

# Journey to Hope

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Richman Family Professor for  
Alzheimer's and Related Dementias

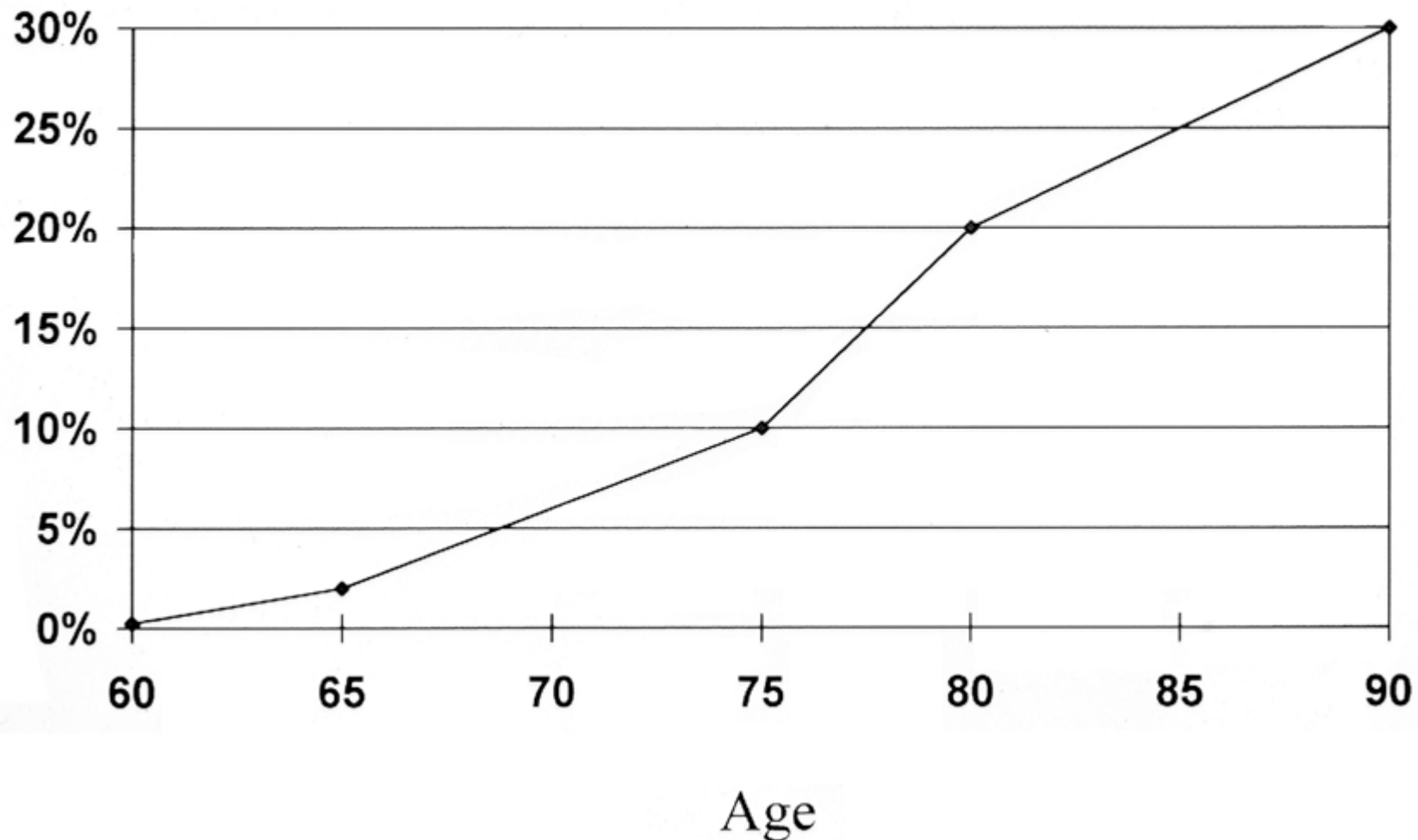
# Dementia Syndrome

- Declines in 2 or more cognitive capacities
- Normal level of consciousness and alertness
- Onset in adulthood

# Mysteries of Dementia

- Dementia is strongly age-associated

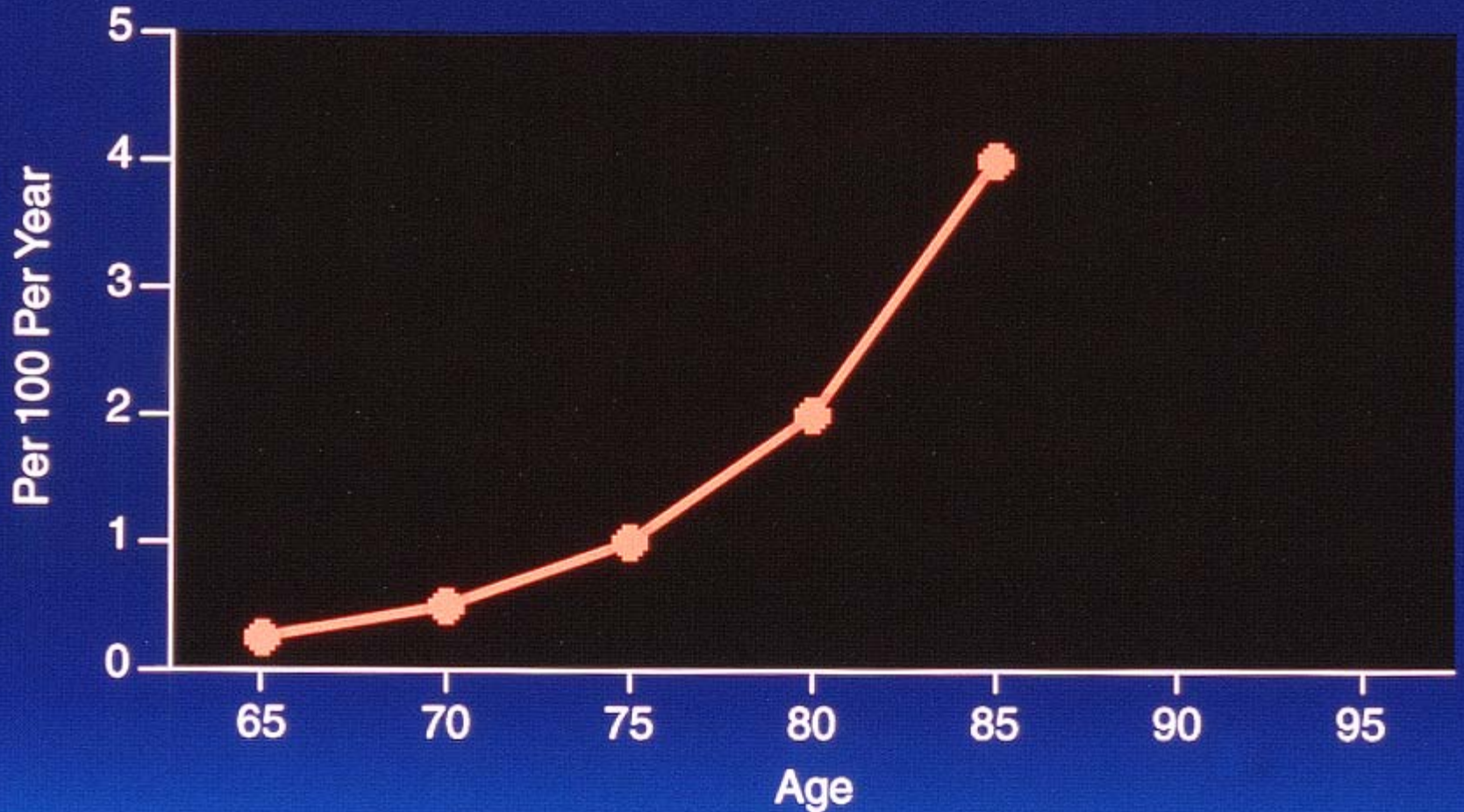
# Prevalence of Dementia



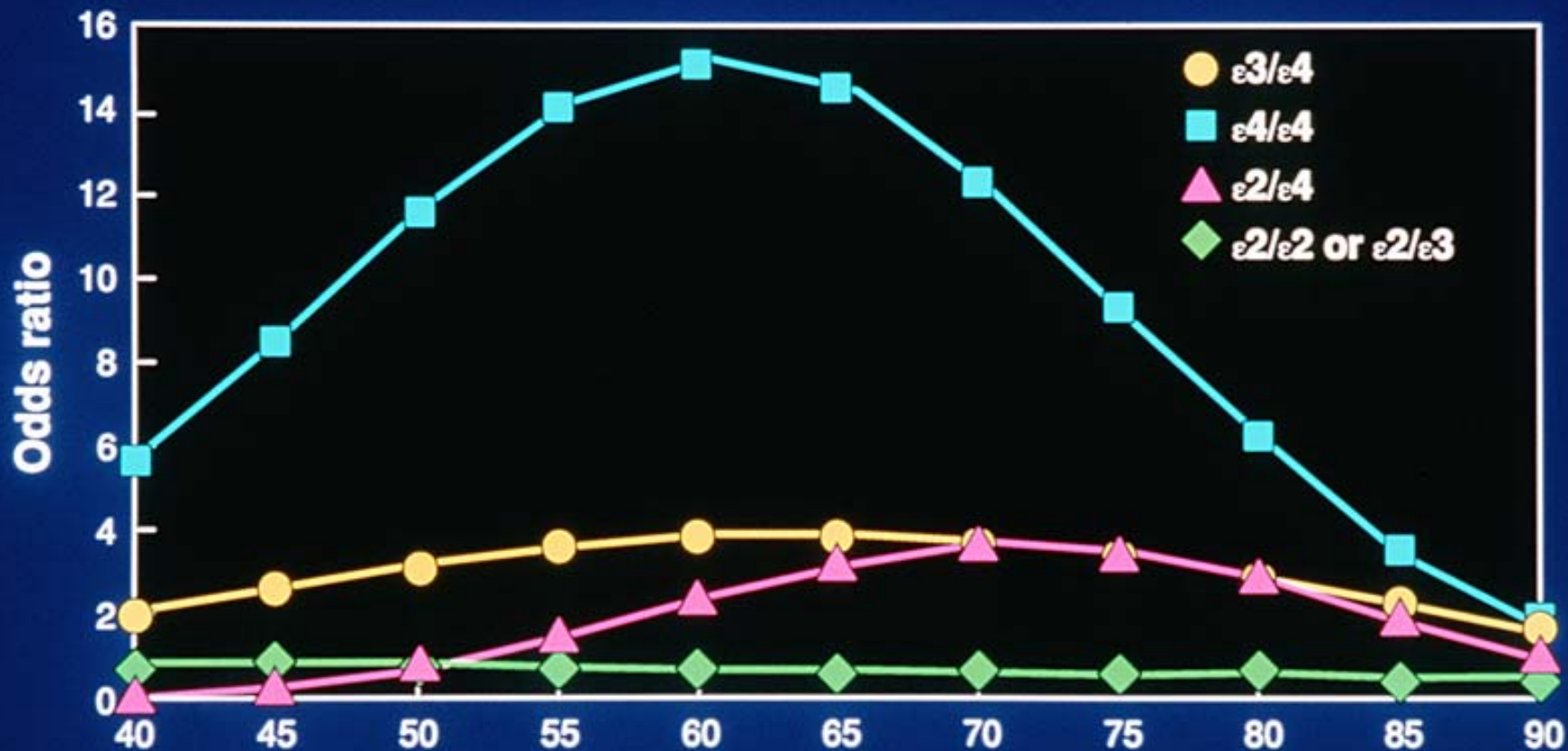
# Mysteries of Dementia

- Dementia is strongly age-associated
- The risk of dementia **DOUBLES** every five years after age 65

# Incidence of Dementia



# APOE Genotyping and AD



Farrer LA, et al. *JAMA*. 1997;278:1349-1356.

# Mysteries of Dementia

- Dementia is strongly age-associated
- The risk of dementia **DOUBLES** every five years after age 65
- Why does disease progression follow a pattern that is unique for each disease?

# Diagnostic Features of Alzheimer Disease

- **Slowly progressive dementia**
- **No other etiology identified:**  
non-contributory neurological examination,  
laboratory evaluation and brain imaging
- **Decline in memory plus either:**
  - aphasia
  - apraxia
  - agnosia

# ALZHEIMER DISEASE

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## Staging Per Sjogren (1953)

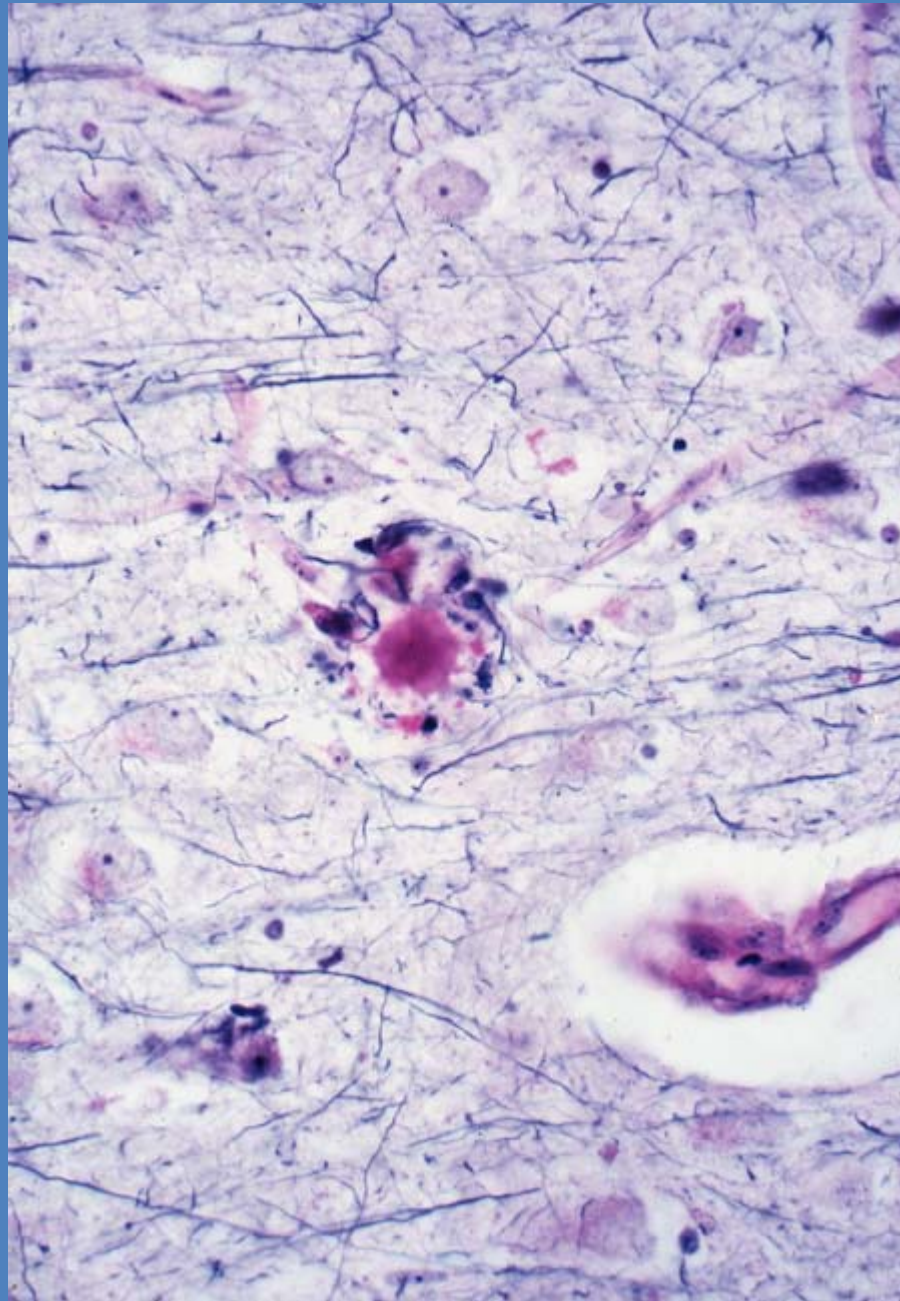
I - Memory impairment  
Personality change

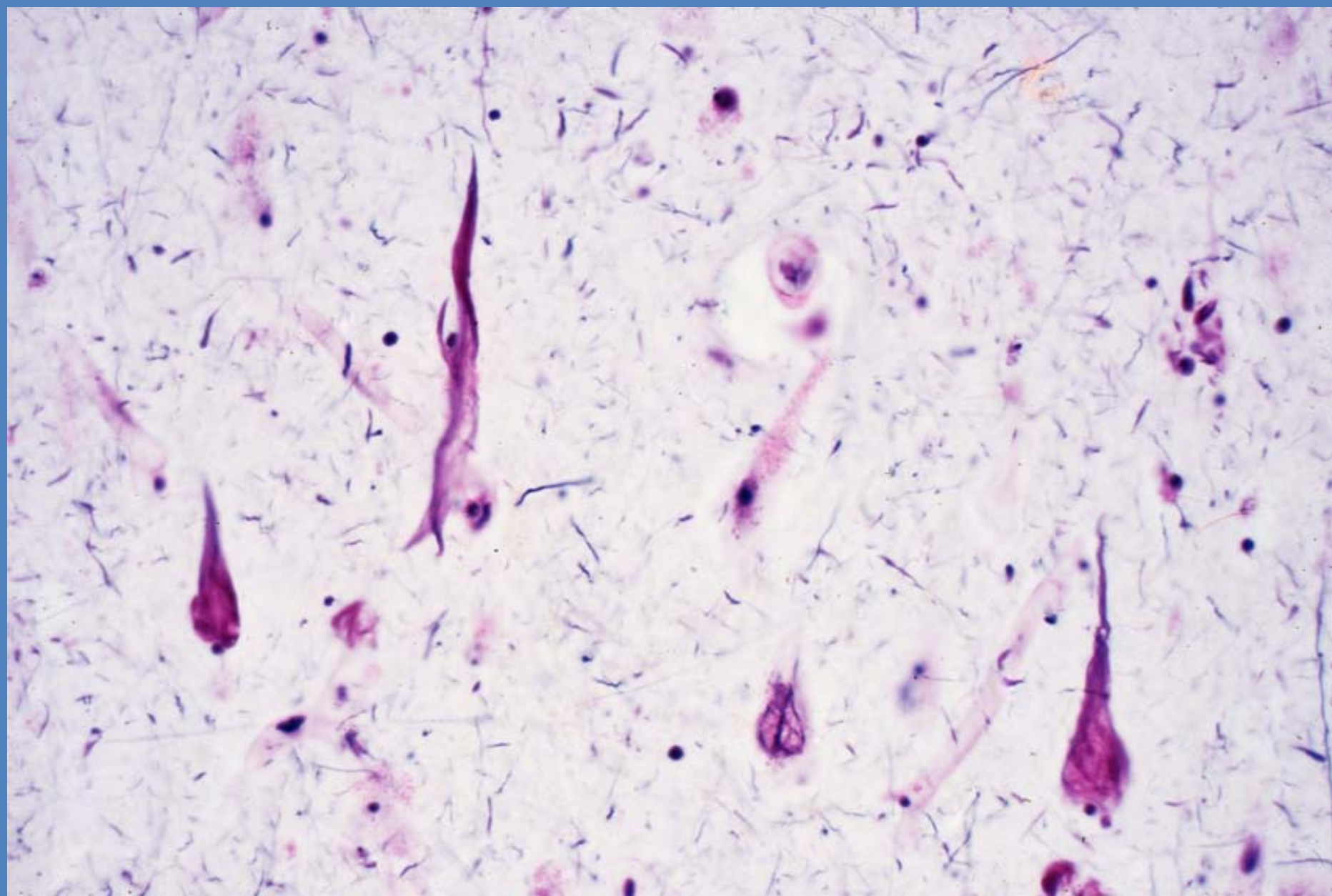
II - Cortical signs - aphasia  
apraxia  
agnosia

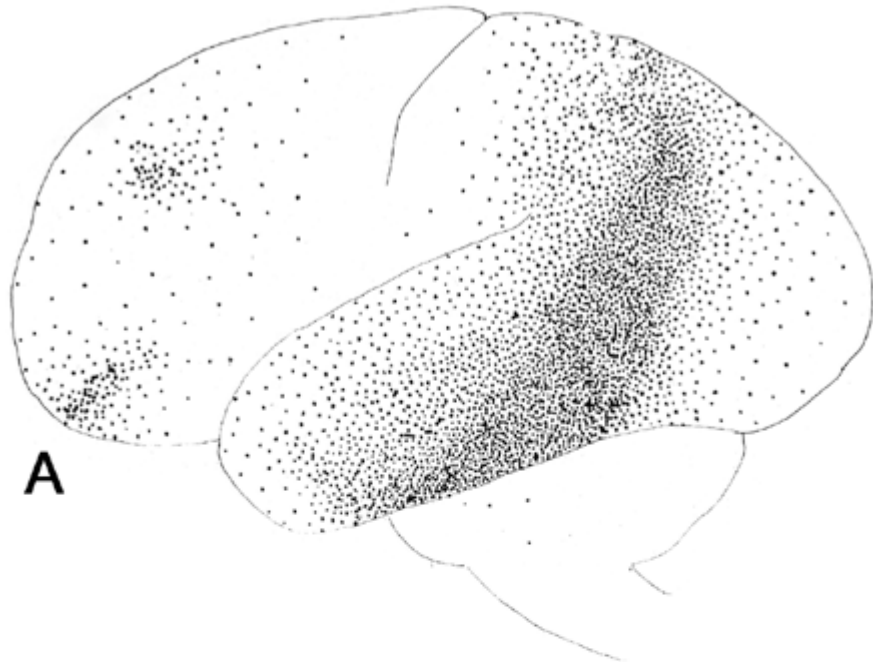
III - Physical decline - incontinence  
- gait disorder  
- muteness  
- feeding difficulty

# COMMON CAUSES OF DEMENTIA

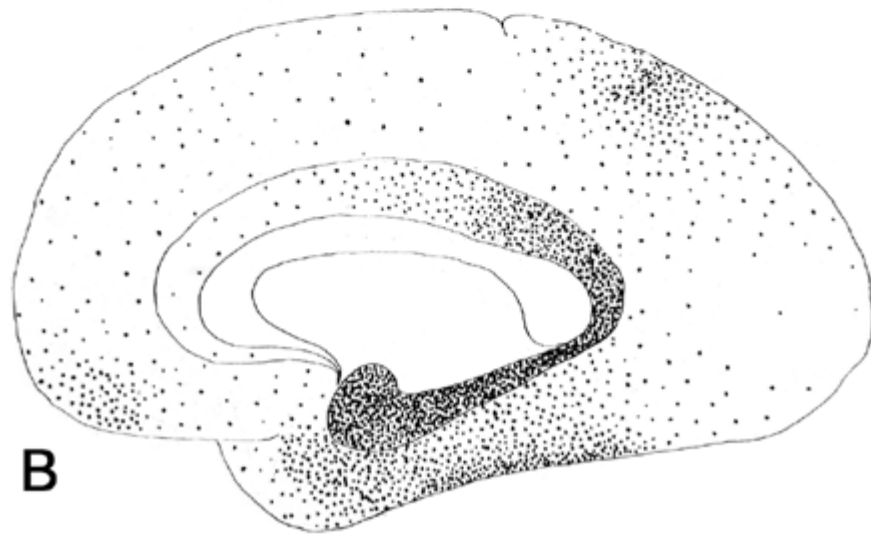
- Alzheimer disease 66%
- Vascular dementia 15-20%
- Dementia with Lewy bodies 8-15%
- Fronto-temporal dementia 5%





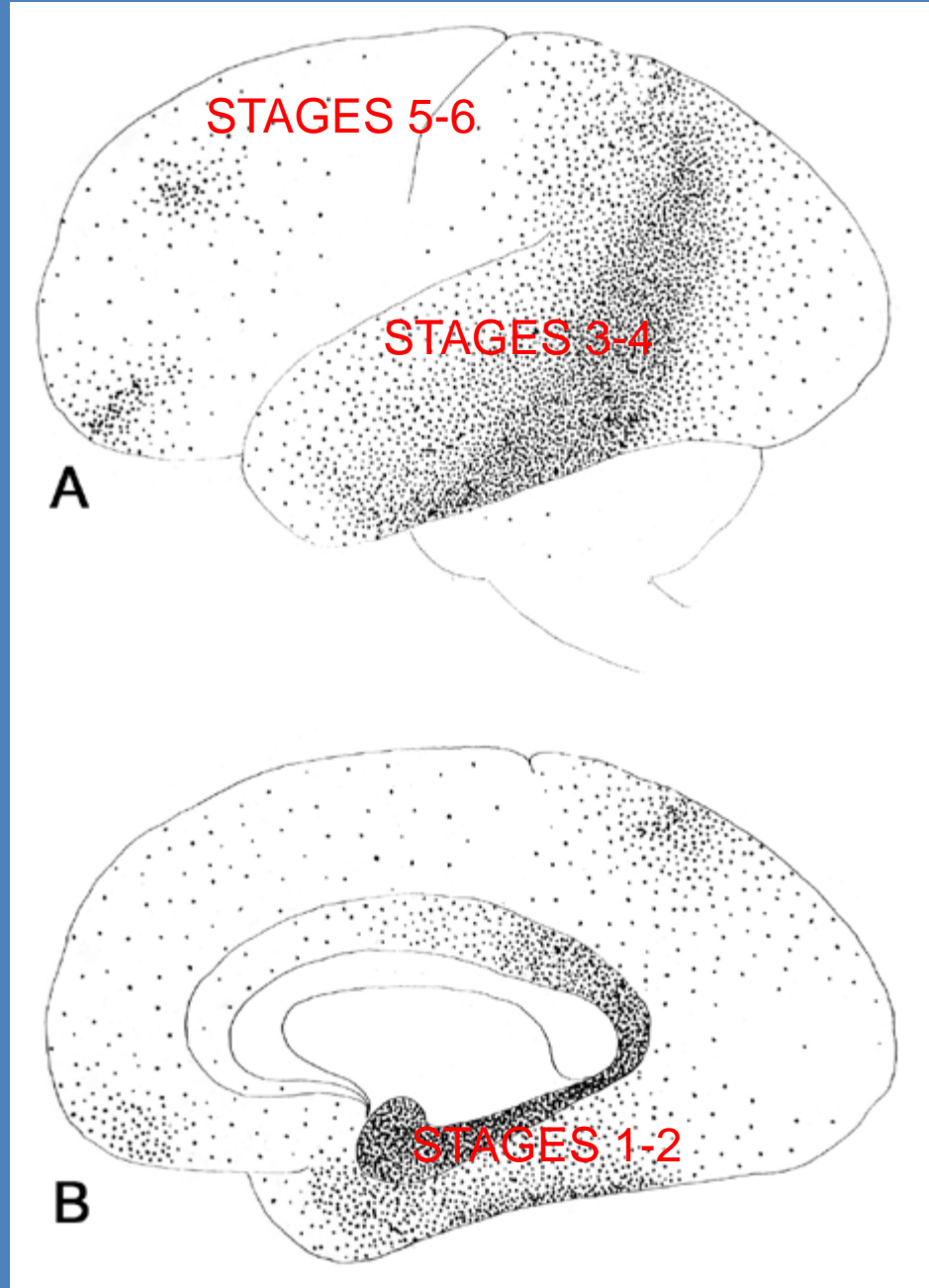


**A**



**B**

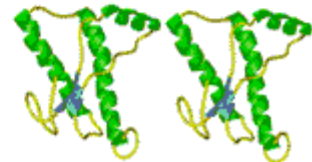
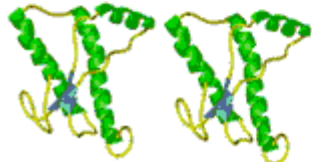
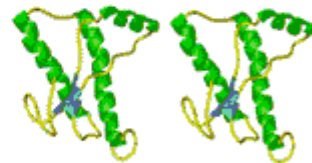
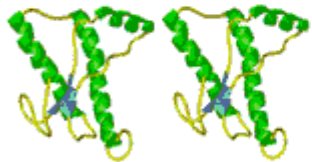
# Braak Stages of Alzheimer Disease Pathology



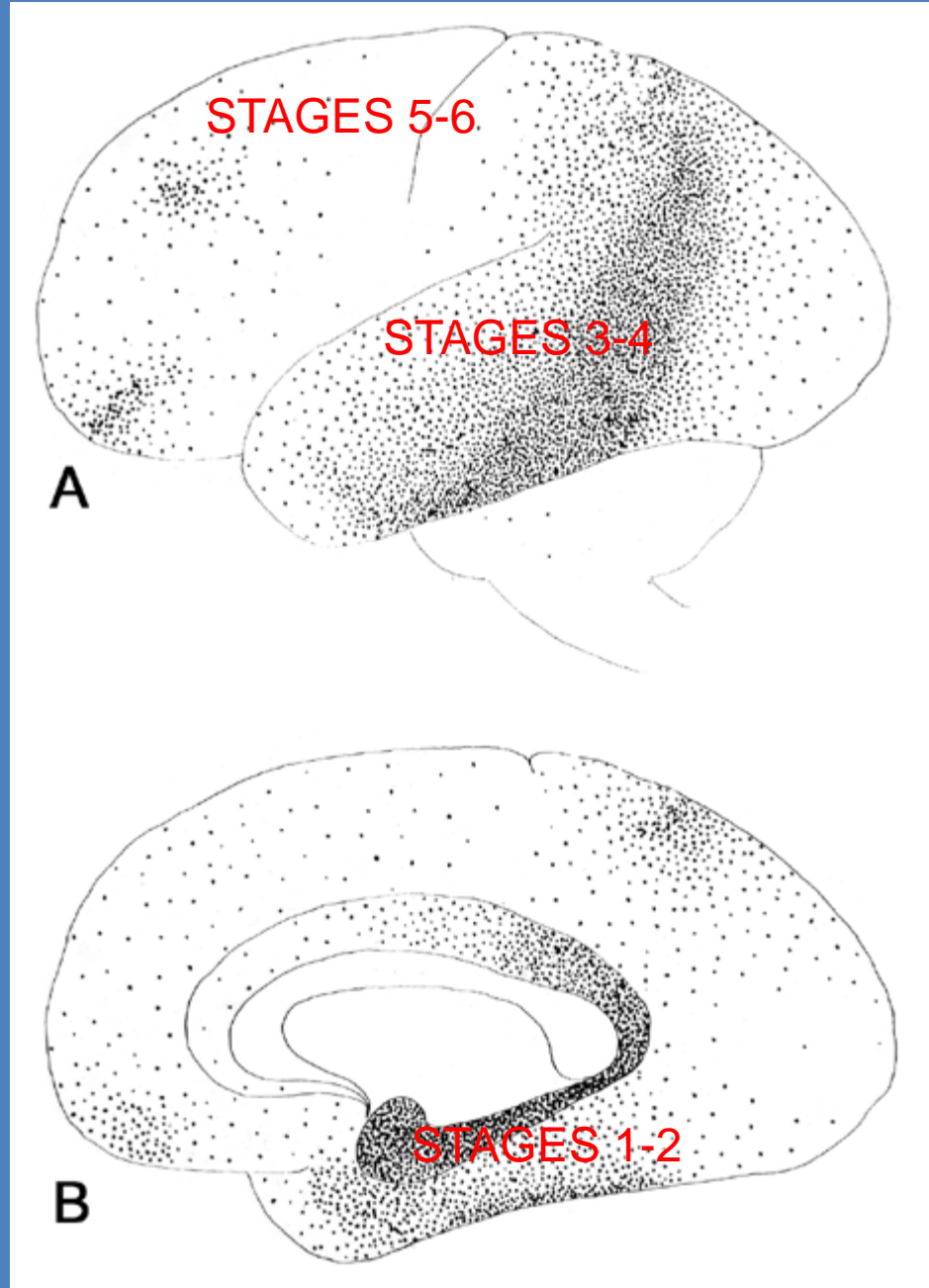
# Creutzfeldt-Jakob Disease (CJD)

- Rapidly progressive dementia (death in 9-18 months)
- Neurological Exam Abnormalities
- Impairments in memory and language early
- Jerking movements (myoclonus)

Cellular PrPS



# Braak Stages of Alzheimer Disease Pathology



# Mysteries of Dementia

- Dementia is strongly age-associated
- The risk of dementia **DOUBLES** every five years after age 65
- Why does disease progression follow a pattern that is unique for each disease?
- Where will we care for people with dementia?

# Point Prevalence of Dementia by Setting

(US Data)

	<u>%</u>
General Population 65+	8
General Hospital	8 – 27
Home Health Care	18
Assisted Living/Foster	50- 68
Nursing Home	50-75
Hospice	6

# 5 Elements of Care

1. Information: Diagnosis, Prognosis, Future planning
2. Focus on specific symptoms
3. Good primary medical care
4. Family/caregiver support
5. Longitudinal care

# PRACTICAL DEMENTIA CARE

PETER V. RABINS

CONSTANTINE G. LYKETSOS

CYNTHIA D. STEELE

"The best guide  
of its kind."

—CHICAGO SUN TIMES

THIRD  
EDITION

# The 36-Hour Day

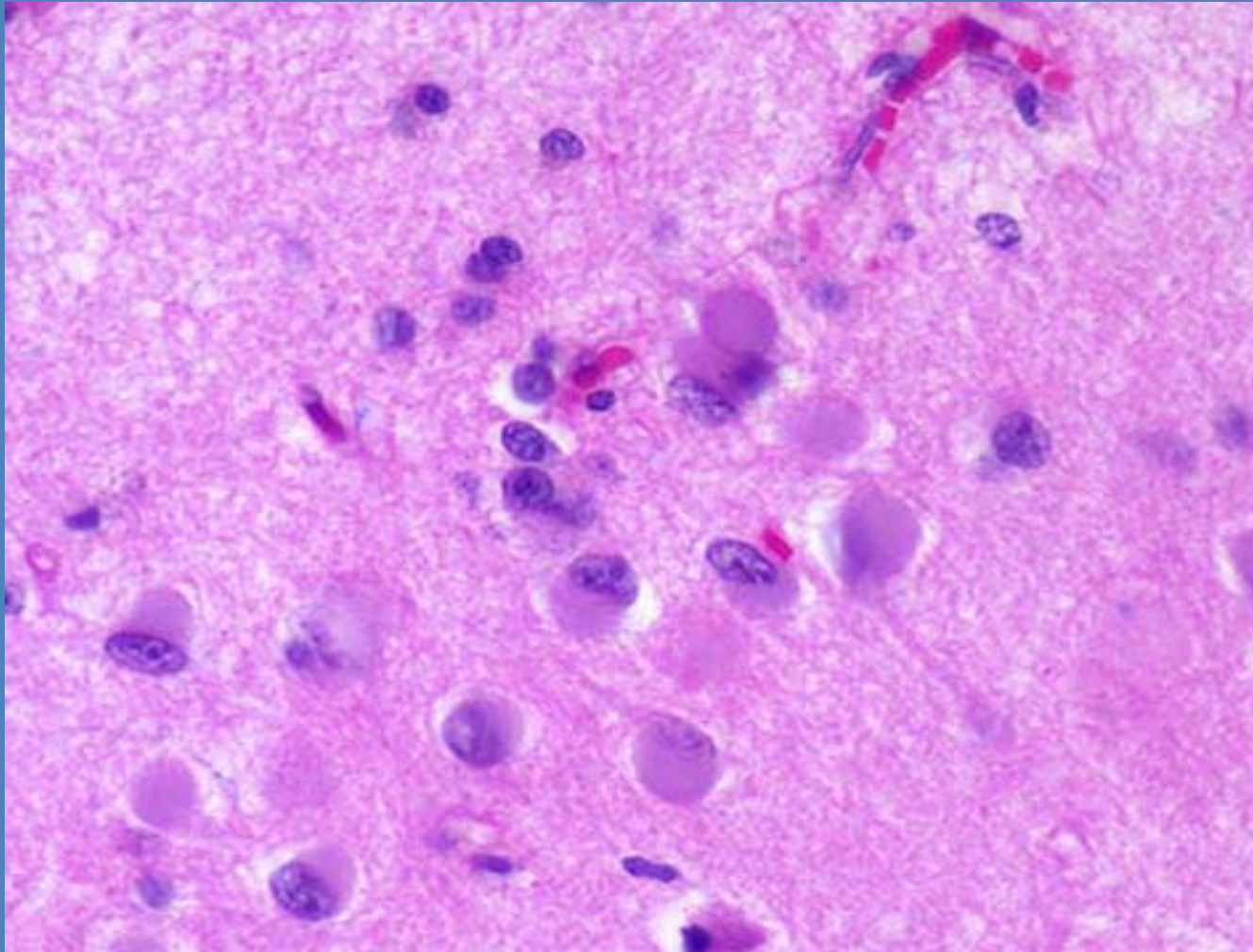
A Family Guide to Caring for  
Persons with Alzheimer Disease,  
Related Dementing Illnesses,  
and Memory Loss in Later Life

NANCY L. MACE, M.A.  
PETER V. RABINS, M.D., M.P.H.

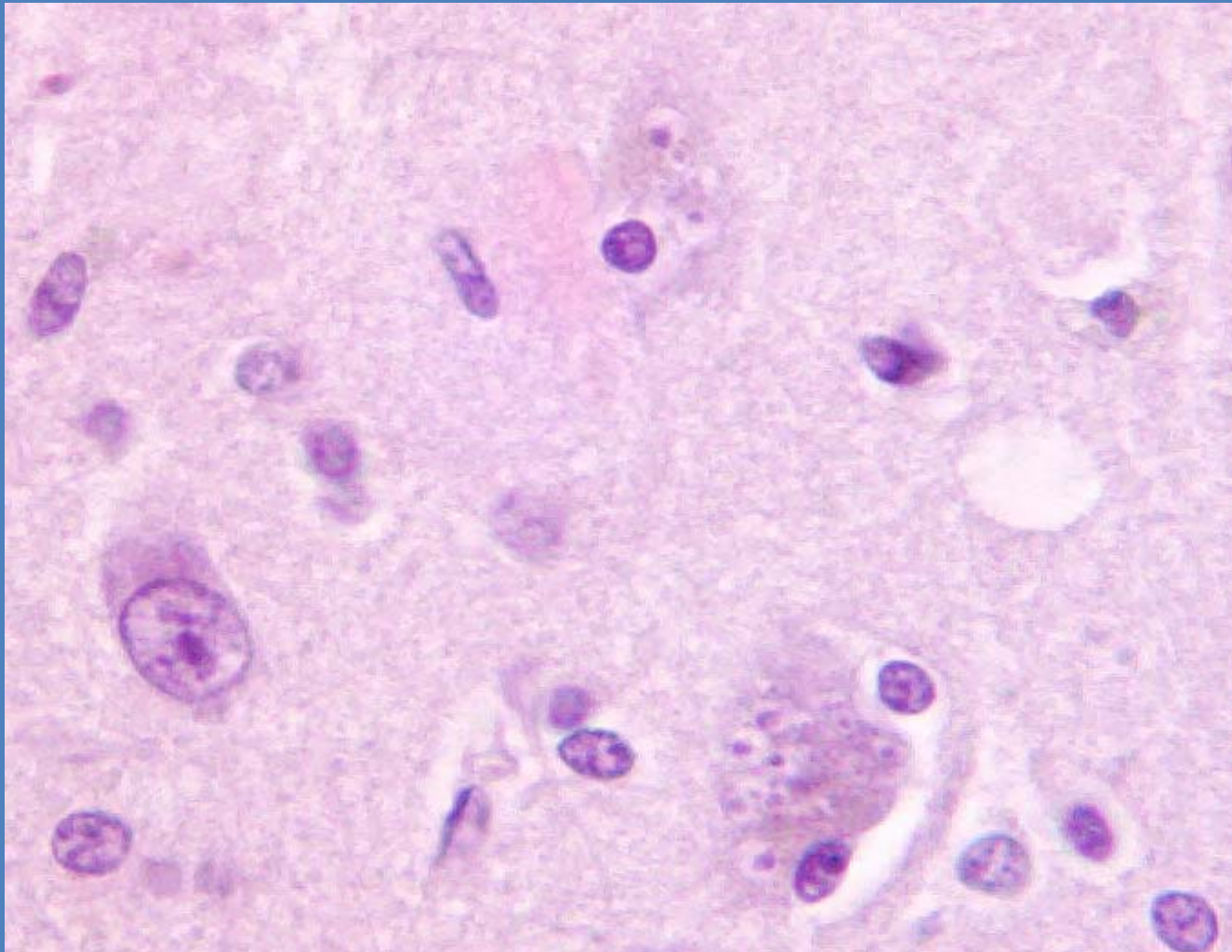
A JOHNS HOPKINS PRESS HEALTH BOOK



# Pick Body



# Granulovacuolar Degeneration



# CONCLUSIONS

Table 1  
Stages in the evolution of PD-related pathology

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Stage 1 <i>N</i> = 21; medulla oblongata	Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone
Stage 2 <i>N</i> = 13; medulla oblongata and pontine tegmentum	Pathology of stage 1 plus lesions in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus–subcoeruleus complex
Stage 3 <i>N</i> = 24; midbrain	Pathology of stage 2 plus midbrain lesions, in particular in the pars compacta of the substantia nigra
Stage 4 <i>N</i> = 24; basal prosencephalon and mesocortex	Pathology of stage 3 plus prosencephalic lesions. Cortical involvement is confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus). The neocortex is unaffected
Stage 5 <i>N</i> = 17; neocortex	Pathology of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex
Stage 6 <i>N</i> = 11; neocortex	Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field

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## Gastric $\alpha$ -synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology

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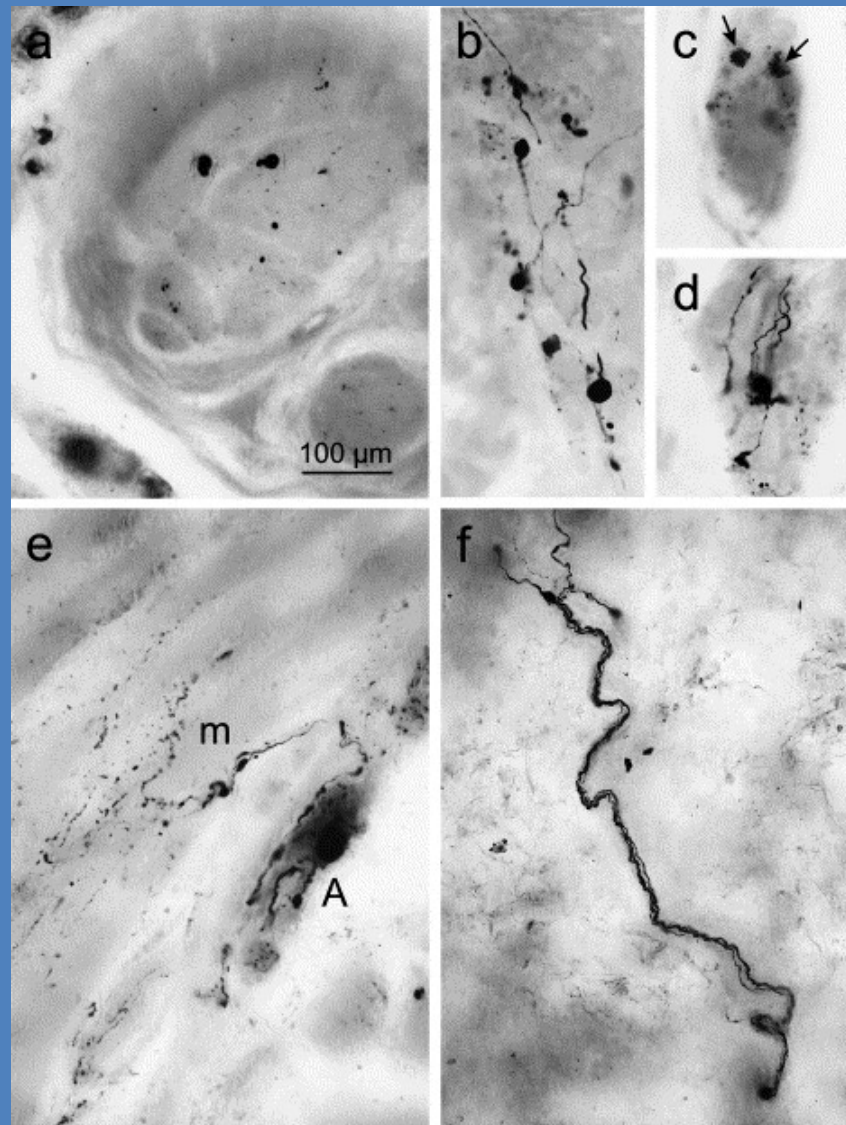


Fig. 1. Aggregated  $\alpha$ -synuclein inclusions in the gastric wall. (a) Immunoreactive inclusions in axons within a peripheral nerve (transverse section) passing through the fundic adventitia (case 4). (b–d) LNs and LBs in the Auerbach plexus of case 5. (b) Note not only the presence of Lewy body pathology but also the fine, immunopositive fiber network in the background. (c) Punctate  $\alpha$ -synuclein aggregations (arrows) distributed throughout the cell bodies of two ENS neurons in the fundus, probably representing early forms of LBs [17]. (d) Thread-like LNs within the fibre strands that interconnect the ganglia of the Auerbach plexus. (e) Some of the immunoreactive fibers generated from the Auerbach plexus (A) bifurcate repeatedly and split into terminal ramifications along the smooth muscle cells of the adjacent muscle layer (m) (case 3). (f) Nerve fiber bundle of Meissner's plexus coursing through the gastric submucosa of case 3. Only a few of the axons are immunoreactive. The abnormal material fills the axon and can be followed for a considerable distance. Syn-1 immunoreactions in 150  $\mu$ m cryosections. Scale bar in (a) is valid for (b–f).

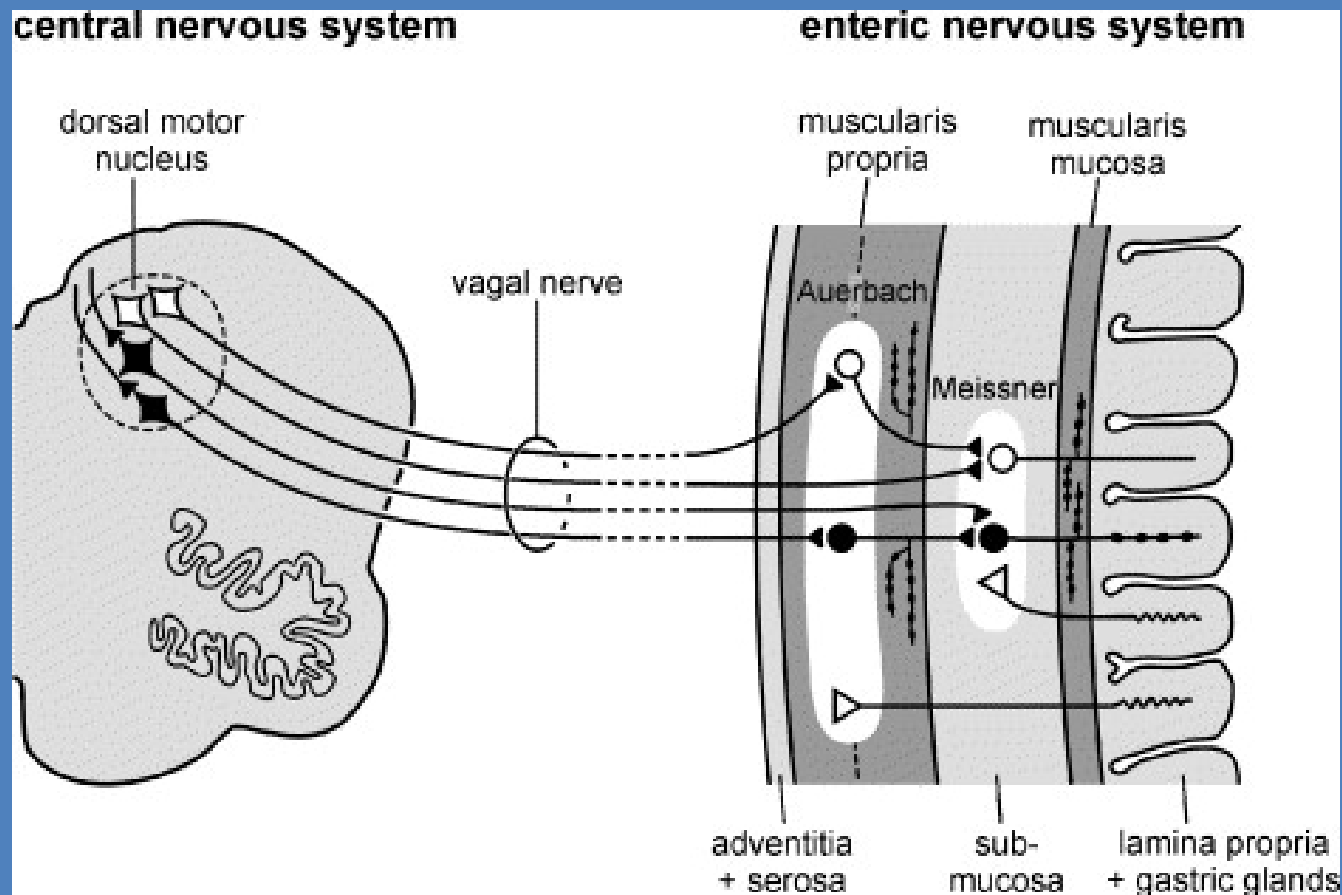


Fig. 3. Schematic diagram showing the interconnections between the enteric nervous system and brain. A neurotropic agent that succeeded in passing the mucosal epithelial barrier of the stomach could enter terminal axons of postganglionic VIPergic neurons (black, rounded cell somata) in the submucosal Meissner plexus and, via retrograde axonal and transneuronal transport (see black, rounded cell somata in the Auerbach plexus), reach the preganglionic cholinergic neurons (black, diamond-shaped cell somata) of the dorsal motor nucleus of the vagal nerve. Two triangular-shaped cells (white) represent primary viscerosensory neurons. Two white, rounded cells stand for cholinergic excitatory visceromotor neurons.

# Genes Associated with L-dopa Responsive Parkinsonism

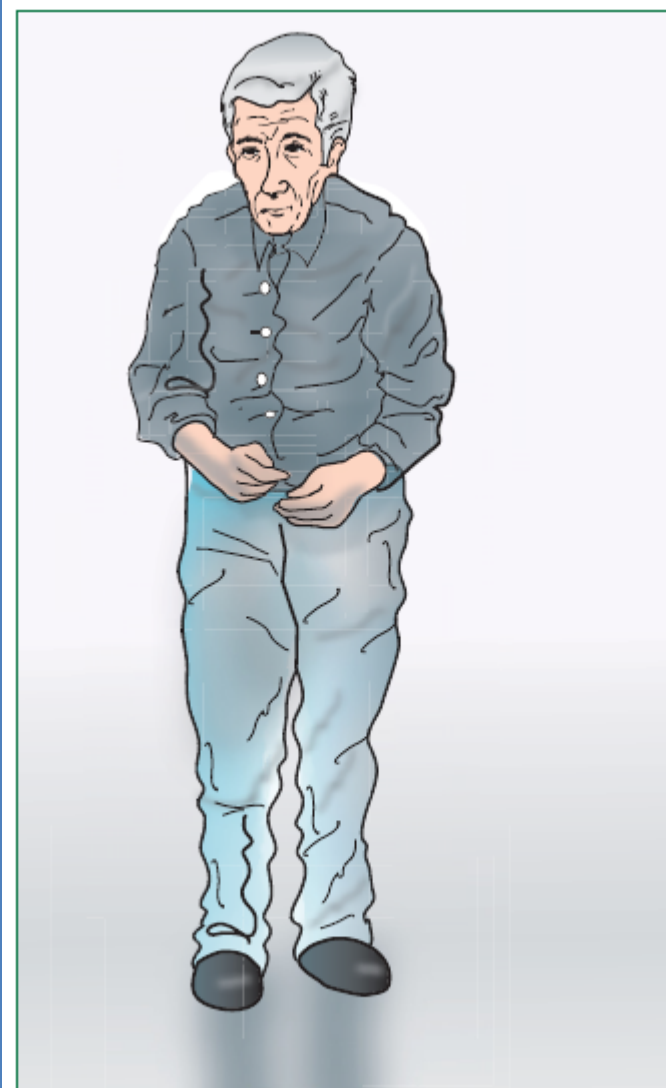
	Pathological aggregates	Comments
<b>Parkinsonism</b>		
Parkin	Substantia-nigra degeneration but usually no Lewy bodies	Recessive, young onset
<i>PINK1</i>	No pathology reported	Recessive, young onset
<i>DJ-1</i>	No pathology reported	Recessive, young onset
<i>ATP13A2</i>	No pathology reported	Recessive young onset
<b>Parkinson's disease</b>		
$\alpha$ -synuclein	Lewy bodies	Dominant point mutations and duplications. Genetic variability contributes to disease
<i>LRRK-2</i>	Usually Lewy bodies	Dominant mutations
<i>GBA</i>	Lewy bodies	Dominant loss of function mutations increase risk

*GBA*=glucocerebrosidase. *LRRK-2*=leucine rich repeat kinase 2. *PINK1*=PTEN-induced putative kinase 1.

**Table:** Genes associated to L-dopa-responsive parkinsonism

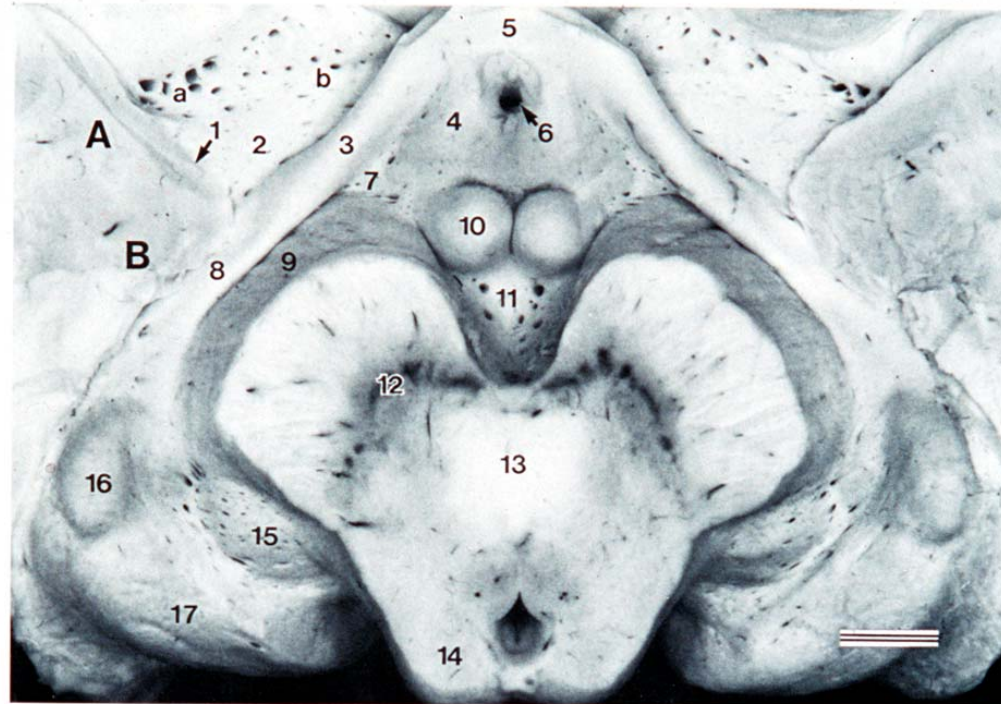
# Mysteries of Dementia

- Dementia is strongly age-associated
- The risk of dementia **DOUBLES** every five years after age 65



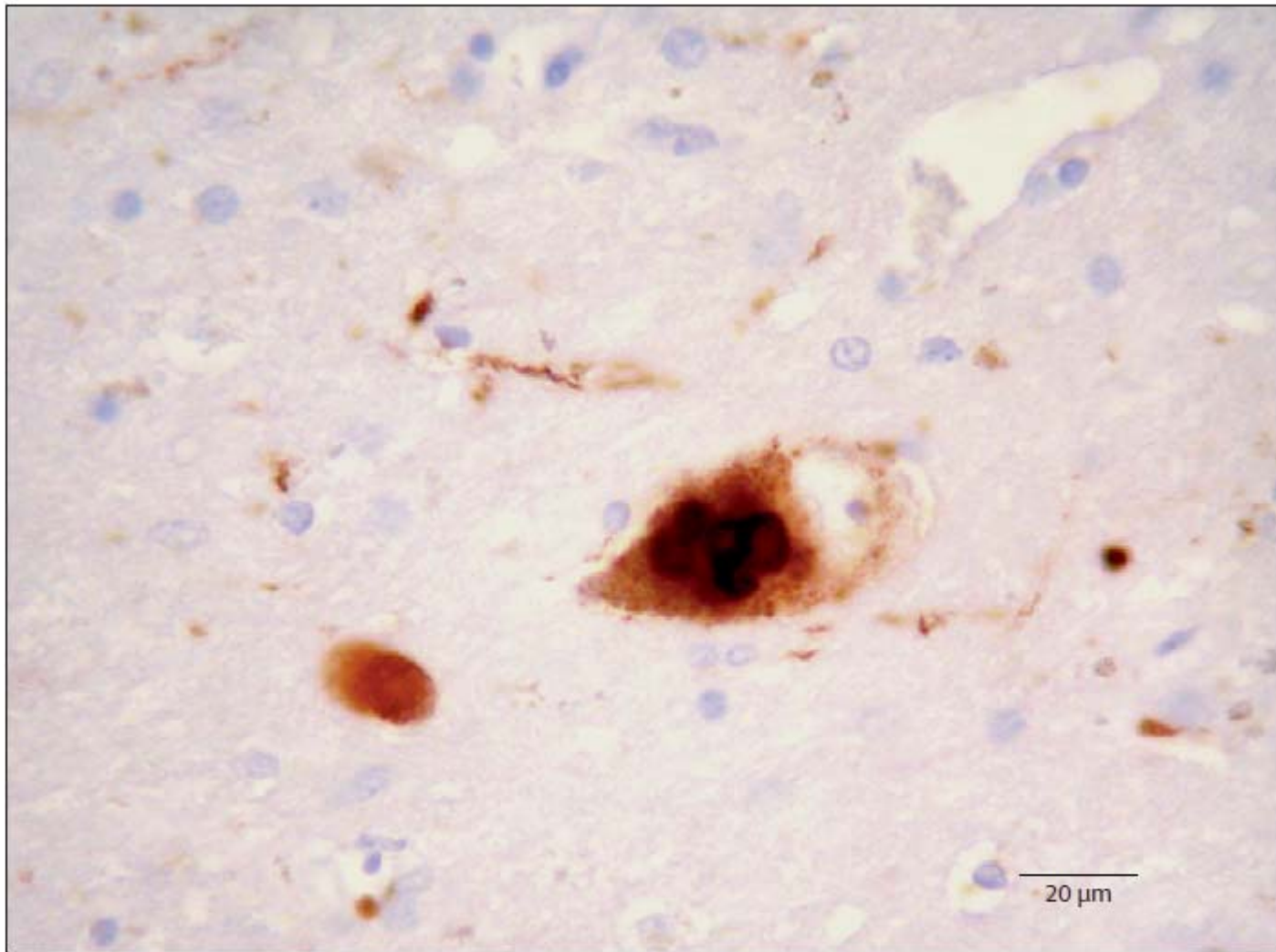
**Figure 1:** Illustration of the slightly anxious frozen face and characteristic flexed posture of a Parkinson's disease patient (courtesy of Nathalie Lees)

# Substantia Nigra

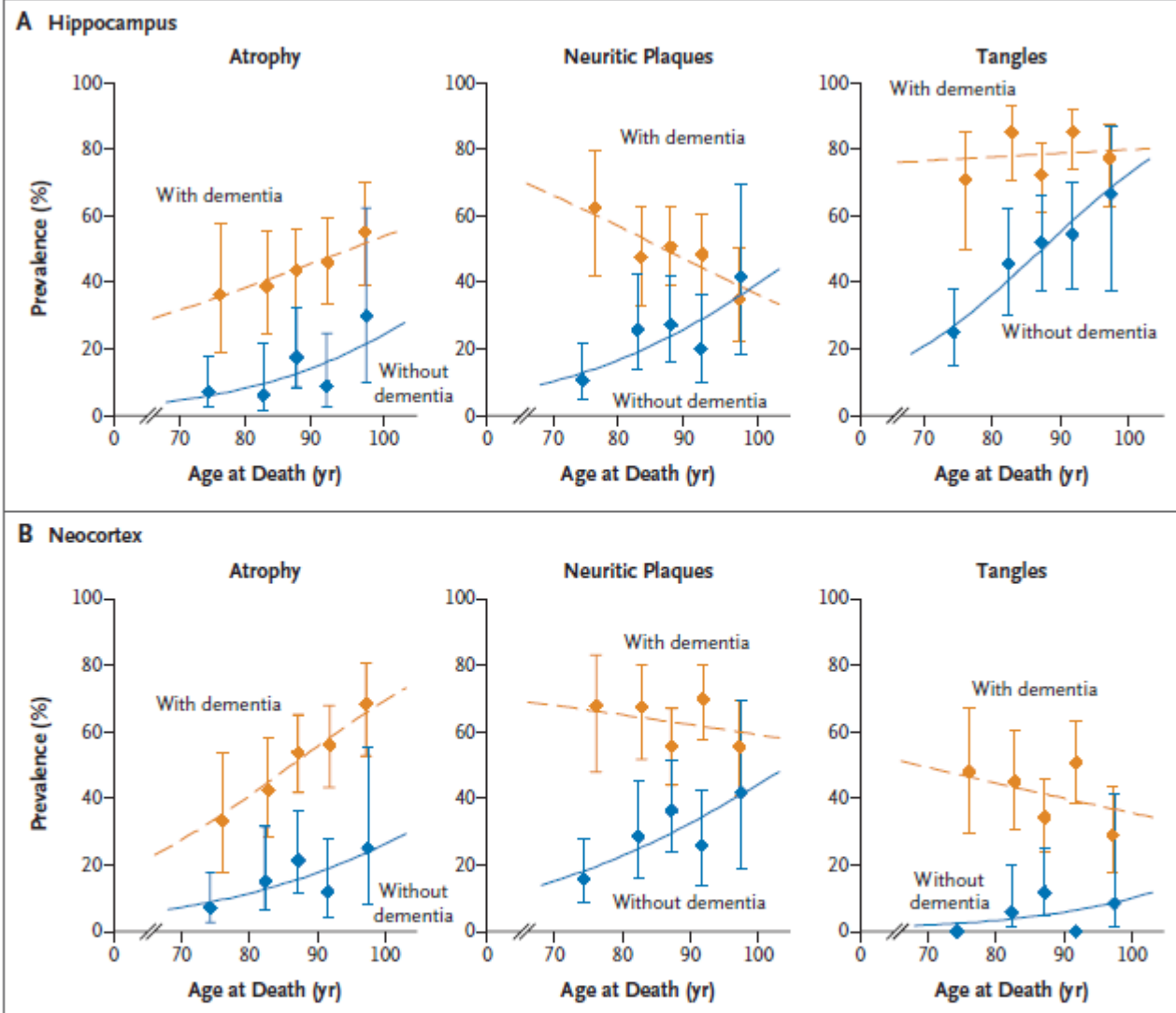


**Fig. 21 B.** Inferior cerebral aspect to show relation of the uncus to basal structures. The uncus and the mesencephalon have been cut off. (Bar: 5.5 mm)

- |    |   |      |                                    |  |  |
|----|---|------|------------------------------------|--|--|
| A  | Anterior segment of the uncus:                          | 5    | Optic chiasma                      |  |  |
| 1  | Endorhinal sulcus                                       | 6    | Infundibulum                       | penetration point of thalamoperforating arteries |  |
| 2  | Anterior perforated substance                           | 7    | Lateral perforated substance       | 12   | Substantia nigra   |
| a: | Penetration point of lateral lenticulo-striate arteries | B    | Posterior segment of the uncus:    | 13   | Brachium conjunctivum  |
| b: | Penetration point of medial lenticulo-striate arteries  | - 8  | Optic tract                        | 14   | Inferior colliculus  |
| 3  | Optic tract   | - 9  | Crus cerebri                       | 15   | Medial geniculate body and penetration point of thalamogeniculate arteries |
| 4  | Lateral tuber   | - 10 | Mamillary body                     | 16   | Lateral geniculate body  |
|    |   | - 11 | Posterior perforated substance and | 17   | Pulvinar   |



**Figure 2:** Light microscopy of a surviving neuron in the substantia nigra of a patient with Parkinson's disease. The neuron is full of  $\alpha$ -synuclein Lewy bodies.



**Figure 1. Modeled and Observed Prevalence of Moderate or Severe Pathological Lesions According to Age.**

Persons who died with dementia (yellow) are compared with those who died without dementia (blue). Filled symbols represent the observed prevalence of moderate or severe pathological lesions, and I bars show the 95% confidence intervals. The solid and broken lines represent modeled prevalence values.

# Mysteries of Dementia

- Dementia is strongly age-associated
- The risk of dementia **DOUBLES** every five years after age 65
- Why does disease progression follow a pattern that is unique for each disease?
- There are multiple 'causes' of each disease that can lead to dementia
- Where will we care for people with dementia?