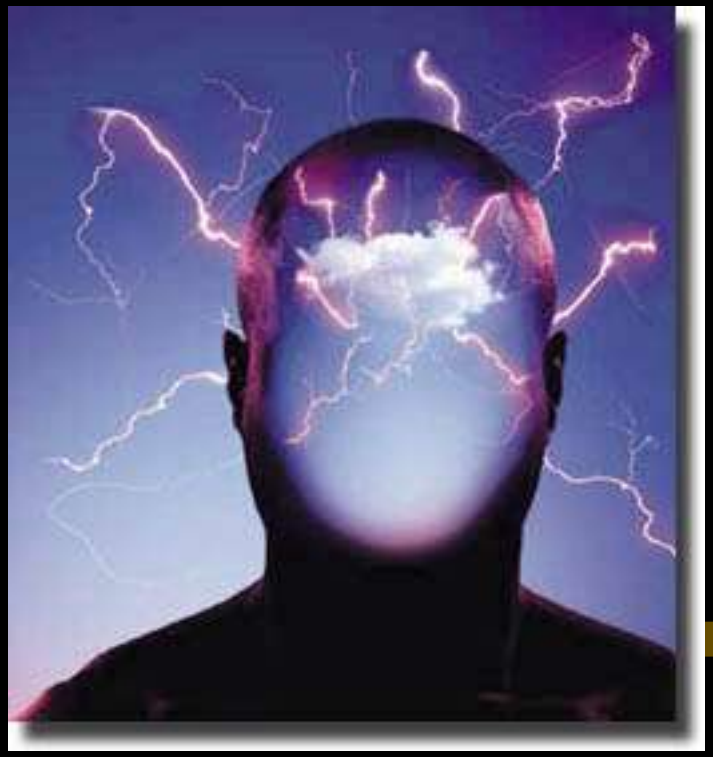

Dementia

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Medical Director
21st Century Neurology
www.neurozone.org

Dementia is a syndrome

- Progressive memory loss, plus
- Progressive loss of one or more cognitive functions:
  - Language
  - Motor control (praxis)
  - Spatial ability
  - Executive function and behavior

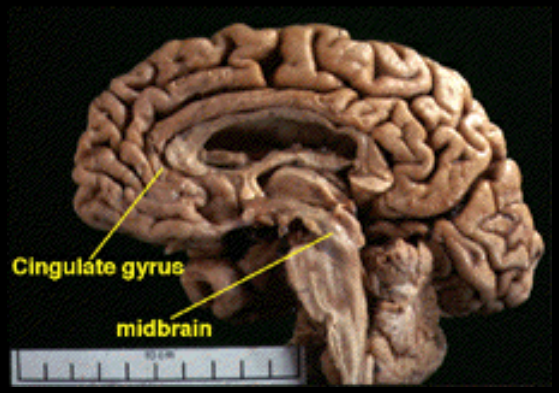
Types of dementia

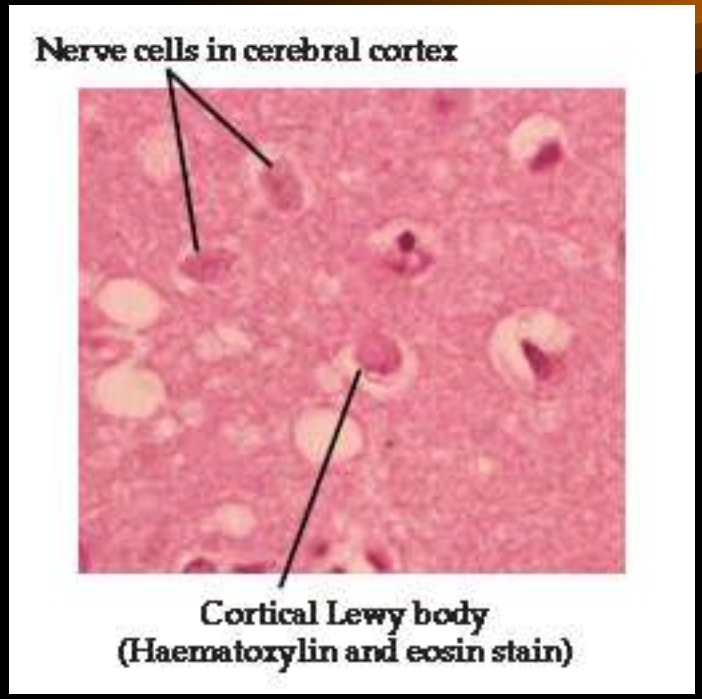
- Cortical
  - Diffuse
  - Focal
- Subcortical
  - Demyelinating
  - Vascular
  - Inherited

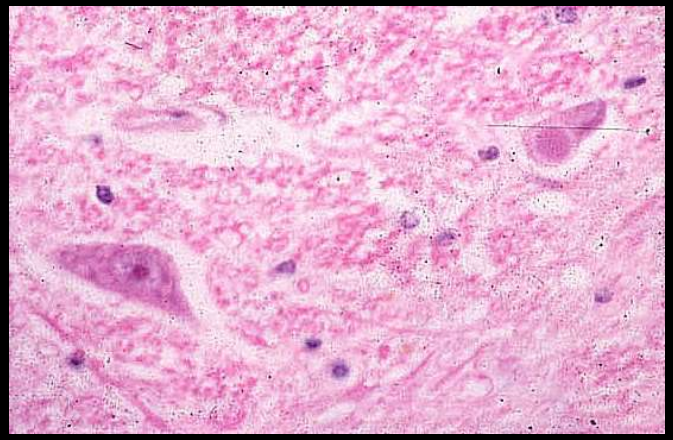
Cortical Dementia

- Diffuse
  - Alzheimer's disease (AD)
  - Diffuse Lewy body disease (DLBD)
  - Creutzfeldt-Jakob disease (CJD)
  - Alcoholic dementia
- Multifocal
  - Multifocal infarct (cerebrovascular) dementia (CVD)

Lewy Body Disease

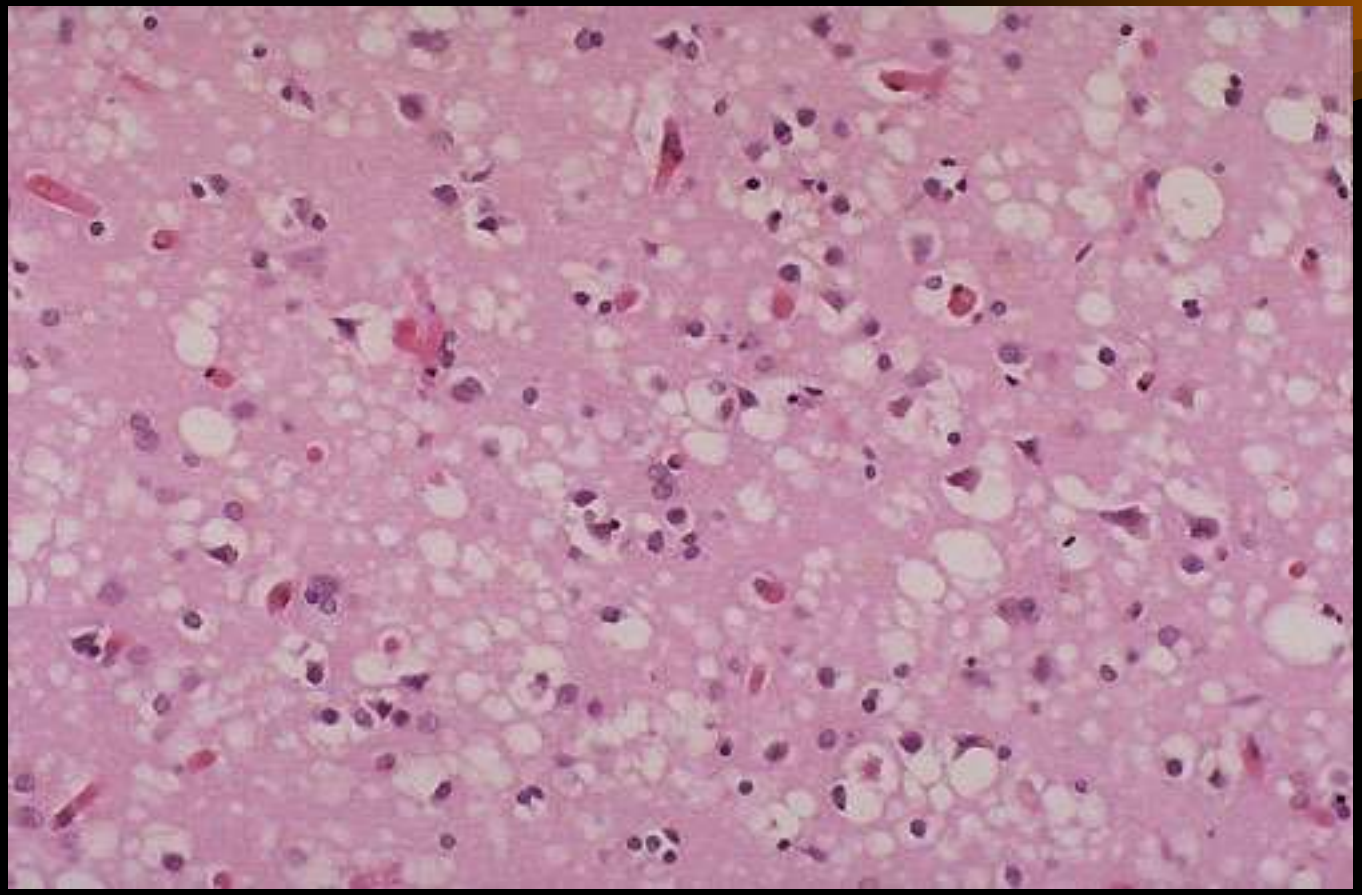






University of Nottingham

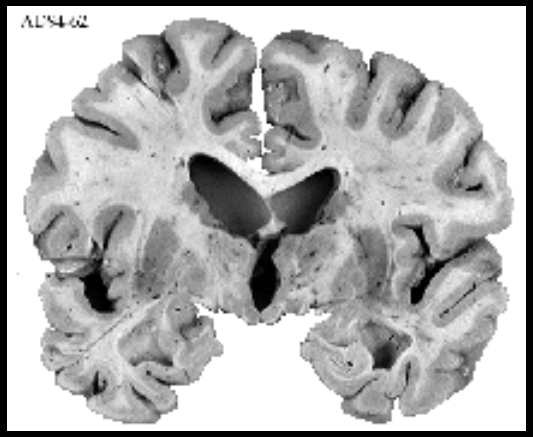
Creutzfeldt-Jakob disease (micro)

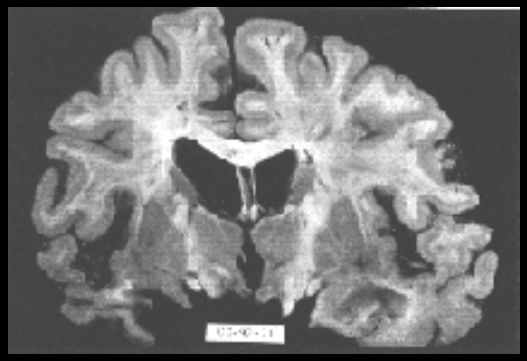


Focal Cortical Dementias

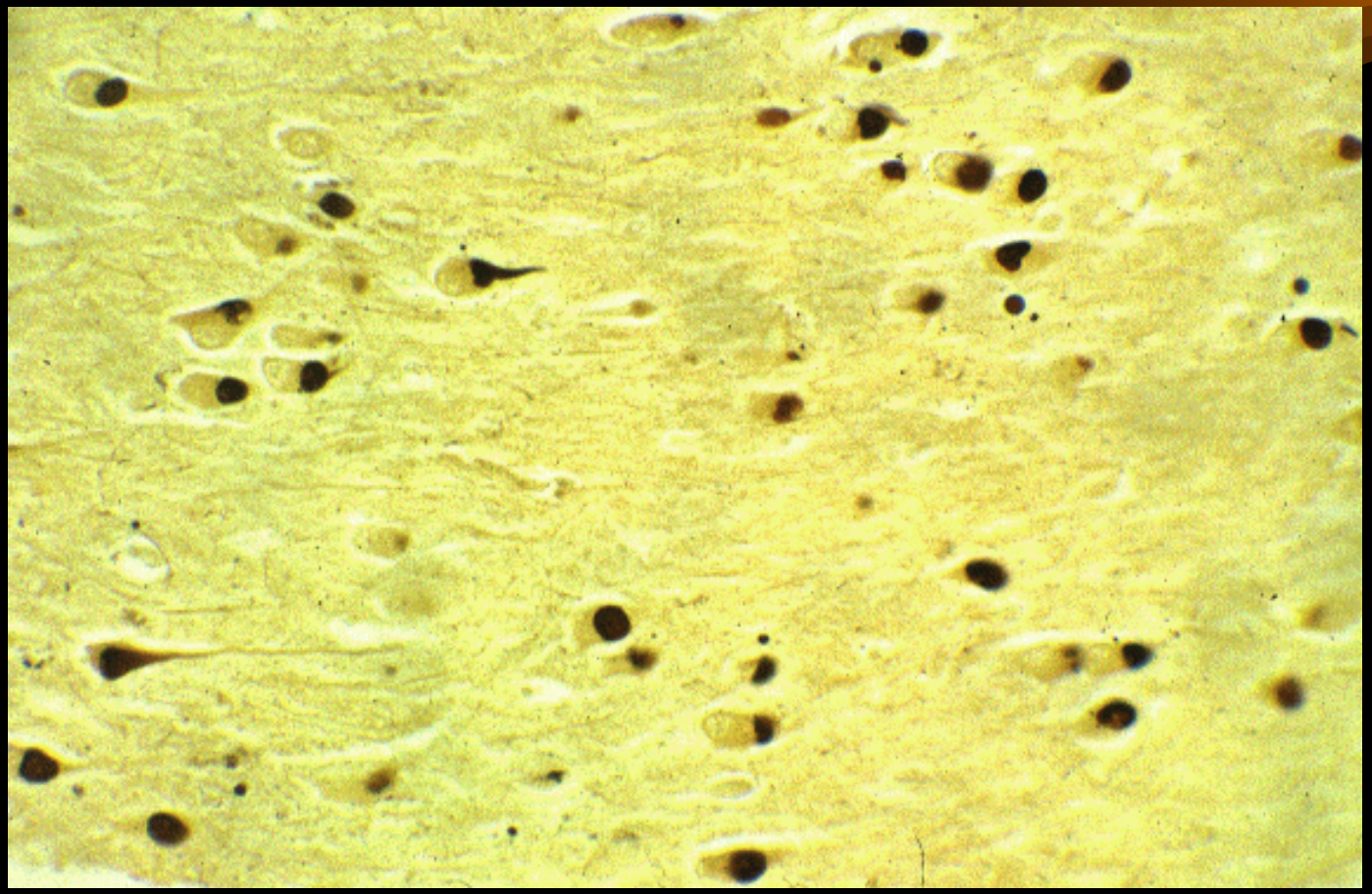
- Tauopathies
  - Pick's disease
  - Frontotemporal dementias (FTD)
  - Dementia lacking distinctive histopathology (DLDH)
  - Cortical basal degeneration (CBD)
- Bulbar ALS
  - Primary motor sclerosis

Pick's disease (macro)

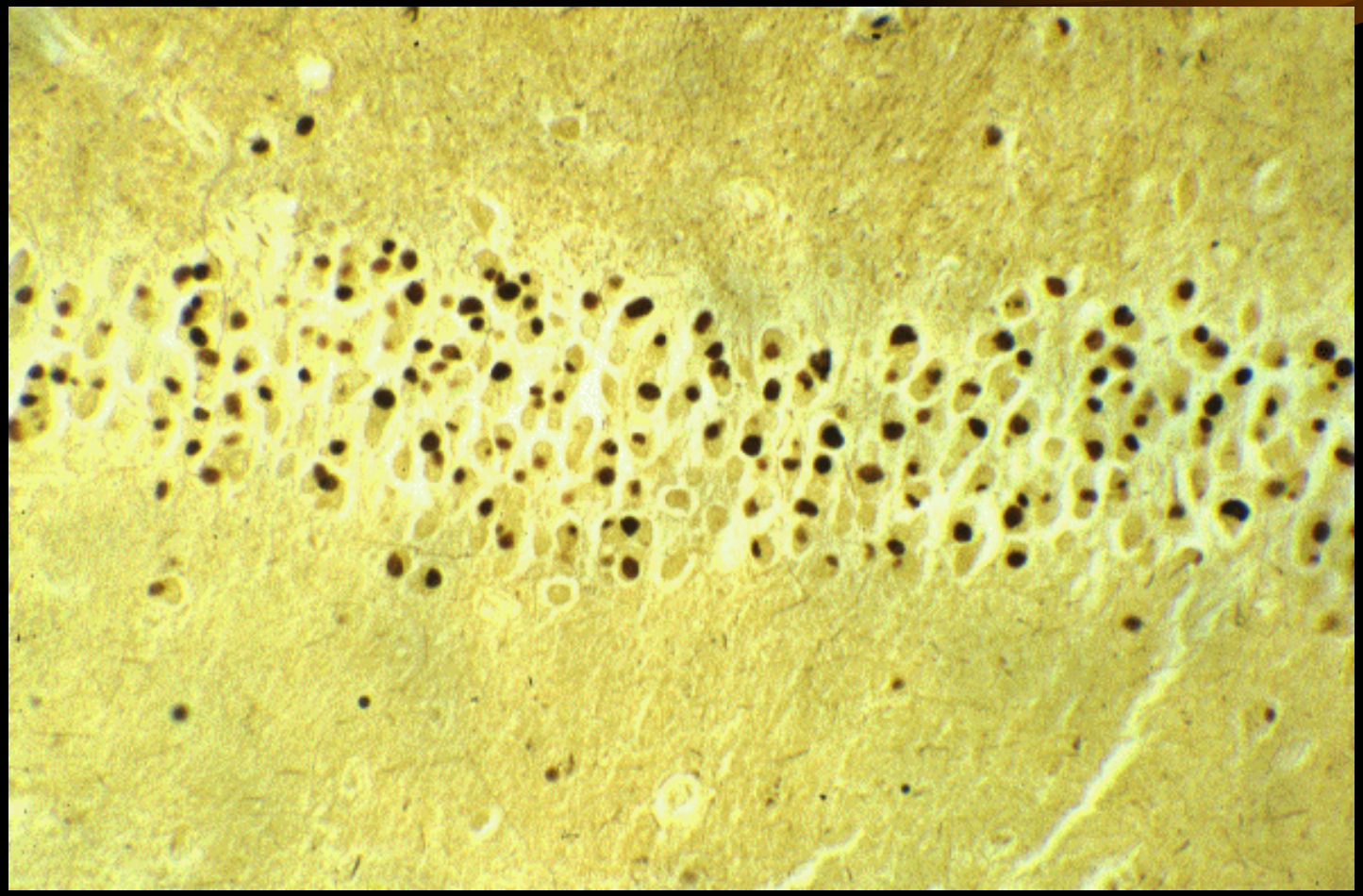




Pick's disease (micro)



Pick's disease (hippocampus)

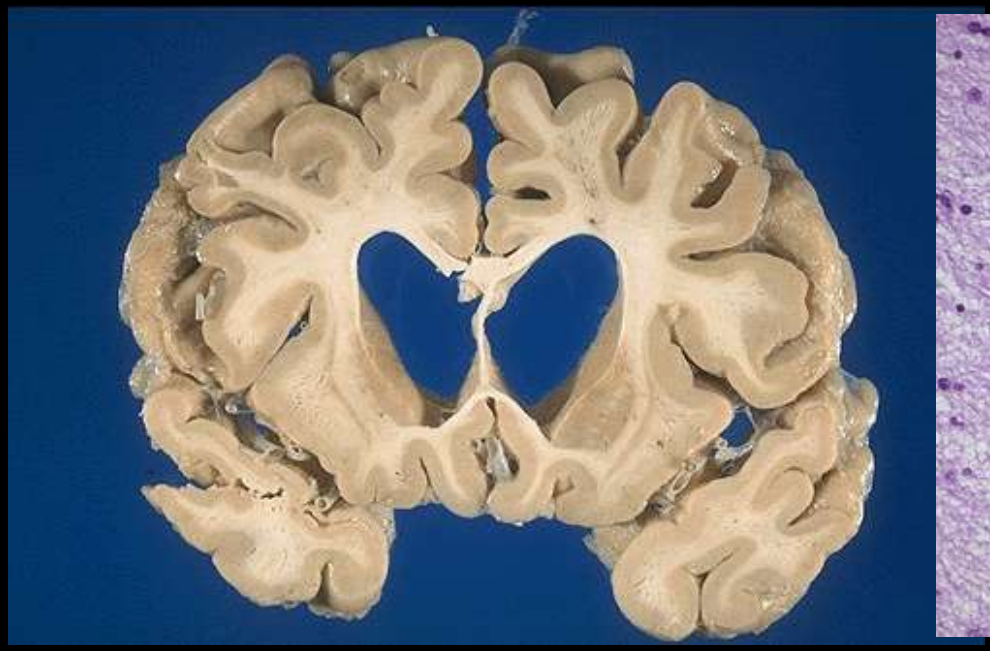


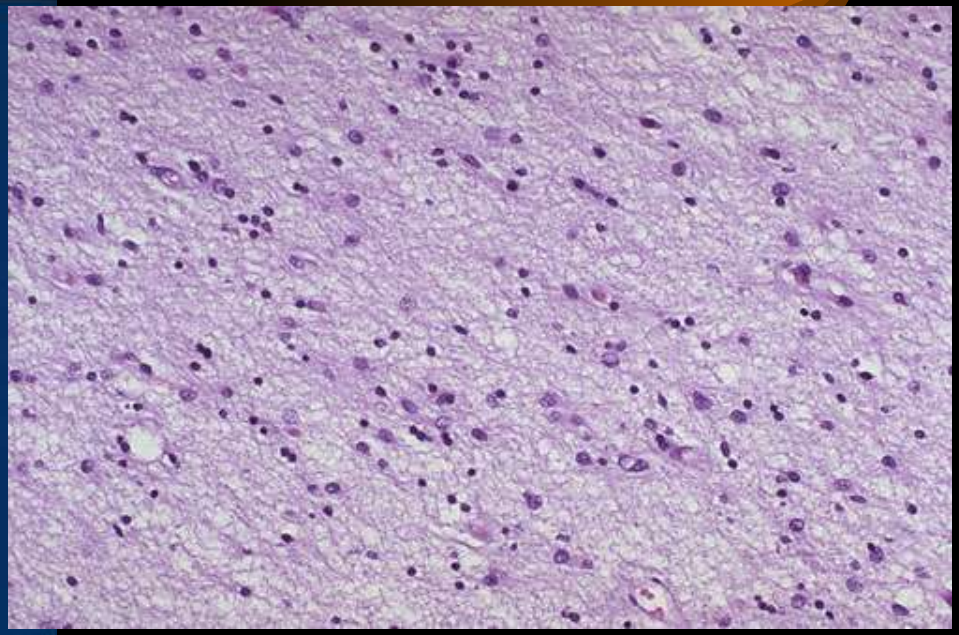
Inherited Subcortical Dementias

- Huntington disease
- Parkinson's disease?
- Progressive supranuclear palsy
- Hallervorden-Spatz disease
- Thalamic degeneration

- All eventually induce cortical atrophy

Huntington's disease





Subcortical Dementias

- Vascular: Binswanger's disease
- Demyelinating
  - Multiple sclerosis
  - Balo's concentric sclerosis
- Dysmyelinating
  - Leukodystrophy
- Inherited
  - CADASIL

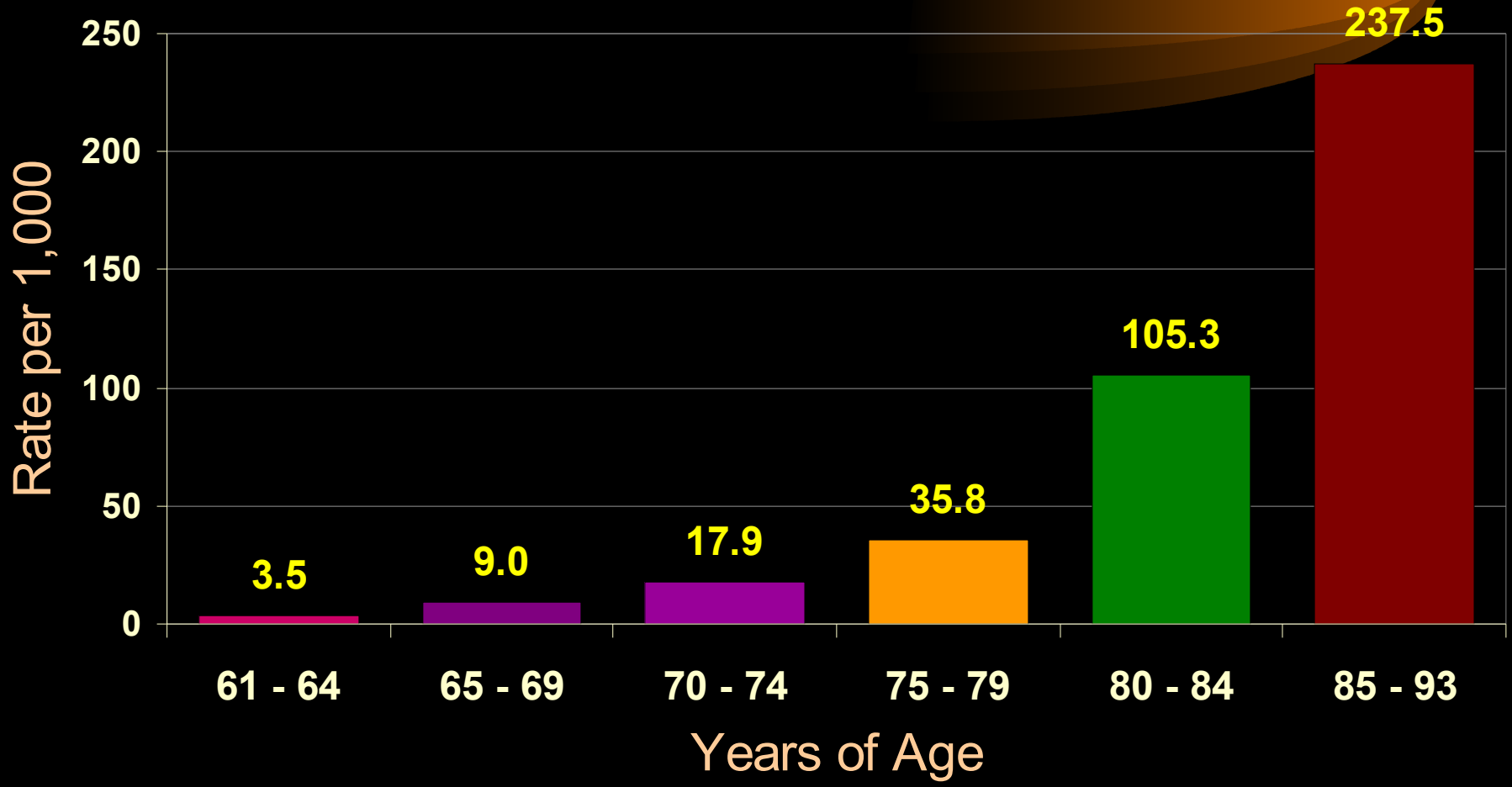
NINCDS-ADRDA Criteria for AD

- **Probable Alzheimer's Disease**
  - Dementia with onset between ages 40 & 90
  - Cognitive deficits in two or more areas
  - Progressive memory and cognitive deterioration
  - No other illness that could account for such deficits
  - No disturbance of consciousness
- **Definite Alzheimer's Disease**
  - Clinical criteria for probable AD
  - Histopathologic evidence from autopsy or brain biopsy

Prevalence of Alzheimer's

- Using NINCDS-ADRDA criteria:
  - Age 65-74: 3.0%
  - Age 75-84: 18.7%
  - Age 85+: 47.2%
  - Overall over age 65: 10.3%
- Fourth leading cause of death in the US after heart disease, cancer, and stroke

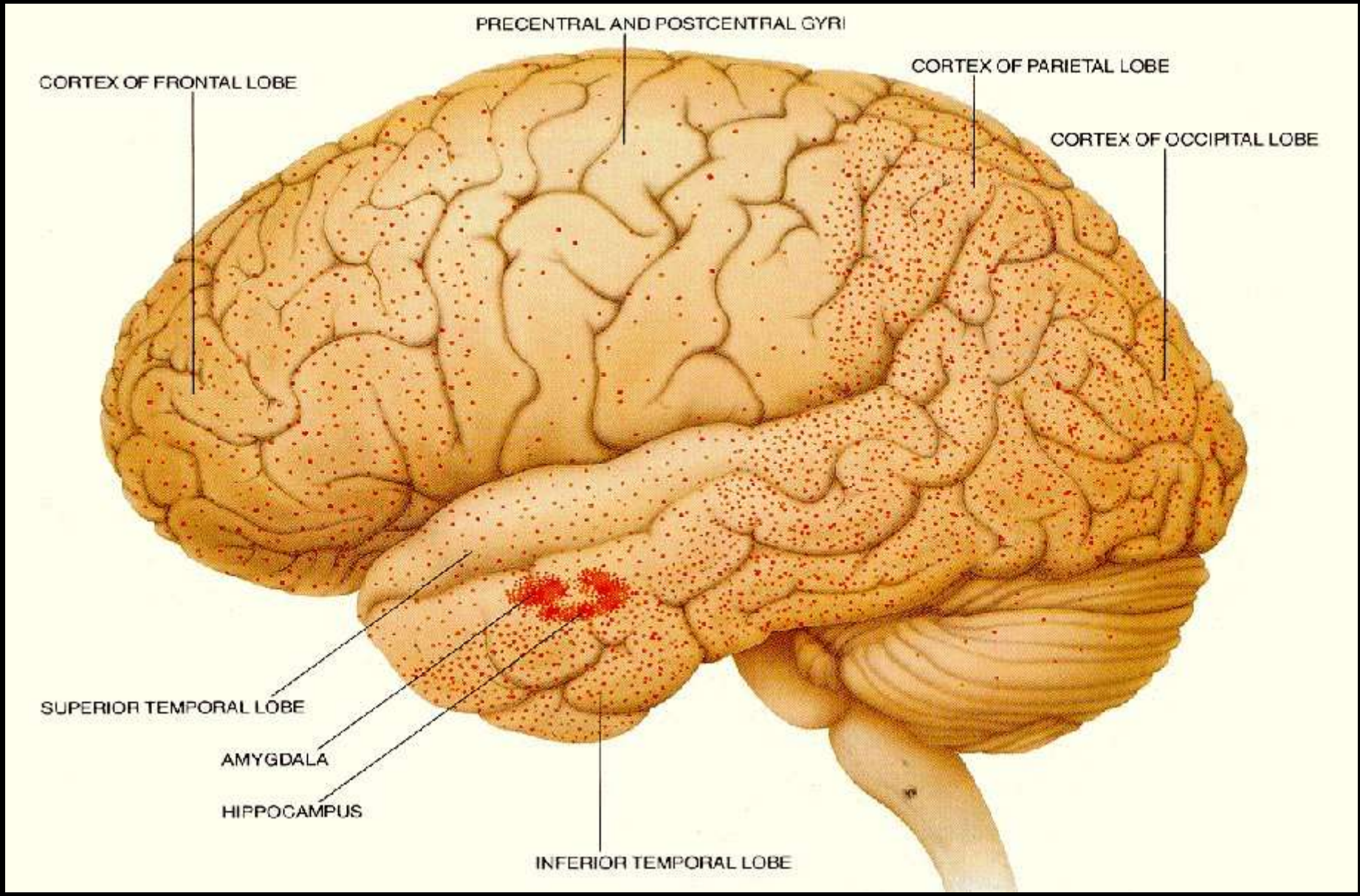
Prevalence of Dementia - The Framingham Study



Source: Bachman et al. *Neurology*. 1992;42:115-119.

Alzheimer's Disease

- Disorder of cerebral cortex grey matter
  - Intraneuronal: Neurofibrillary tangles
  - Extraneuronal: Senile (amyloid) plaques
- Population affected
  - Age of onset 40-90
  - Prevalence 2-4% at age 65+, increasing >75
  - 4 million Americans

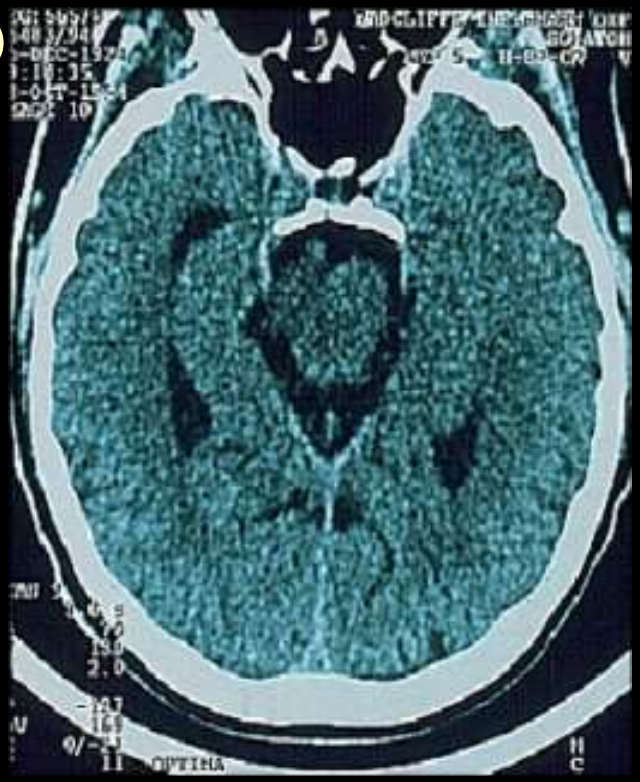


Brain of Alzheimer Patient shows numerous plaques of amyloid beta-protein in specific brain areas. These plaques become centers for the degeneration of neurons.

Axial CT scan section through the temporal lobes: (A) Normal; (B) Alzheimer's Disease

Anterior

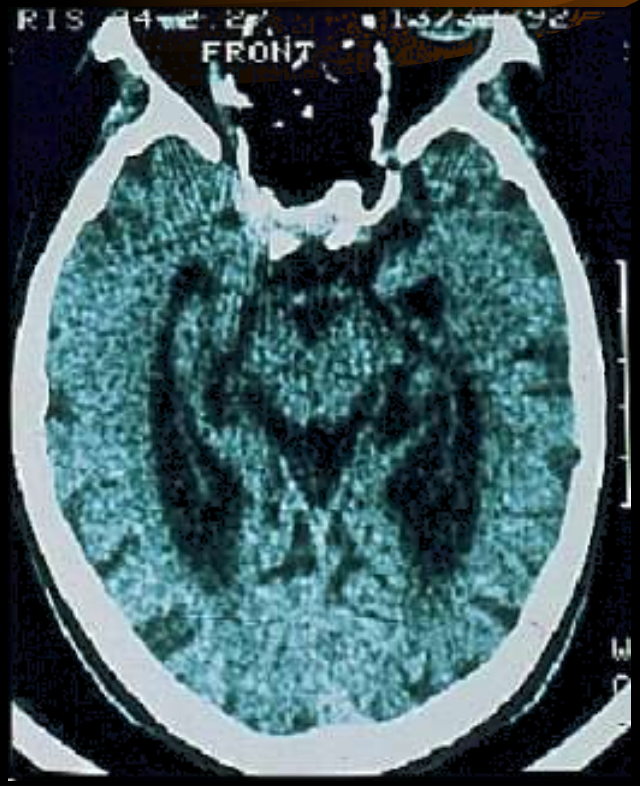
(A)



Posterior

Anterior

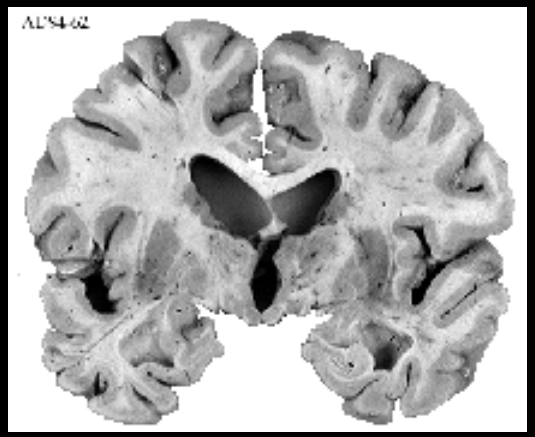
(B)

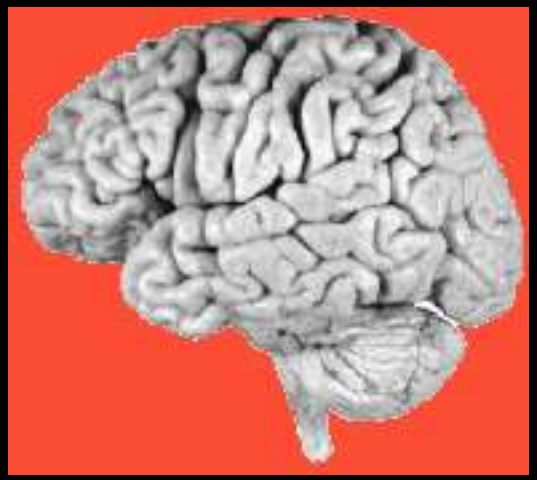


Posterior

Courtesy of James King-Holmes and Science Photo Library

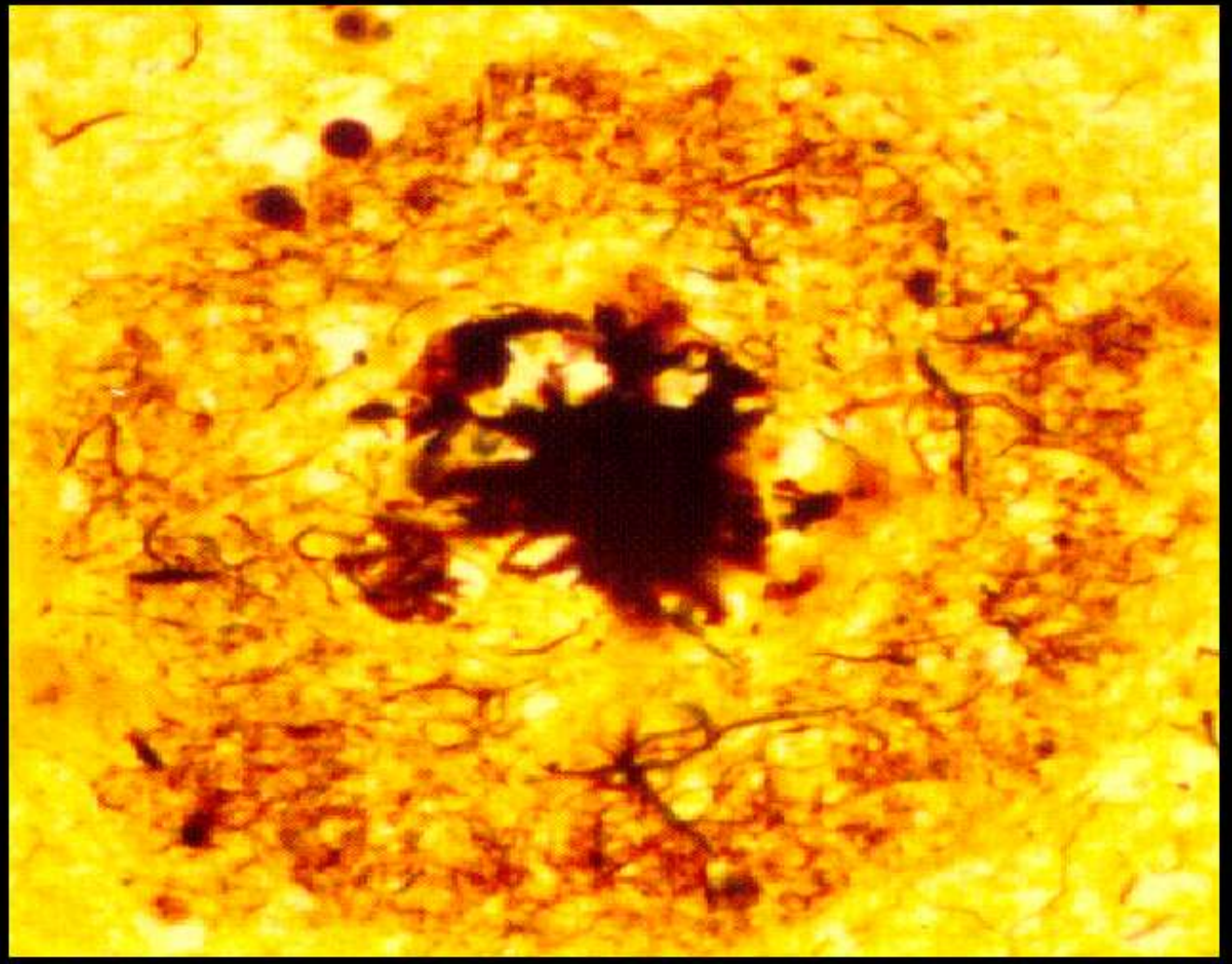
Alzheimer's disease gross pathology





Alzheimer's Disease

- **Neuritic plaques** consist of a core of β-amyloid formed by beta protein fibrils from the aggregated 42 amino acid A/β peptide, surrounded by swollen, dystrophic neurites.
- **Neurofibrillary tangles** fill the interior of degenerating neurons. The presence of plaques and tangles at autopsy is used to confirm a diagnosis of AD.



Plaque of Amyloid Beta-Protein. Visible as a black globular mass when stained. The plaque is surrounded by abnormal neurites and degenerating neurons.

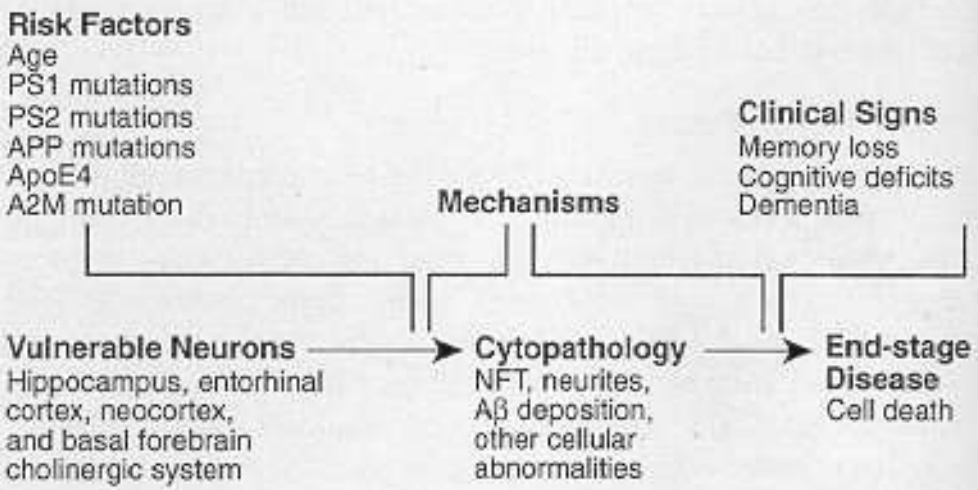


Fig. 2. Alzheimer's diseases. Schematic showing the relations between clinical or pathological phenotypes and mutant genes, other risk factors, and vulnerable populations of neurons. Genetically engineered mice can reproduce some of the clinical, biochemical, and pathological features of AD.

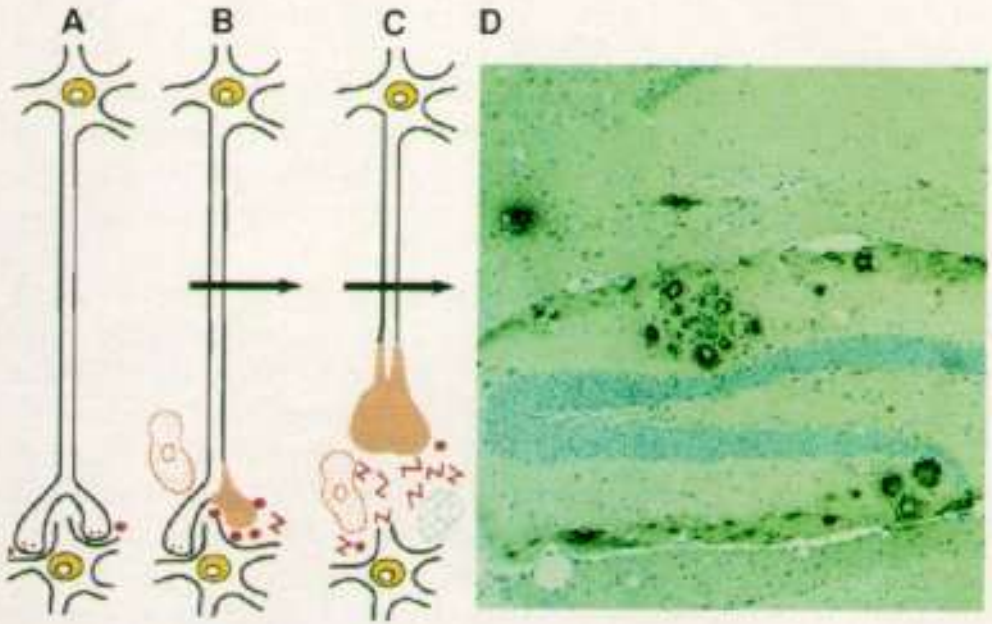


Fig. 4. Postulated evolution of structural abnormalities in APPswe transgenic mice and evidence of Aβ deposits in the hippocampus. (**A**) This two-neuron circuit is intact, but amounts of Aβ (red dots) are increased near the synapse. (**B**) Large APP-containing neurite associated with elevated amounts of Aβ and early Aβ deposits (red Z's). (**C**) Neuritic plaques with APP-enriched neurites, Aβ deposits, astrocytes, and microglia. Synaptic interactions are increasingly compromised progressing from (A) to (C). (**D**) Aβ42 deposits (brown) in the hippocampus of a 24-month-old Mo/Hu-APPswe transgenic mouse.

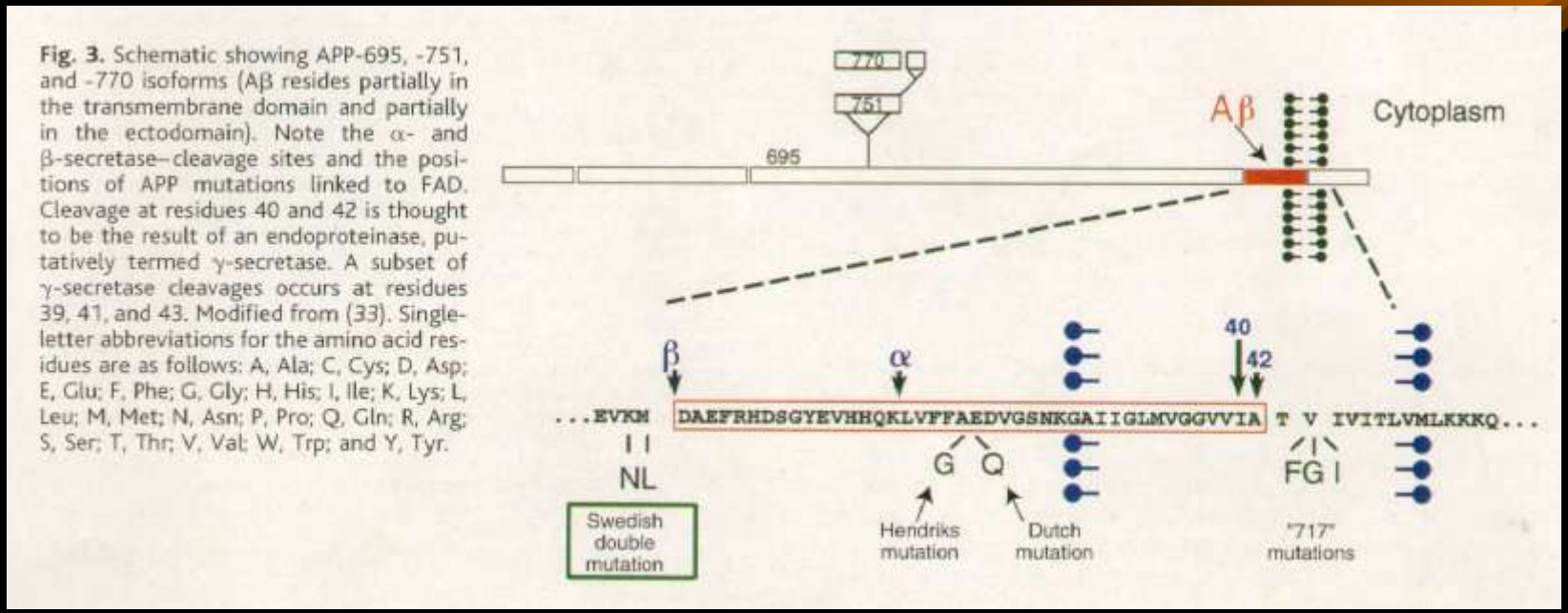
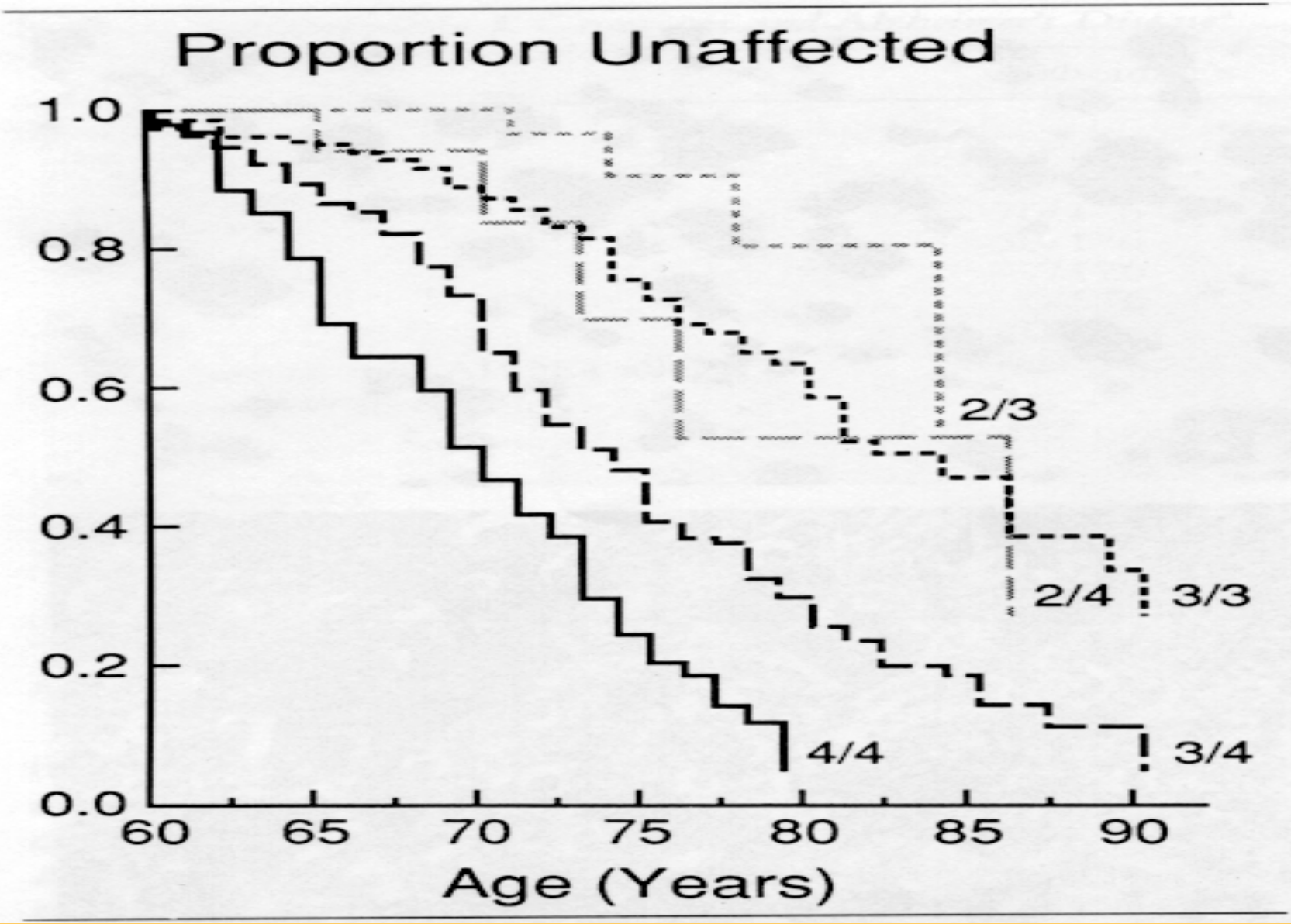


Fig. 3. Schematic showing APP-695, -751, and -770 isoforms (Aβ resides partially in the transmembrane domain and partially in the ectodomain). Note the α- and β-secretase–cleavage sites and the positions of APP mutations linked to FAD. Cleavage at residues 40 and 42 is thought to be the result of an endoproteinase, putatively termed γ-secretase. A subset of γ-secretase cleavages occurs at residues 39, 41, and 43. Modified from (33). Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.



APOE genotype -specific risk of remaining unaffected

The ApoE Test

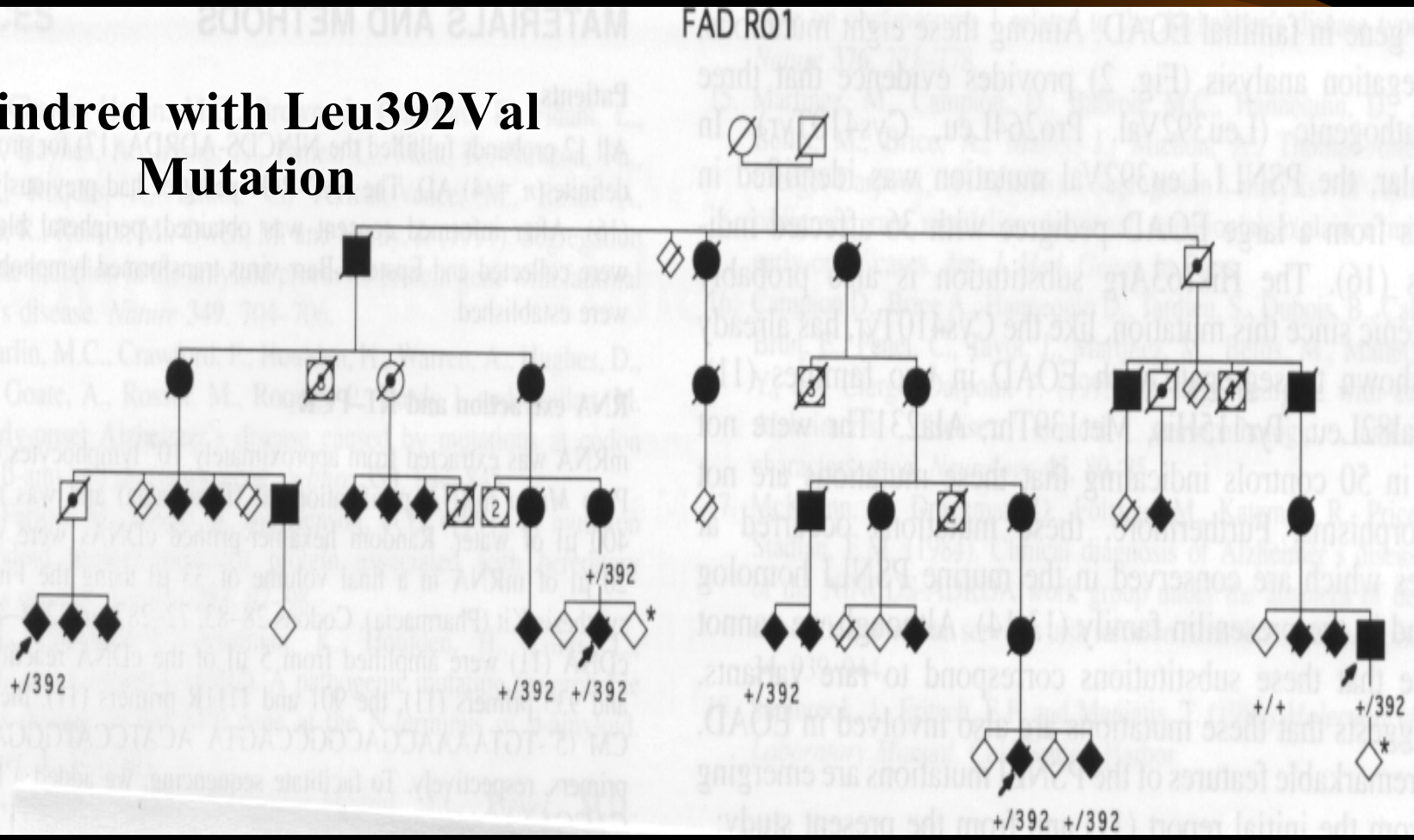
- Test Result Positive
  - 1 or more e4 alleles
  - Rule in AD
  - Appropriate treatment and action
- Test Result Negative
  - No e4 alleles
  - Non-diagnostic

Presenilin-1 (PS-1)

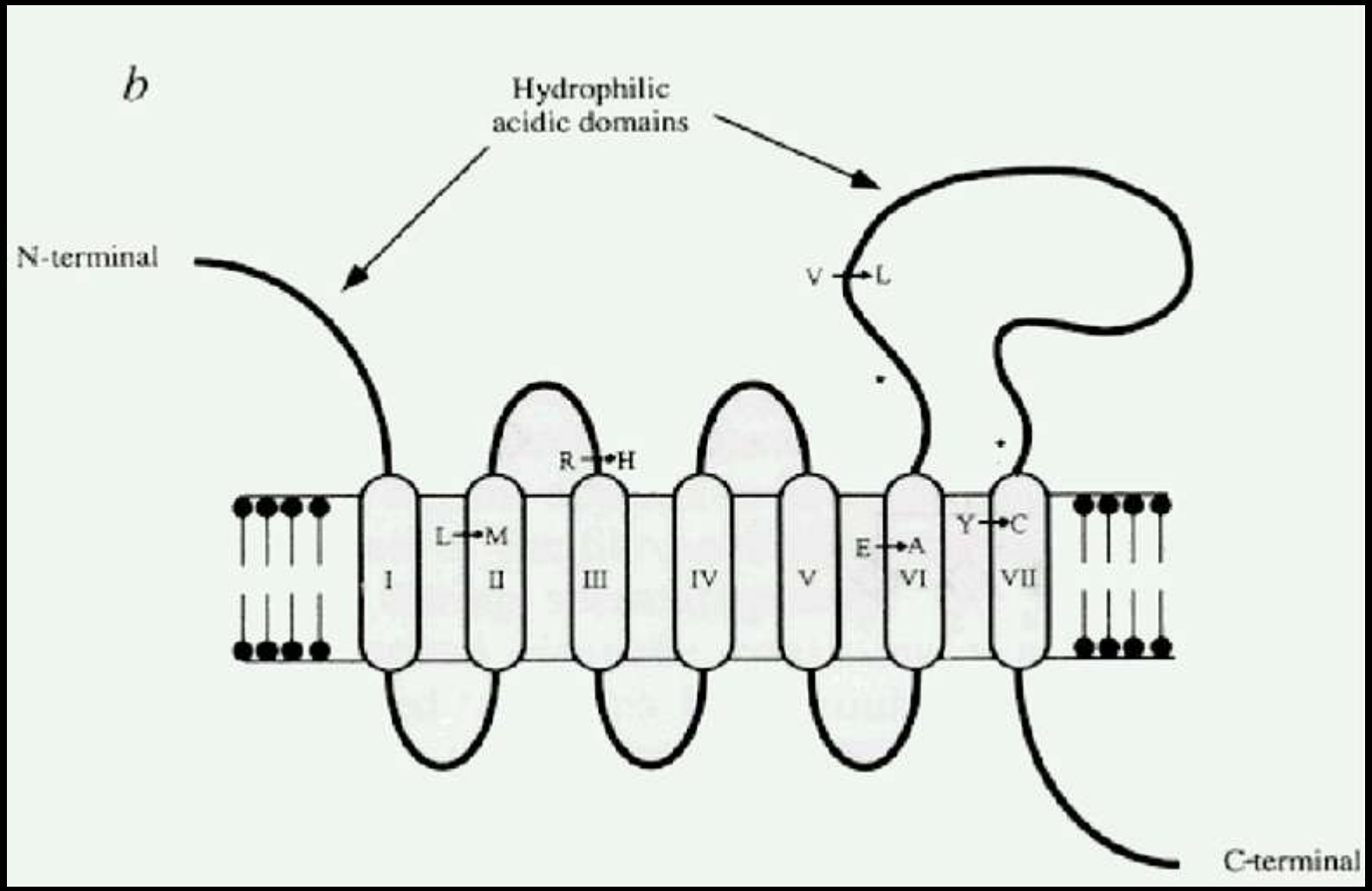
- Largest portion of EOFAD cases (>50%)
- 40+ mutations in over 50 families of varied ethnic origin
- Age range 29 to 62 years old
- Over 99% penetrant
- Unrelated families with same mutation have similar age of onset

Presenilin-1 Linkage Analysis

Kindred with Leu392Val Mutation



Filled Symbols - EOAD Patients Open Symbols - Asymptomatic Individuals Dots - Obligate Carriers whose status was unknown +/+ Wild Type observed in asymptomatic individuals over 60 years of age



Structure of the Putative S182 Protein

Reversible Causes of Dementia

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

Source: Costa PT et al. Agency for Health Care Policy and Research. 97-0703; November 1996.

Differential Diagnosis I

ALZHEIMER'S DISEASE	NORMAL AGING
• Irreversible decline in short-term memory • Irreversible decline in other cognitive abilities • Functional impairment • Psychiatric symptoms	• Benign decline in short-term memory (maybe*)

Source: Costa PT et al. Agency for Health Care Policy and Research. 97-0703; November 1996.

Differential Diagnosis II

ALZHEIMER'S DISEASE	VASCULAR DEMENTIA
• Gradual onset, relentless progression • Underlying vascular disorder not always present • Deterioration in a broad range of intellectual abilities	• Abrupt onset • Underlying vascular disorder present (eg, hypertension or heart disease) • Early impairment in motor skills • Brain scan shows evidence of strokes or stroke-related changes

Source: Alzheimer's Association, 1995.

Differential Diagnosis III

ALZHEIMER'S DISEASE

- Gradual onset, relentless progression
- Parkinsonian signs are rare (gait only)
- Visual hallucinations of psychosis are a late finding

LEWY BODY DISEASE

- Prominent fluctuations
- Parkinsonian signs
- Neuroleptic sensitivity
- Early visual hallucinations and psychosis

Differential Diagnosis IV

ALZHEIMER'S DISEASE

- Relatively older age of onset
- Very slow rate of progression
- Late findings:
  - Personality change
  - Hallucinations
  - Psychosis
  - Aphasia

PICK'S DISEASE

- Younger age of onset
- More rapidly progressive
- Anterior atrophy
- Early findings:
  - Personality change
  - Hallucinations
  - Psychosis
  - Aphasia