Research Advances in Neurodegenerative Diseases: Alzheimer & Parkinson

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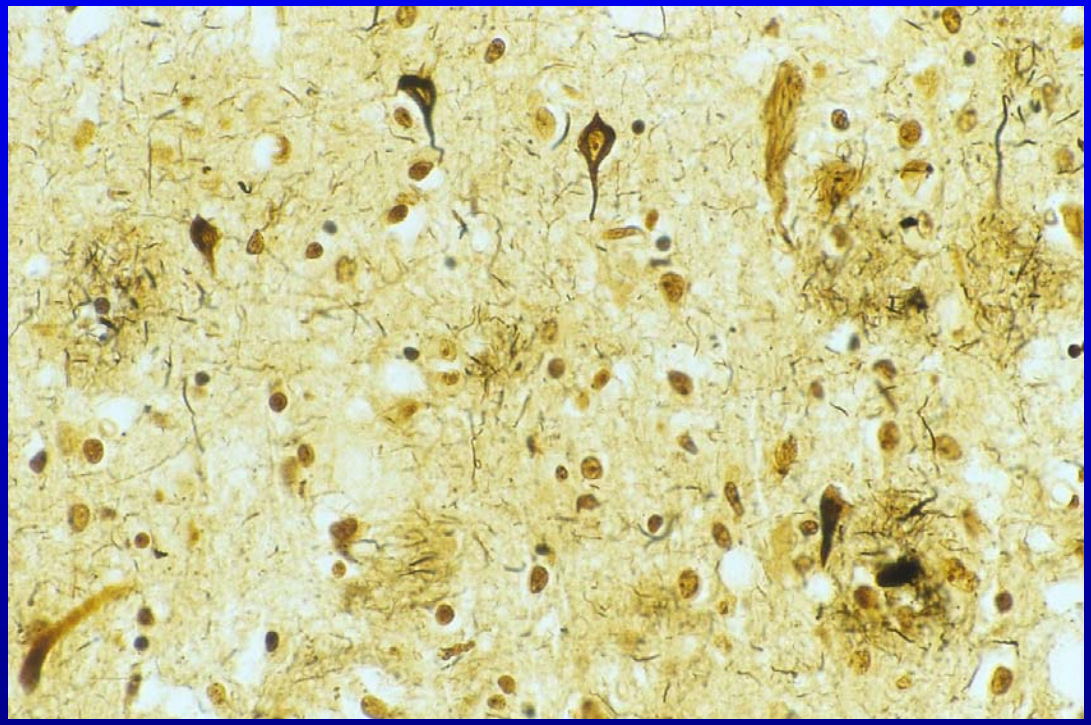
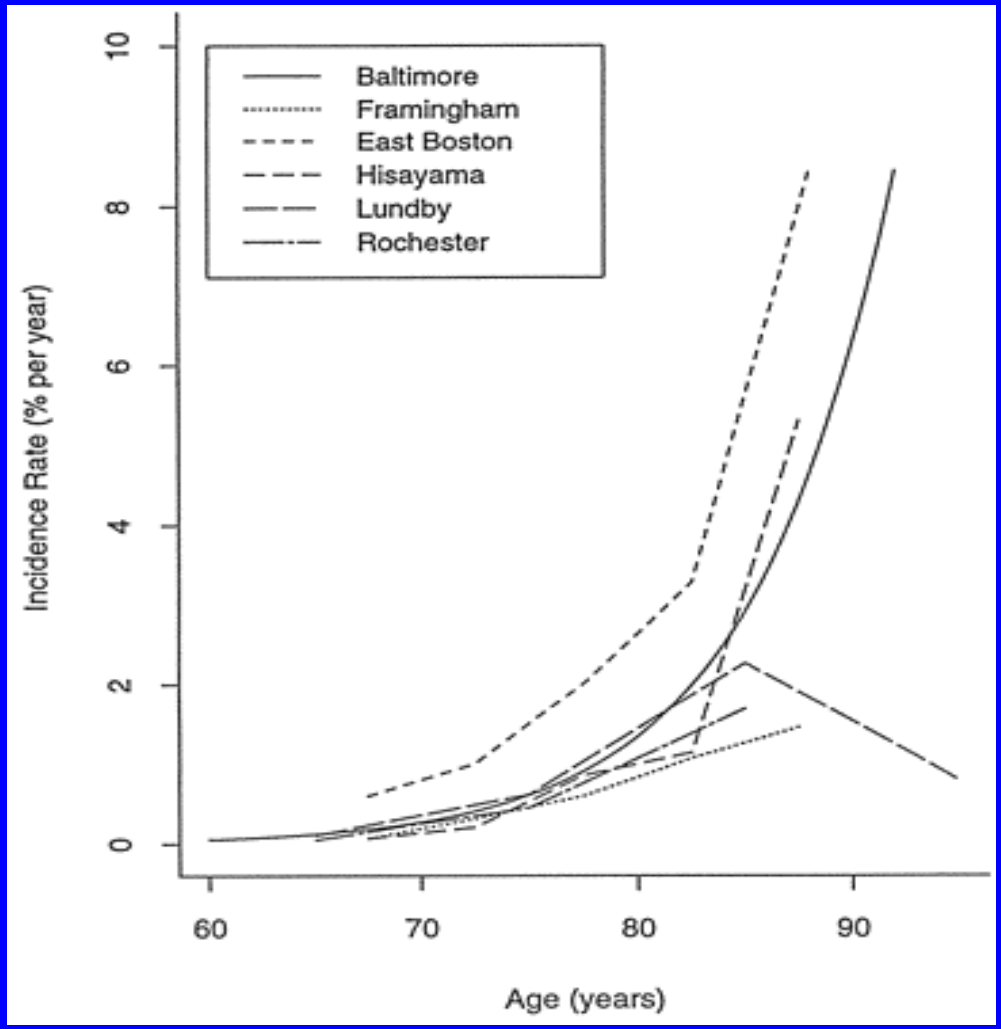
Alzheimer

Neuropathologic Hallmarks of AD Include Neurofibrillary Tangles and Neuritic Plaques



The incidence of AD increases from <1%/year at age 60-65 to 6.5% at age 85+

Kawas et al. Neurology 2000;54:2074-2077



Clinical Features of AD

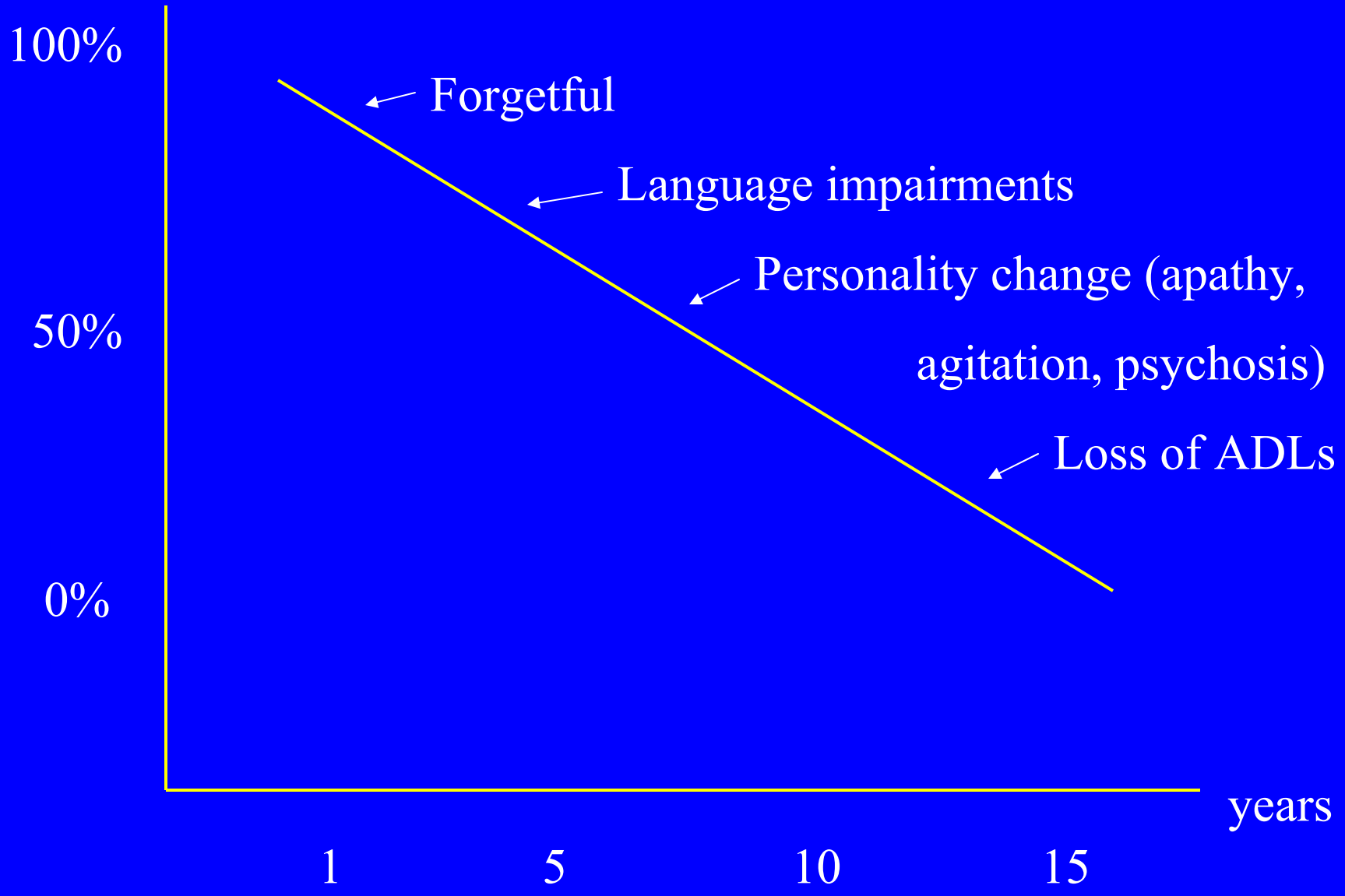
- Amnesia – memory loss
- Aphasia – loss of speech
- Apraxia – inability to handle objects
- Visuospatial deficit
- Executive function impaired – impaired reasoning abilities
- Personality change
- Psychosis – hallucinations

- Normal Strength
- Normal Coordination
- Normal Sensation
- Normal Balance
- Normal Gait

Clinical Features of AD: Family Perspective

- Repeatedly asking the same questions
- Obstinance - “Nothing wrong with me”
- Motor restlessness, pacing, shouting
- Fearful, afraid to be left alone…”follows me everywhere”
- Delusions, hallucinations
- Sleeplessness, day-night reversal
- Getting worse day by day
- Resists changing clothes, bathing
- Aggressive physically

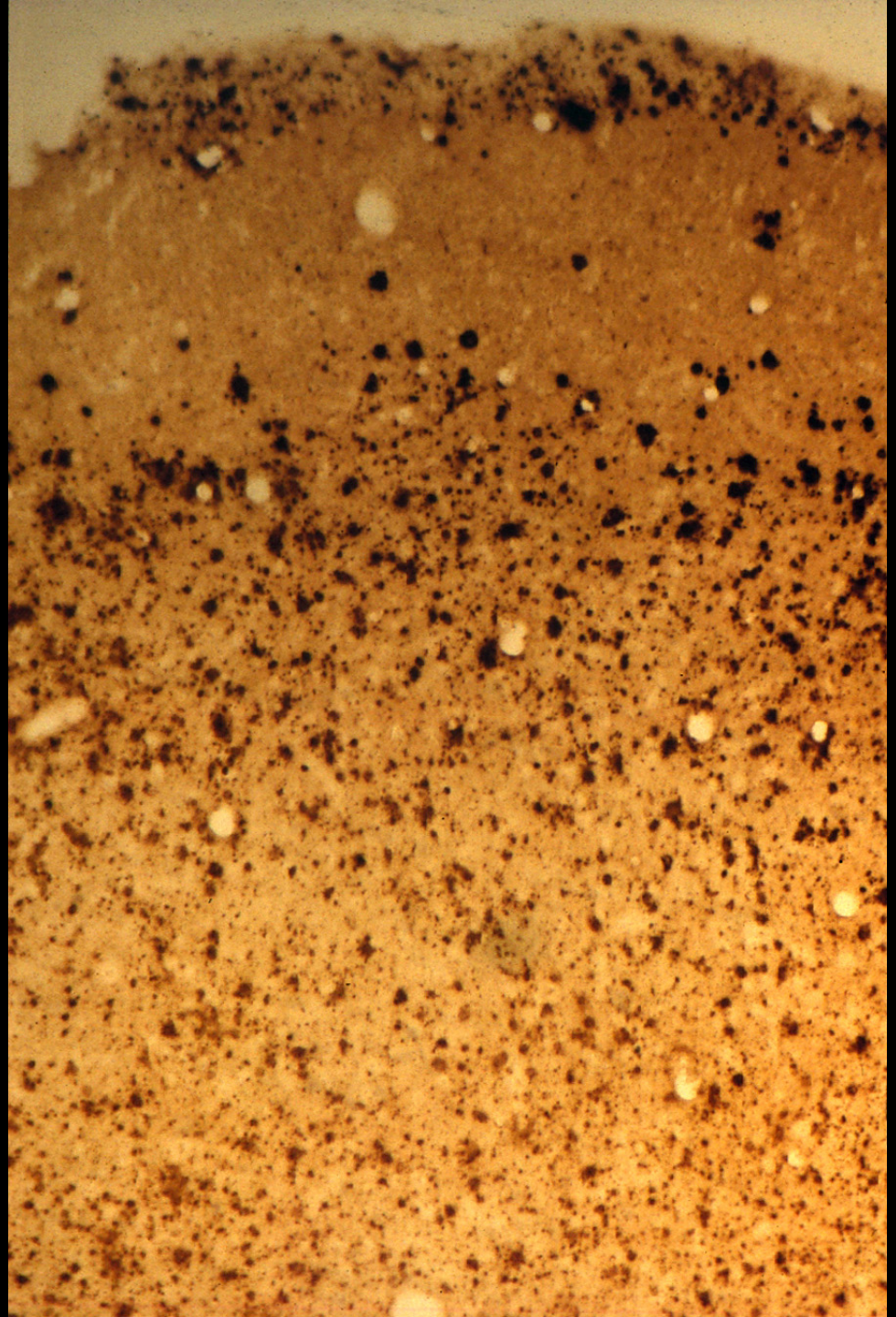
The Stereotyped Course of AD is Steady Progressive Deterioration



FDA approved drugs for AD

- Tacrine 40-120 mg/day. Rarely Rxd now because of liver toxicity.
- Aricept (donepezil) 5-10 mg/day
- Exelon (rivastigmine) 3-6 mg bid
- Reminyl (galantamine) 4-12 mg bid
- Namenda (memantine) 10 mg bid

All induce similar short-term improvement in cognitive test scores in some but not all patients and may slow dementia progression somewhat.



Genetic Aspects of AD

Early-Onset Autosomal Dominant Familial AD. Rare, <5% of all AD cases.

APP	**Chromosome 21**	**onset 40-50s**
PS 1	**Chromosome 14**	**onset 30-50s**
PS 2	**Chromosome 1**	**onset 40-60s**

Late-Onset (>60 years old) AD. Risk factor polymorphisms in genes for:

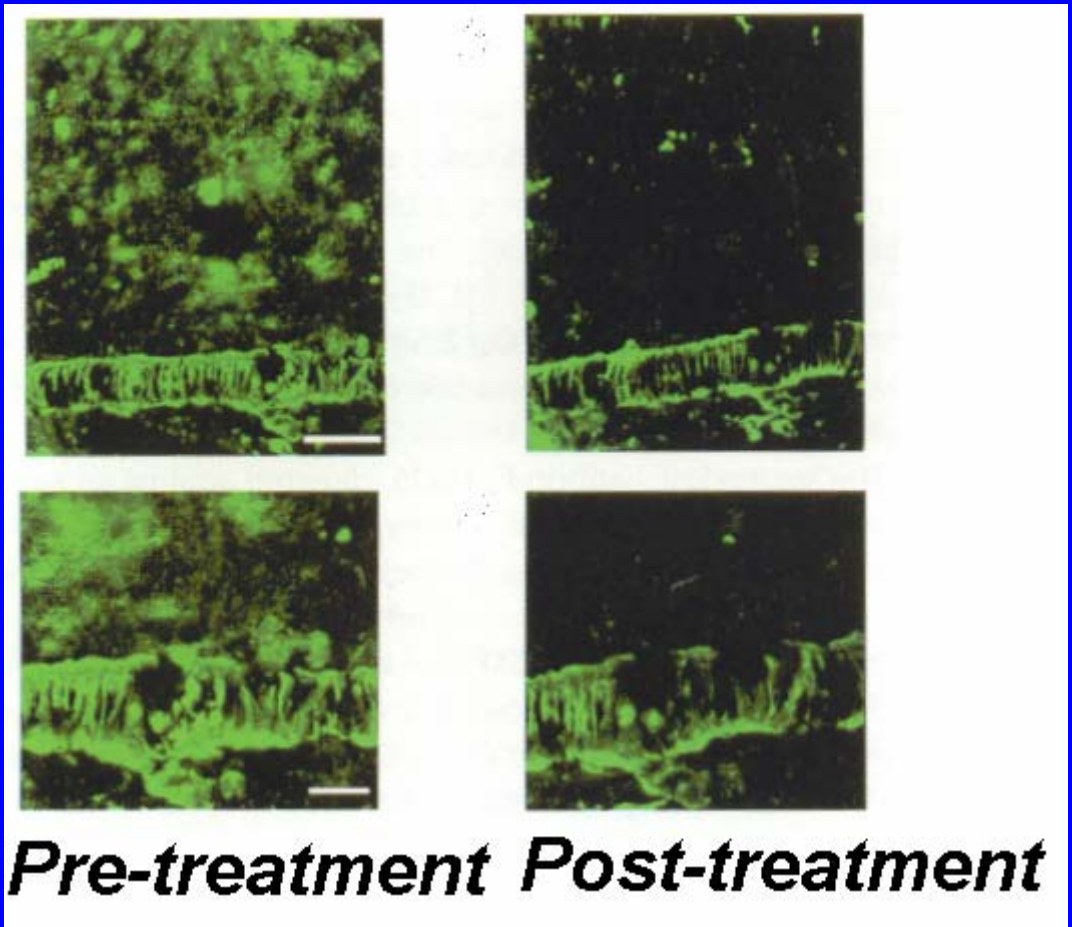
APOE - best known & influences 30-40% of AD onset 60-75 years old.

α2Macroglobulin, Cystatin C, ubiquilin, LRP, IL-1 & 20 other gene association risk factors are likely but are less well established.

The Amyloid Hypothesis of AD

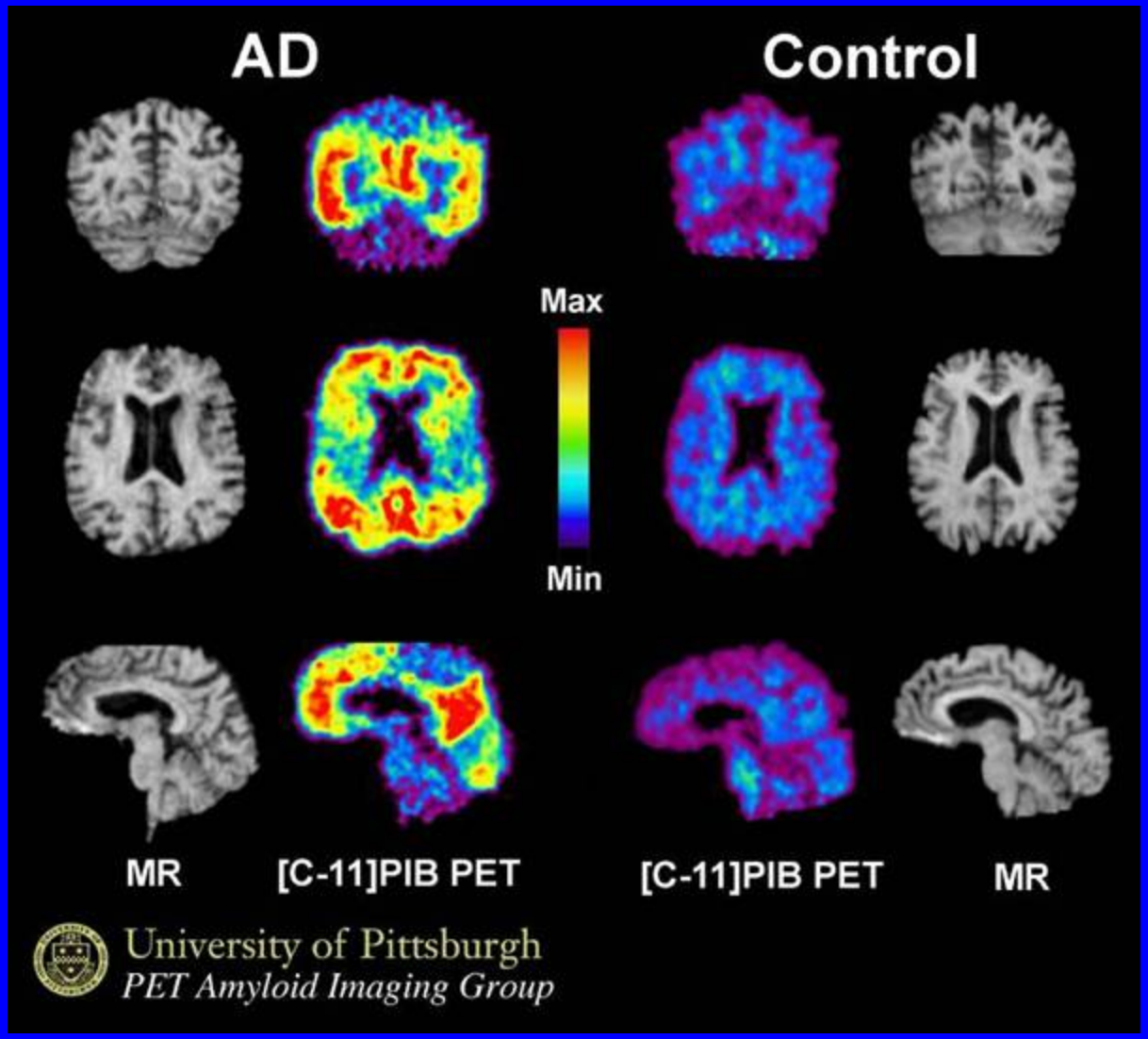
- Neuropathology. Senile plaques with Aβ deposits in brain are an early event in AD.
- Experimental. Aβ, especially the 1-42 peptide, promotes neurofibrillary tangle formation and neuronal death.
- Genetic. All genetic causes of AD increase Aβ in brain. All Down syndrome patients with trisomy 21 have excess amyloid in the brain and eventually develop AD pathology.

Anti-Aβ antibody treatment clears plaques



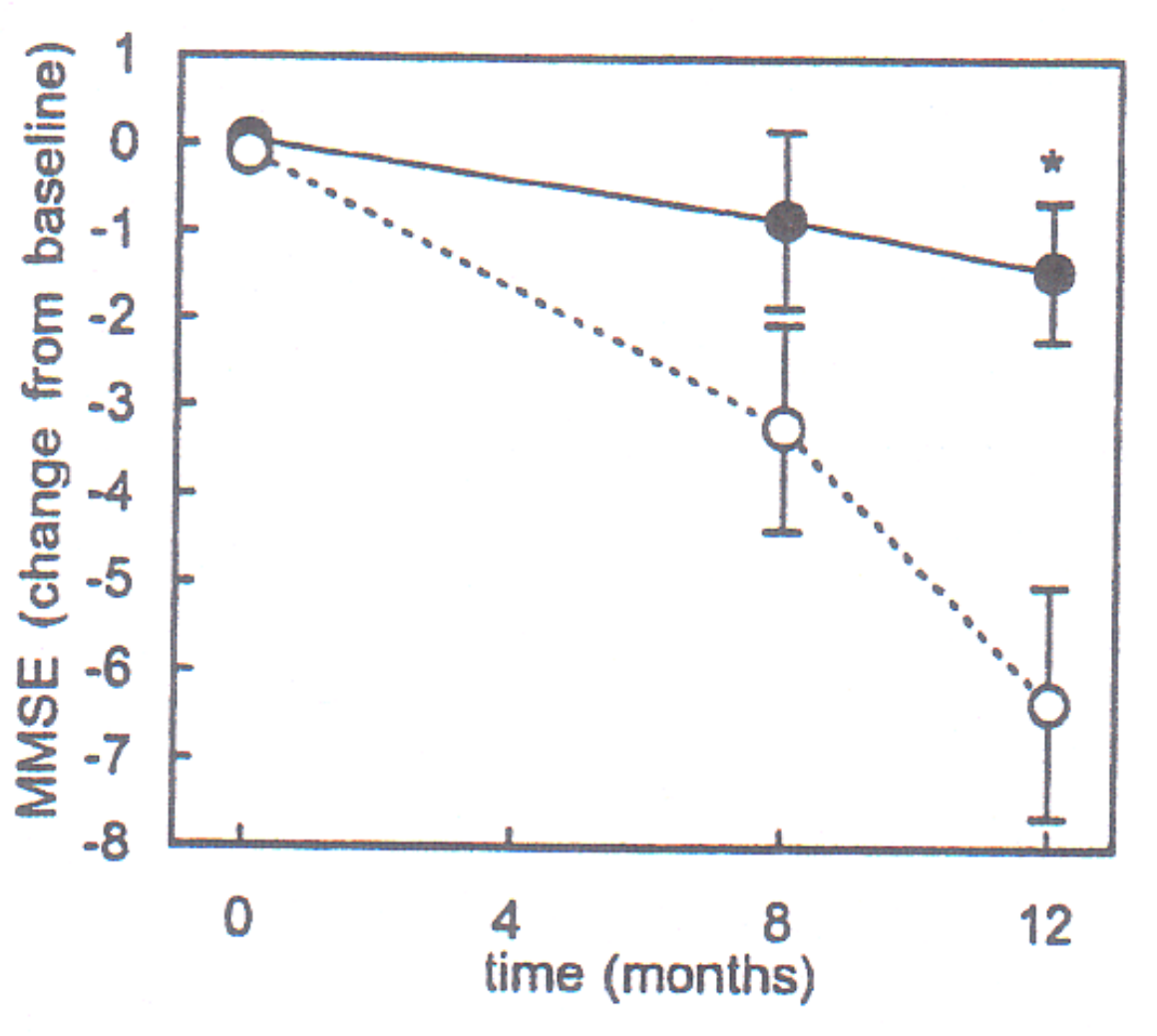
Bacskai et al 2001

Novel biomarkers: Diagnostic PET



Antibodies against β-amyloid slow cognitive decline in AD

Hock et al. Neuron 38:547-554, 2003



MMSE scores of dementia severity. AD patients who generated antibodies (n=19; black circles) tested better (* p<.008) than those without antibodies.

AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

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FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

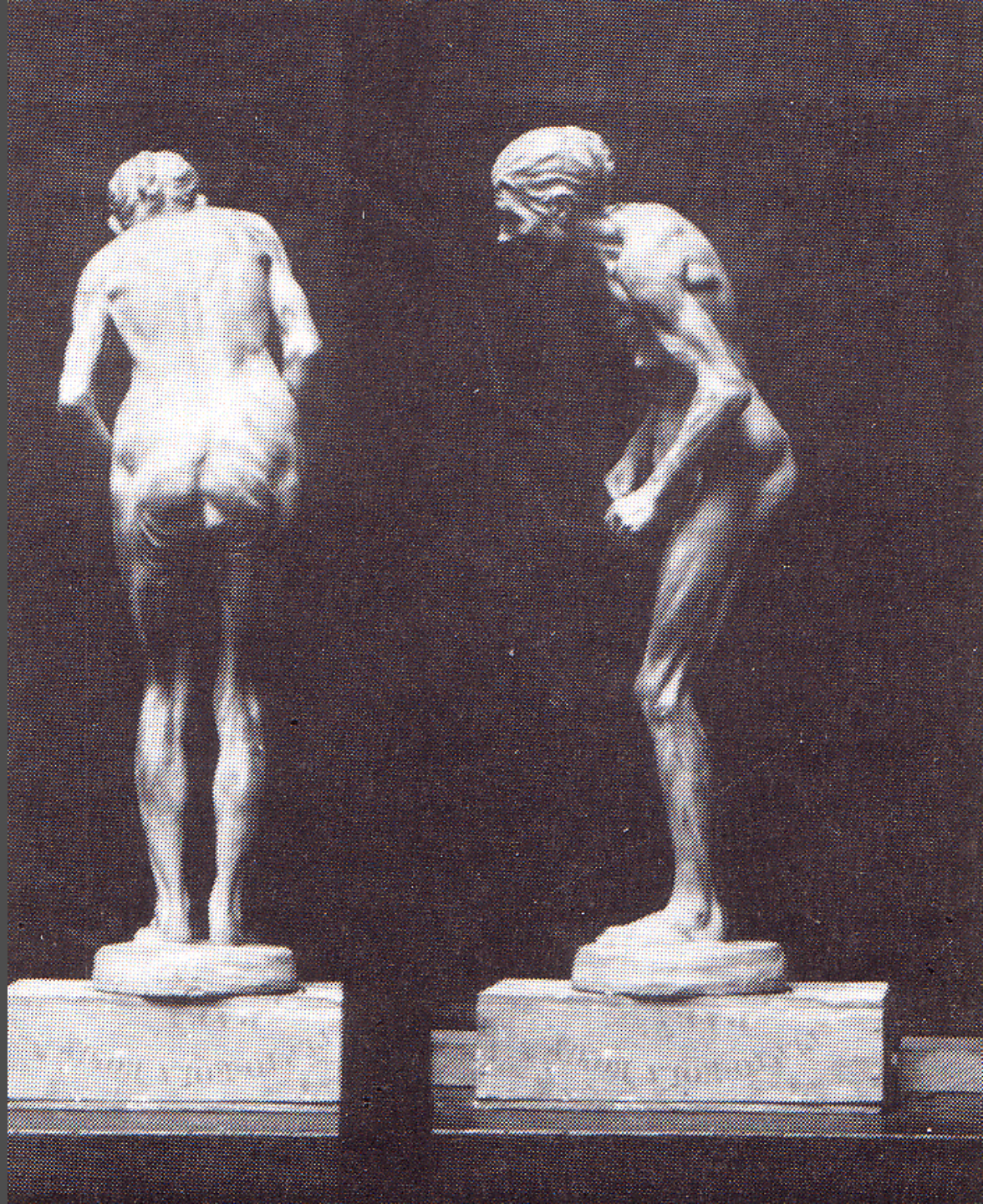
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

THE term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-

Statuette d’une femme atteinte de la maladie de Parkinson



Platre patine de Paul Richer

Epidemiology of Parkinson's Disease

Prevalence: 150-200/100,000

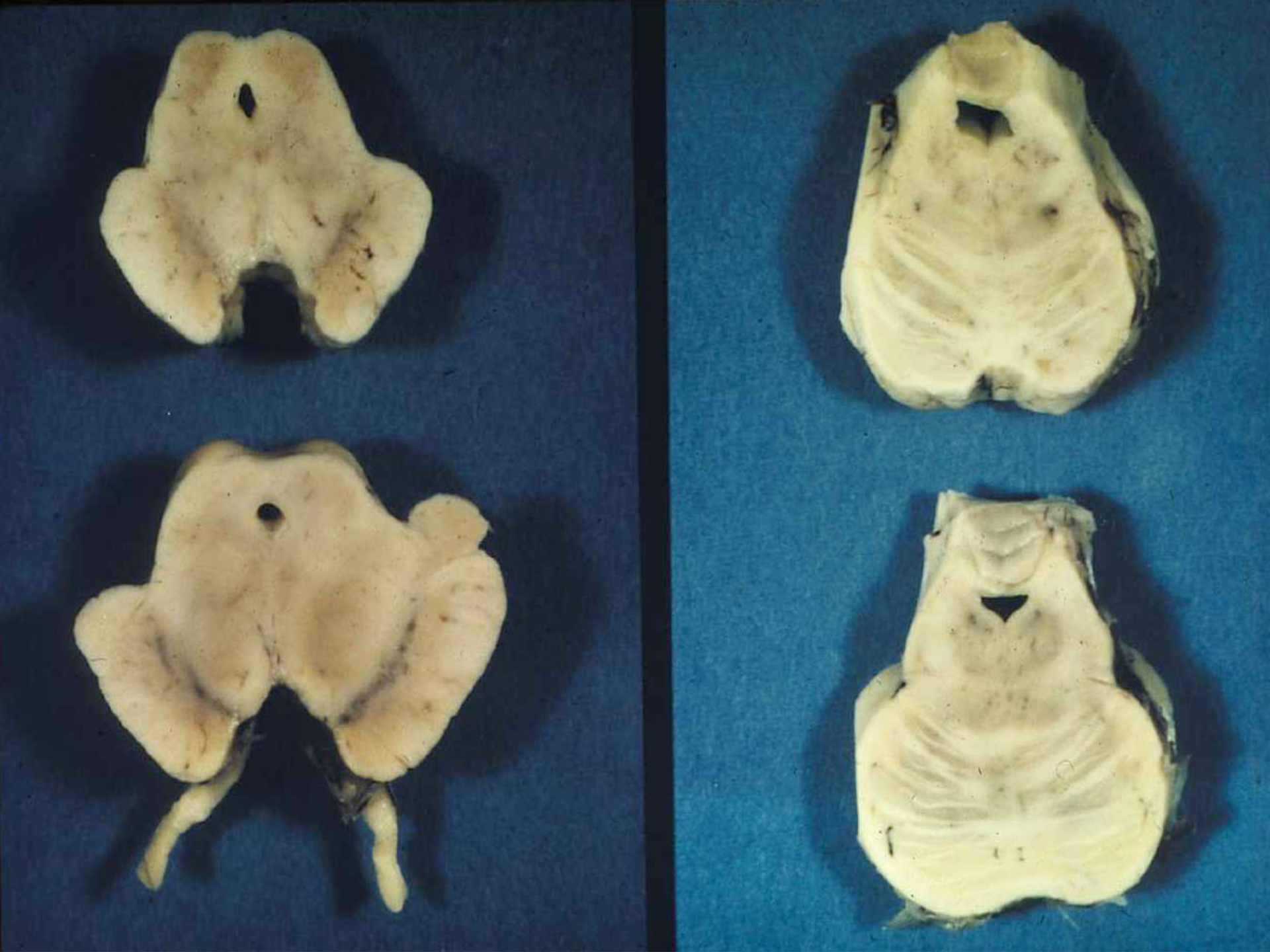
Incidence: 20/100,000

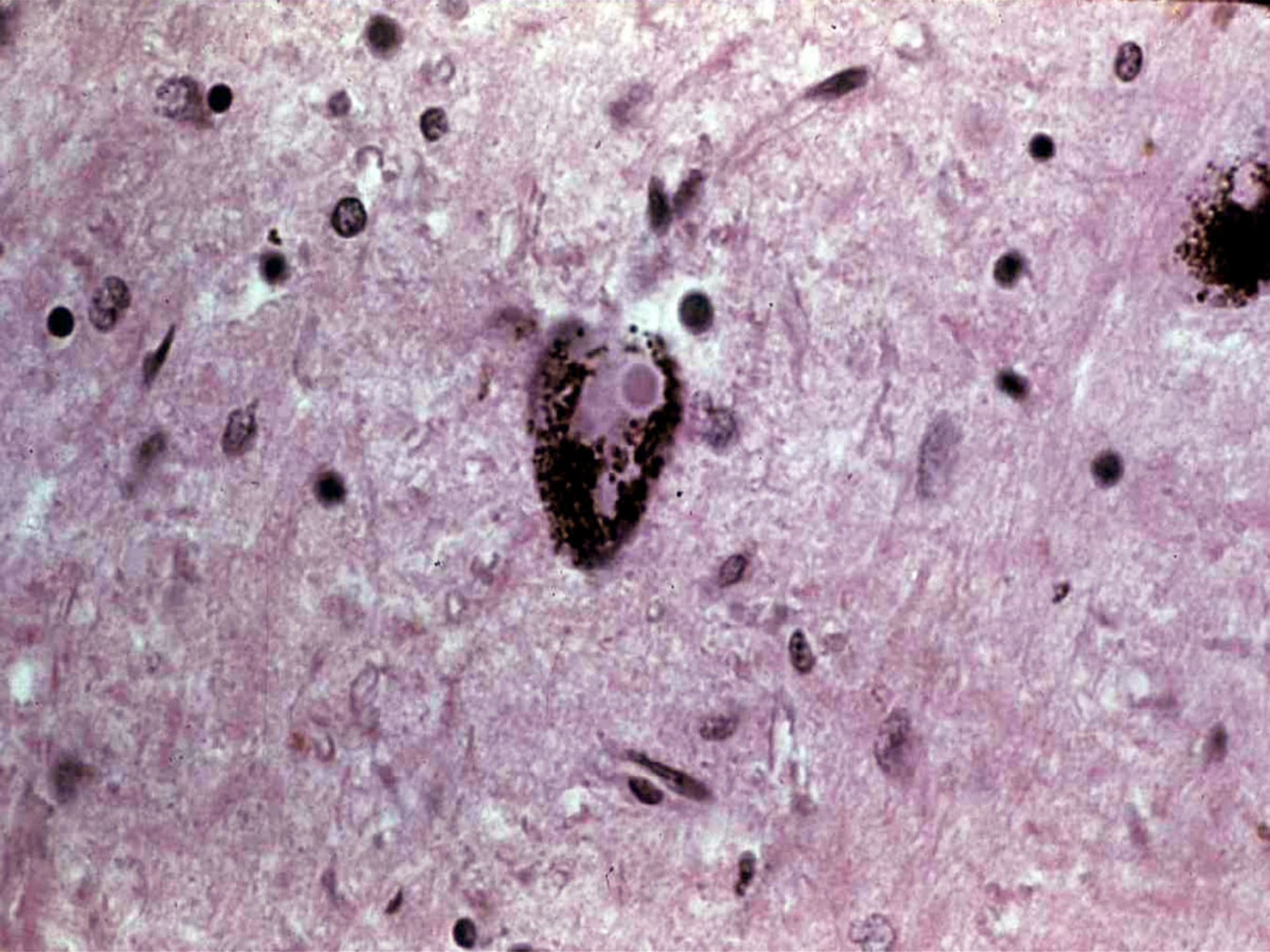
Slight male predominance: male:female = 1.2:1

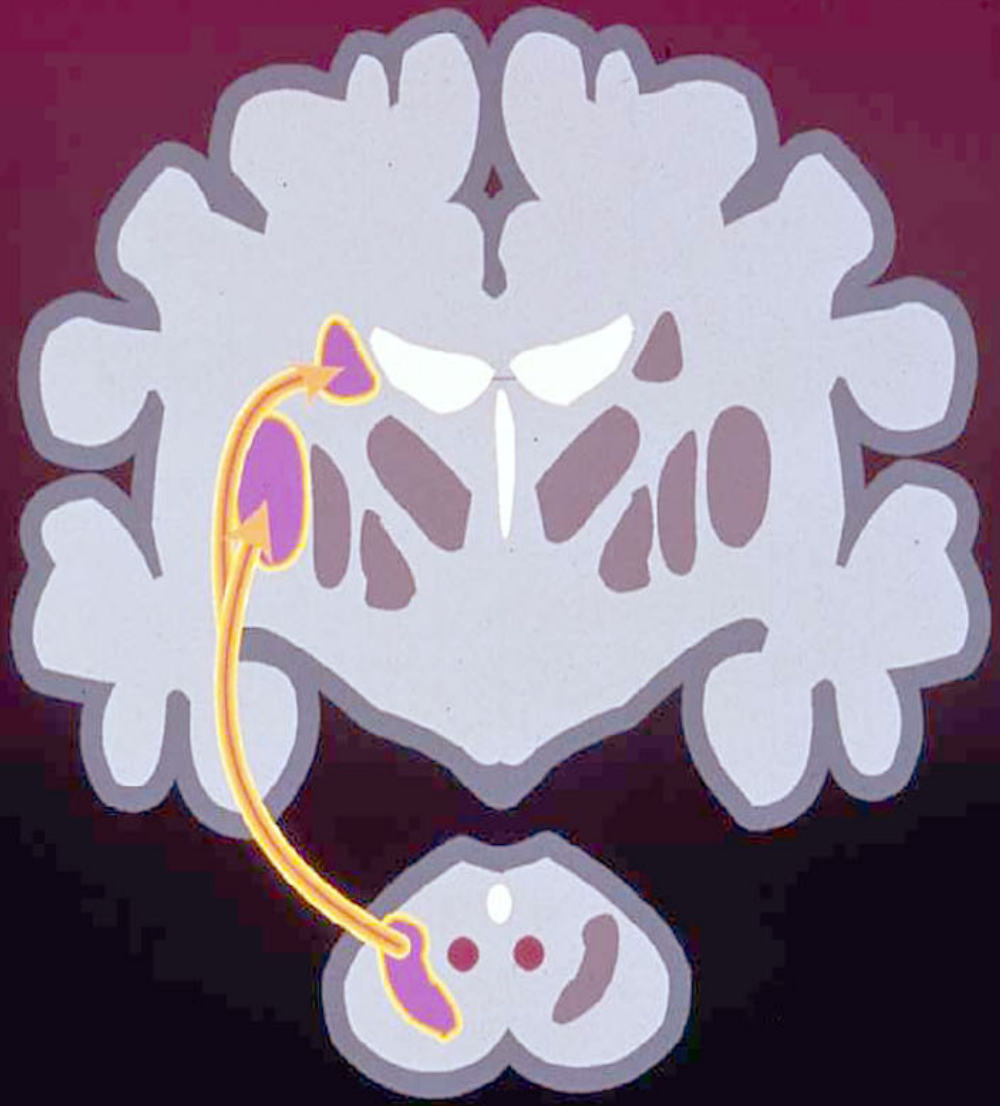
PD is the most common basal ganglia disease, and the second most common neurodegenerative disease, after Alzheimer's disease.

Cardinal Signs of PD

- Resting Tremor, often unilateral onset
- Muscular Rigidity, often “cogwheel”
- Bradykinesia
- Gait abnormality, often with reflex postural impairment
- Psychiatric symptoms, e.g. Depression
- Cognitive Impairments, often leading to Dementia







PSG

Levodopa Improves Motor Performance in PD

Figure 1. Levodopa administration significantly decreased UPDRS scores (improved motor performance).

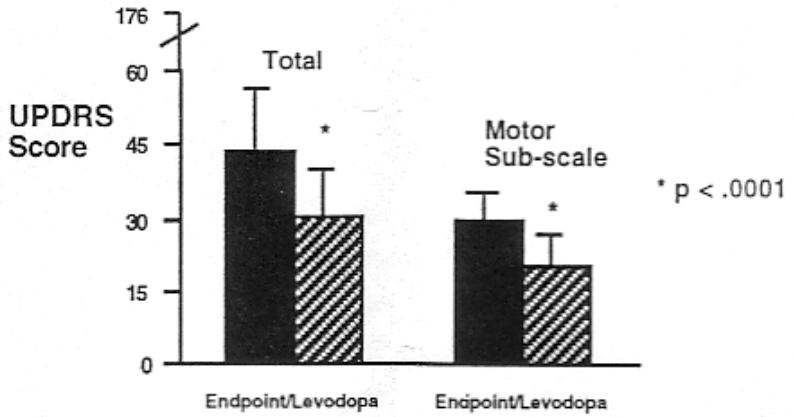
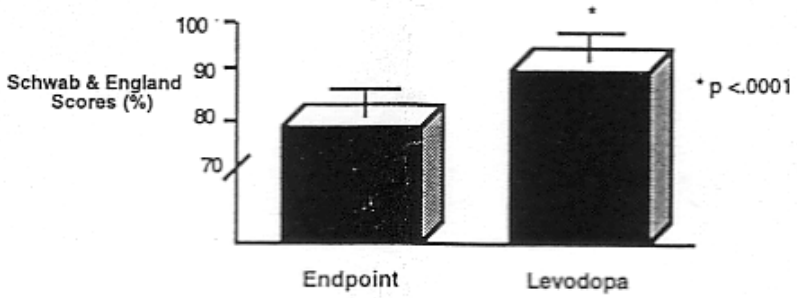


Figure 2. Levodopa administration significantly improved functional activities.



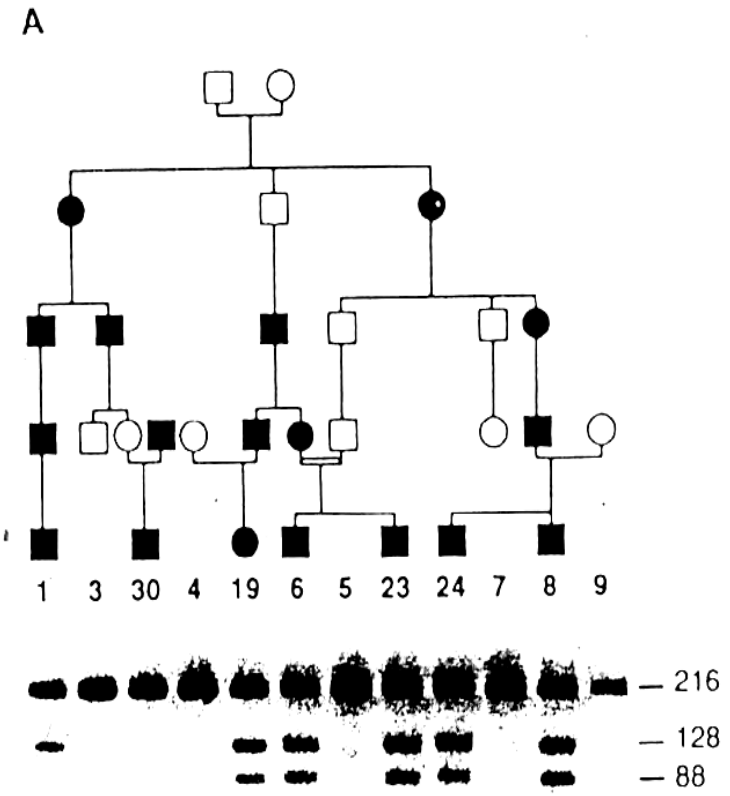
Growdon et al., Neurology 1998;50:1327-1331

Clinical Course of PD

- Mean onset 60 years old
- Duration of illness ranges from 5-25 years
- Most patients retain benefit from DAergic Rx, but many develop dyskinesias over time
- Specific cognitive deficits are common early in PD, & dementia is common late
- Depression affects 50% of PD patients
- All current medical & surgical treatments provide temporary symptomatic benefit; there is a pressing need for preventive and curative therapies

G209A mutation in the *a-synuclein* gene causes autosomal dominant PD

- Polymeropoulos et al.



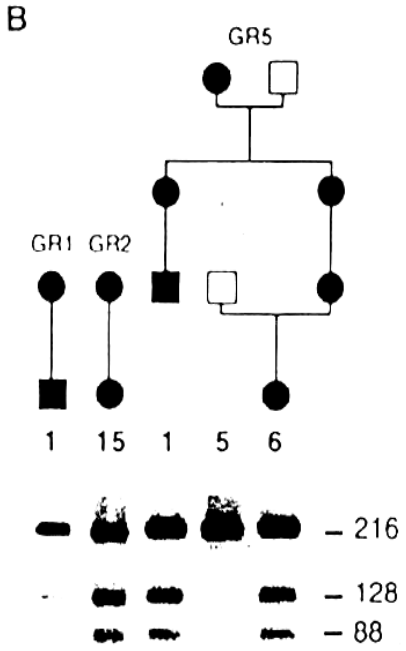
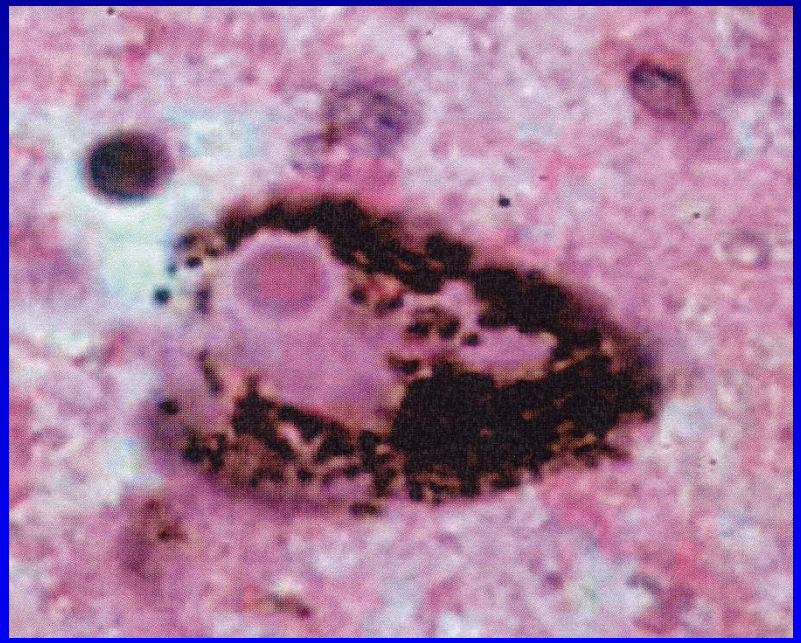


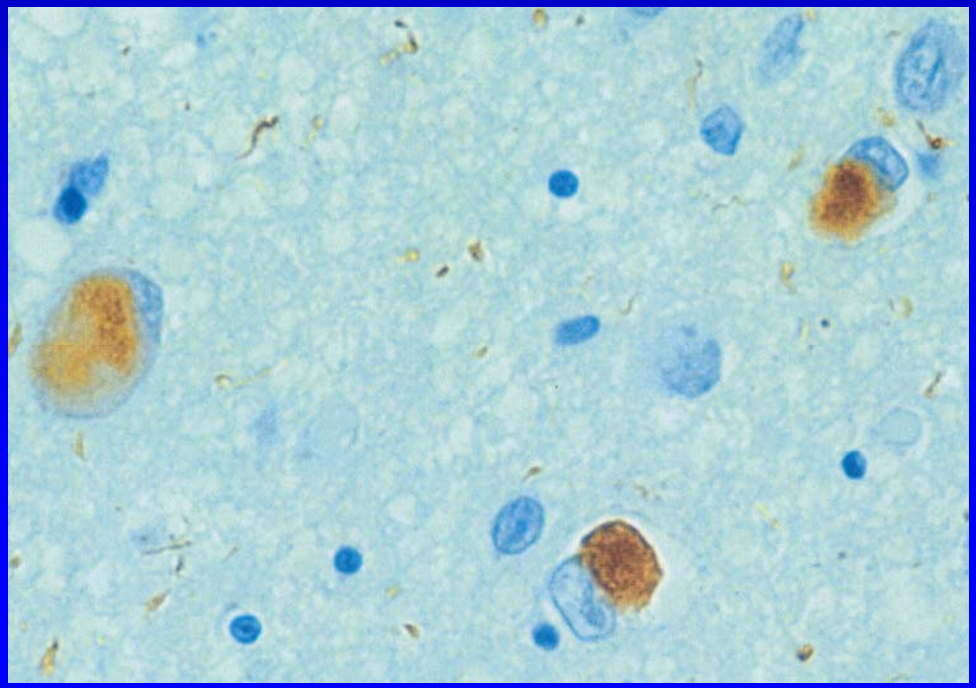
Fig. 2. Mutation analysis of the G209A change is shown in a subpedigree of the Italian kindred (**A**) and the three (GR1, GR2, GR5) Greek PD kindreds (**B**). Filled symbols represent affected individuals. Numerical identifiers denote the individuals immediately above. Isp45 I digestion of PCR products (5) is shown at the bottom of the figure, and fragment sizes are indicated on the right in base pairs.

Biomarkers for Lewy Body Diseases

Idiopathic PD

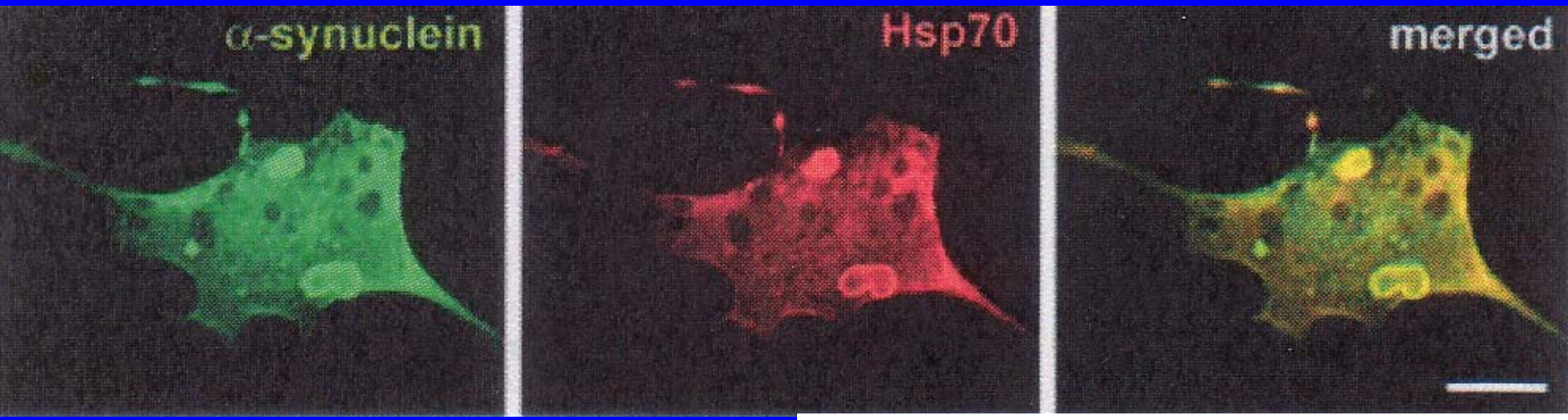


α-synuclein immunostain



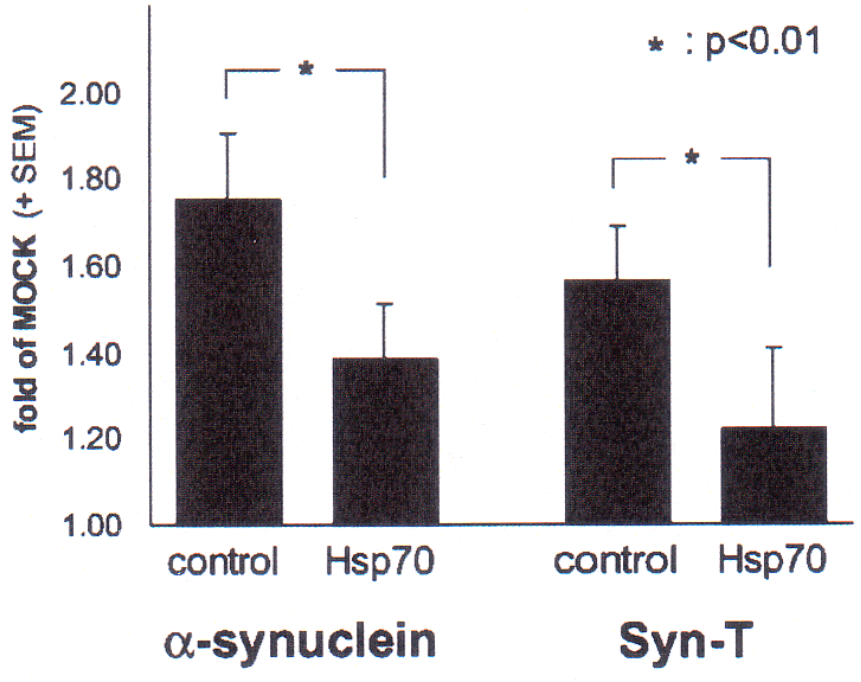
Hsp70 reduces α-synuclein aggregation and toxicity

Klucken et al. JBC 2004



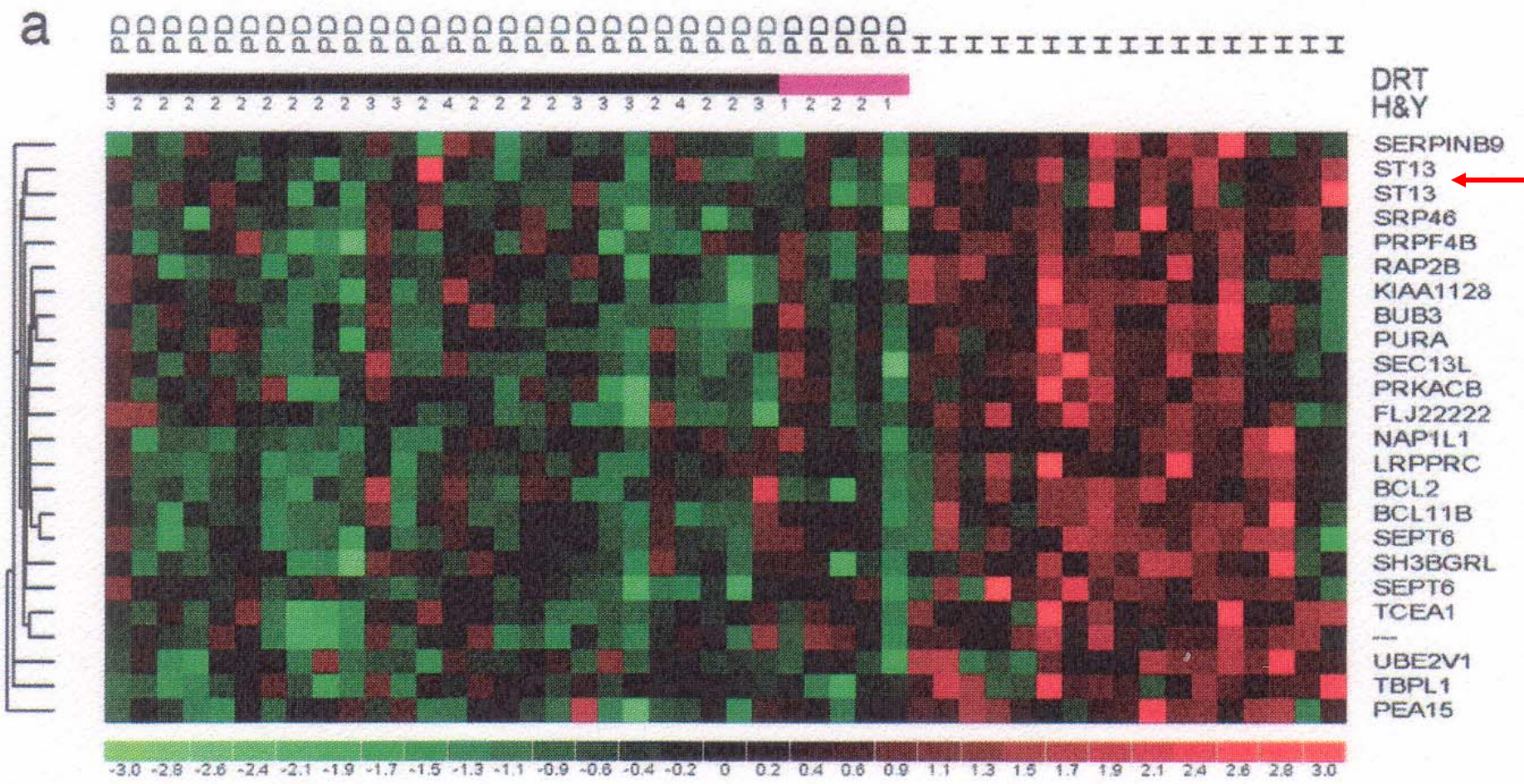
↑ α-synuclein and Hsp70 co-localize in H4 neuroglioma cells

Hsp70 protects against wild-type and C-terminal tagged (Syn-T) α-synuclein toxicity *in vitro* ($p<0.01$) →



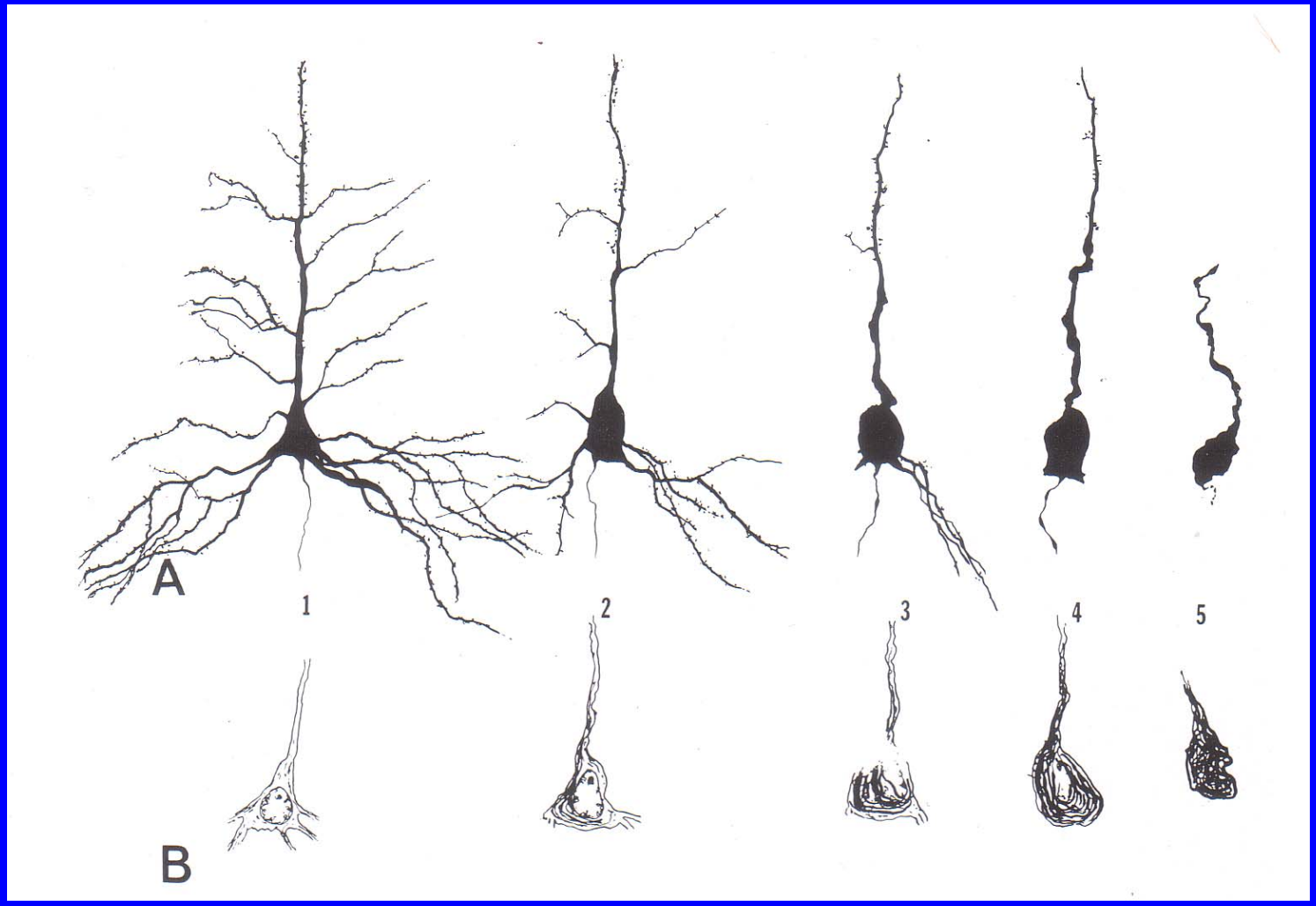
Molecular markers of PD based on gene expression in blood

-Scherzer et al. PNAS 2007



One of the genes most underexpressed is *ST13*, a co-factor of Hsp70 that stabilizes its chaperone activity.

Progression of senile changes in human cortical pyramidal neurons.
A. Golgi impregnation. B. Bielschowsky silver stain (nfts).



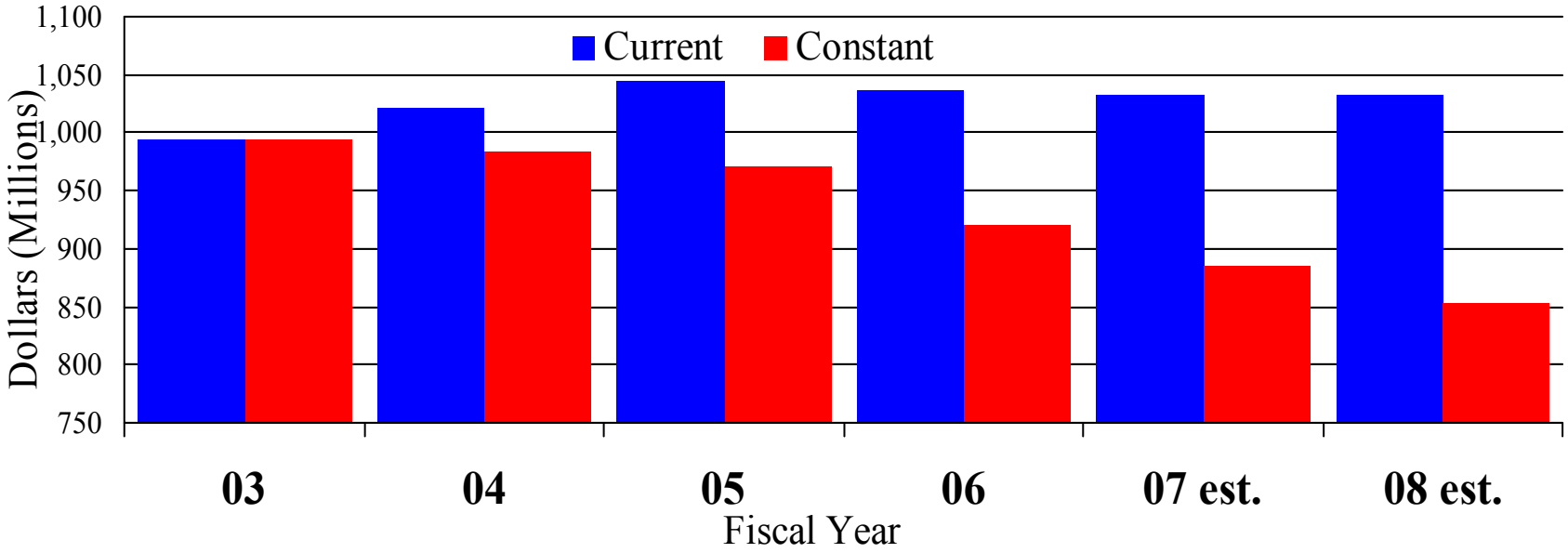
Scheibel, 1978

National Institute on Aging

(Fiscal Years 2003 – 2008)

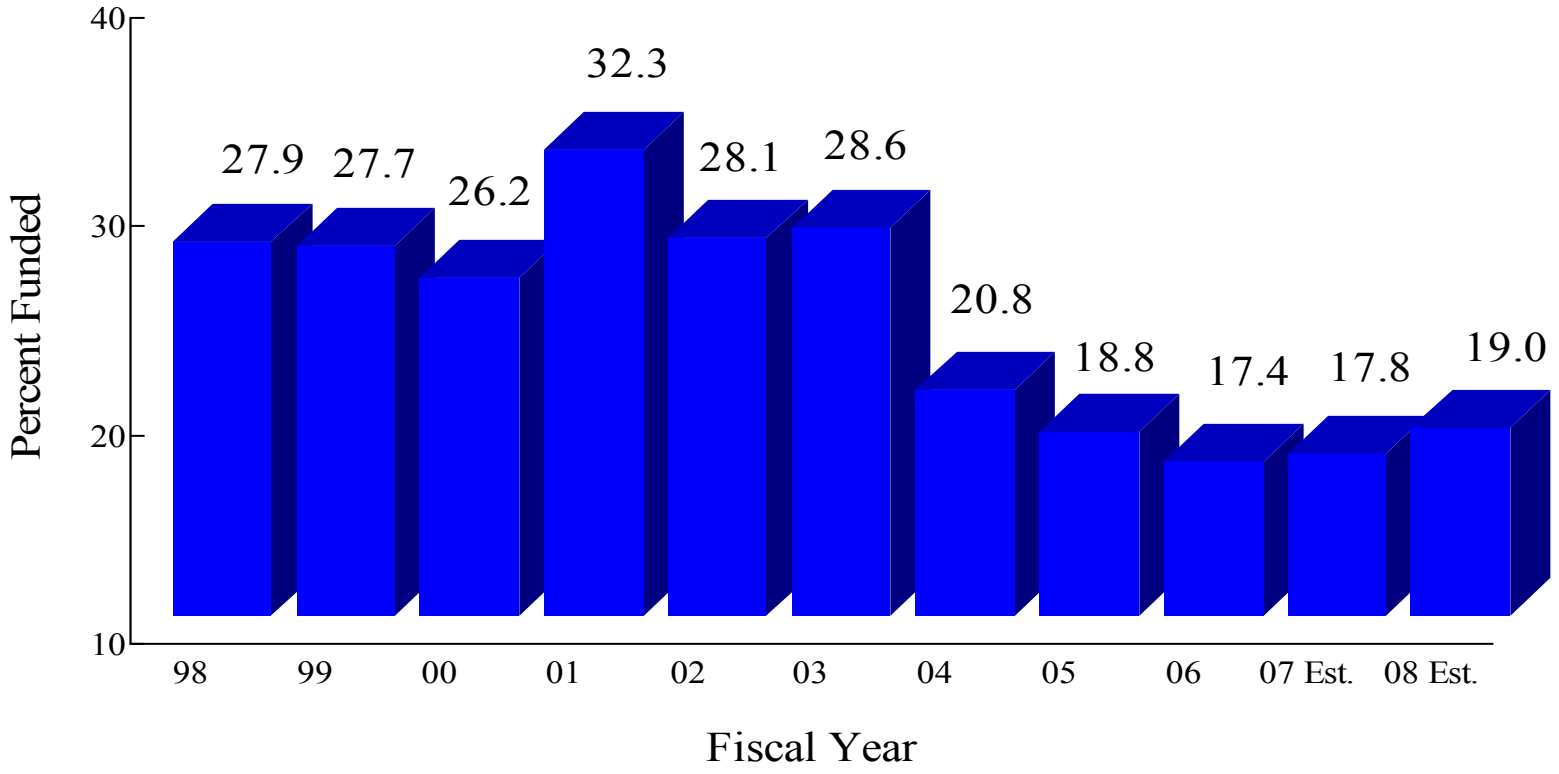
Funding Levels in Current and FY 2003 Constant Dollars

Percent change (estimated) current dollars: +4.0%
Percent change (estimated) constant dollars: -14.1%



* **Current dollars** - dollar value of a good or service in terms of prices prevailing at the time the good was sold or service rendered.
* **Constant dollars** - dollar value adjusted for inflation to demonstrate "real" increases. Determined by dividing current dollars by an appropriate price index, a process generally known as "deflating."

National Institute on Aging
Research Project Grant Success Rates*
Fiscal Years 1998-2008



* Success rate: The success rate is the proportion of applications reviewed that is actually awarded.
** Beginning in FY 1994, SBIR and STTR applications are not included in success rate calculations.