

# Alzheimer's Disease



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# Differential Diagnosis

Source: Costa PT et al 1996

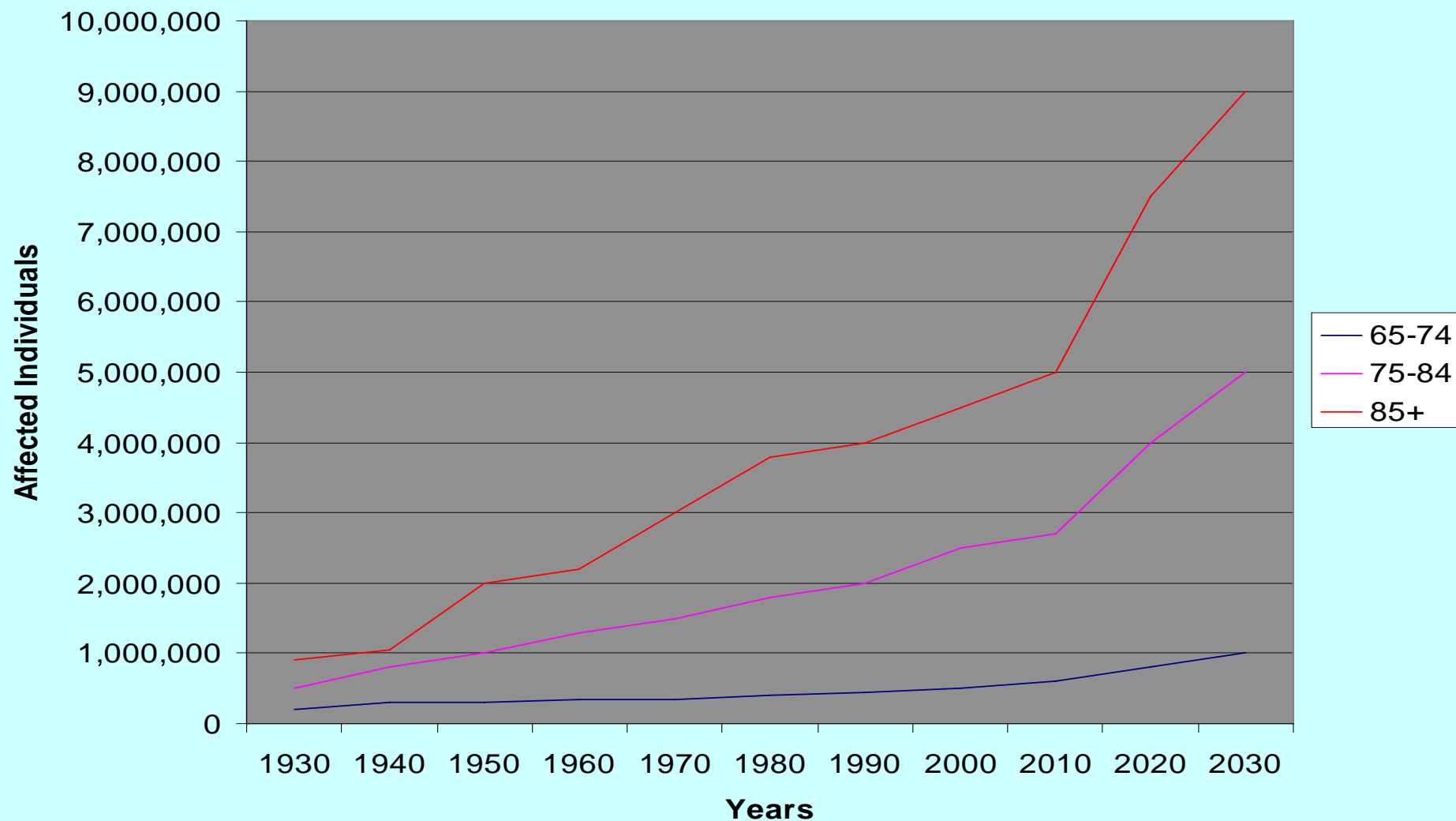
## ALZHEIMER'S DISEASE

- Irreversible decline in short-term memory
- Irreversible decline in other cognitive abilities
- Functional impairment
- Psychiatric symptoms

## NORMAL AGING

- Benign decline in short-term memory

# Alzheimer's Disease Prevalence



# Alzheimer's Disease (AD)

- AD is one of the top 10 leading causes of death in Americans over 65 years of age.
- AD is the 3rd most costly disease, after heart disease and cancer.
- Federal funding for AD is 4-7 times lower than for heart disease , cancer or AIDS.

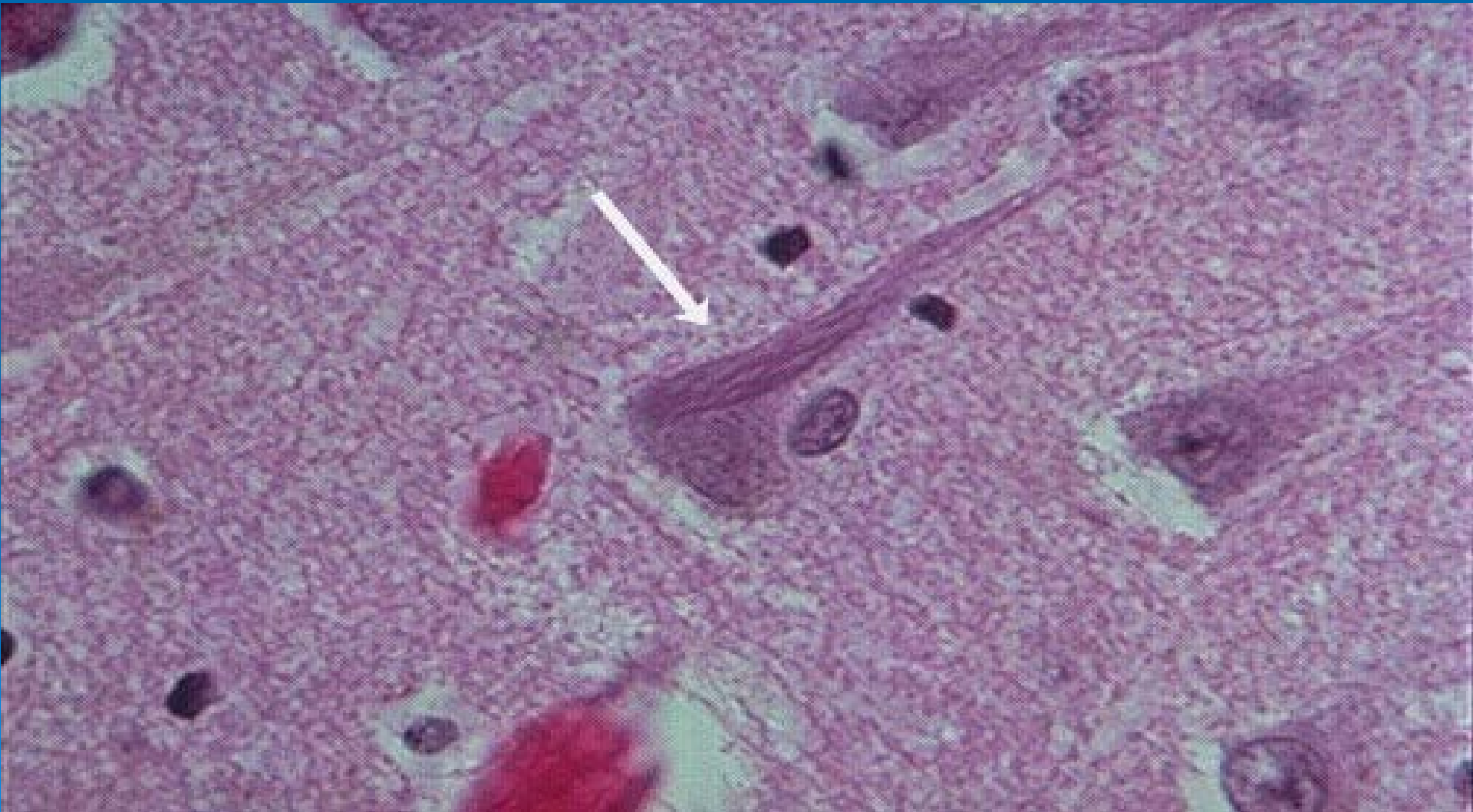
# Estimated Annual US Incidence (1983) of AD by Age and Gender

Age group (yr)	Males (%)	Females (%)
65-69	0.37	0.20
70-74	0.70	1.16
75-79	1.37	1.16
$\geq 80$	3.00	2.25

# Signs and Symptoms at Different Stages of AD

Mild	Confusion & memory loss	Dis-orientation in space	Problems w/routine tasks	Changes in Personality; judgement
Moderate	Difficulty w/ADLs	Anxiety, paranoia agitation	Sleep disturbance	Difficulty recognizing Family & friends
Severe	Loss of speech	Loss of appetite; Weight loss	Loss of Bladder & Bowel control	Total dependence on caregiver

# Neurofibrillary Tangles



# Hormones and Paragraph Recall

- Women who received any of the active hormonal preparations maintained their scores on Paragraph-Recall pre- to postoperatively (hysterectomy and bilateral salpingo-oophorectomy) while scores decreased significantly in women receiving placebo.

# Treatment with Estrogen Replacement Therapy

➤ Open label clinical trials and 1 randomized trial have shown cognitive impairment in female patients with dementia who were treated with estrogen replacement therapy.

- Haroutunian et al. 1998; 1999
- Heyman et al. 1987

# Donepezil HCL (Aricept) ADAS-cog Placebo Washout Effect

