Neurodegenerative diseases

Dementing disorders	**Alzheimer disease**
	Frontotemporal dementia Pick disease Chromosome 17-linked dementias
Movement disorders	**Parkinson disease (PD)** **(30% develop dementia)**
Movement disorders & dementia	**Dementia with Lewy bodies** **Diffuse Lewy body disease (DLBD)** **Alzheimer disease Lewy body variant (ADLBV)**
	Huntington disease (HD)

Prevalence of dementia

Number of patients ALIVE with dementia in a defined population, & time frame

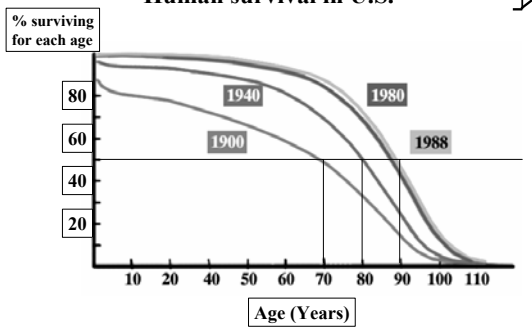
Prevalence is biased by differences in **SURVIVAL**

Incidence of dementia

Number of patients that are NEWLY DIAGNOSED with dementia in a defined population, & time frame

Incidence is preferable to **prevalence**
Increased **AWARENESS** of dementing illnesses influences the rates of diagnoses, hence of **incidence**

Human survival in U.S.



U.S. Bureau of Census

Alzheimer disease (AD) in the US

In 2000, there were 4.5 million persons with AD (*)

By 2050 -> 13.2 million AD patients (*)

Estimated cost of AD
$100 billion / year (1993)

4th or 5th leading cause of death

n AD patients will continue to increase unless discoveries contribute prevention of the disease (*)

(*) Archives of Neurology, 2003. 60:1119-1122
Neurology, 2005(Suppl 3). 65:S31-S32)

Alzheimer disease in the US

Most common cause of dementia

90 percent are sporadic; 10 percent are familial

Prevalence rate over the age of 60 years (y)
1900-5500 patients per 100,000 population
> 50 percent of nursing home residents

Annual incidence rate
increases exponentially with advancing age
2.4 patients / 100,000 population aged between 40 & 60 y
127 patients / 100,000 population aged 80 y & over

Usual aging vs. morbidity

Aging

Diseases

Neuronal loss

Lewy body

Neurofibrillary changes

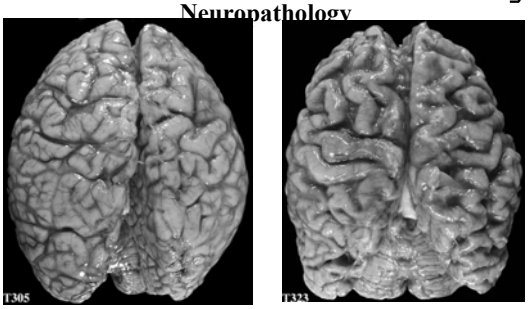
Neuritic plaques

Pick body

Hirano body

Granulovacuolar degeneration

Usual aging v.s Alzheimer disease (AD)
Neuropathology



74 year-old, Control

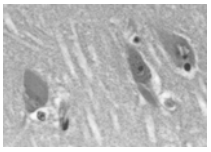
89 year-old, AD

Usual aging

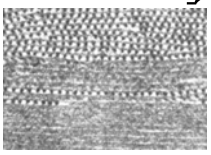
QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.

Mild cognitive impairment
Occurrence of amnesia without impairment of Activities of daily living (ADL)

Hirano body

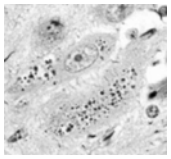


10 - 30 µm adjacent or within cytoplasm pyramidal neurons of hippocampus



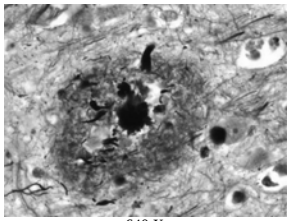
Granulovacuolar degeneration

Vacuole: 3 - 5 µm
Granule: 1 - 2 µm
Cytoplasmic especially seen in pyramidal neurons of hippocampus



Found in 70 percent of brains of neurologically normal individuals

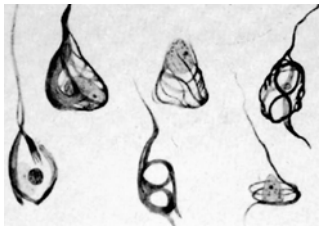
Neuritic (senile) plaques (Bielschowsky)

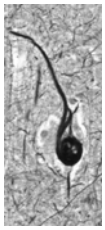


640 X

Neuritic plaque
180 µm diameter
replaces about 100 neurons
& 10^6 synapses

Neurofibrillary tangles of Alzheimer

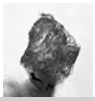




Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. Zeitschrift für die gesamte Neurologie und Psychiatrie (Berlin) **1911**;4:356-85. (Fig8 “Fortgeschrittene Erkrankung”)

Amyloid

β– pleated sheet conformation, insoluble



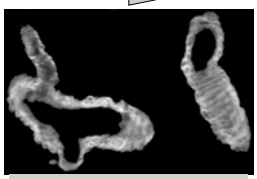
Salmon pink

Congo red stain

Under polarized light

birefringent

Apple green

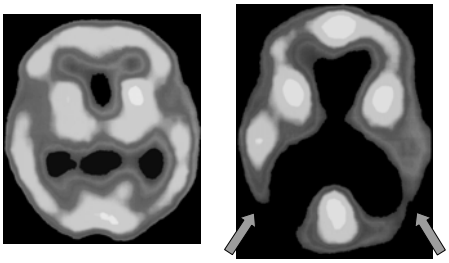


Fluorescent with Thioflavine stain

Alzheimer disease (AD)
Early stage

- Irreversible neurodegenerative disease
- Destroys memory & ability to think ->
- Insidious onset
- Continuous, slow decline in cognition
- Currently, no cure
- Definite diagnosis: Neuropathologic examination

Control **Alzheimer disease (AD)**

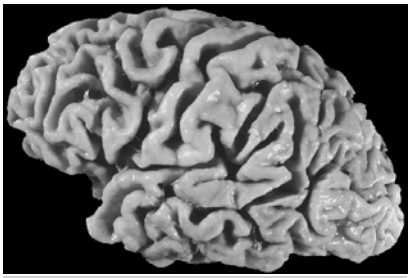


Single photon emission computerized tomography (SPECT)
In AD: Parietal hypoperfusion

From: The Neuropathology of Dementia, M. Esiri & J. Morris
Cambridge University Press. 1997

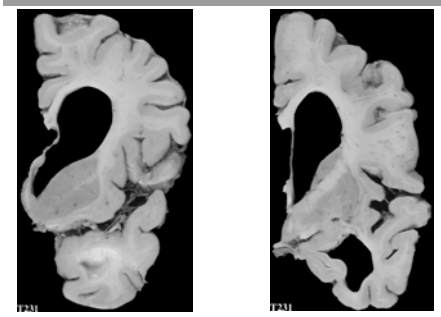
Alzheimer disease (AD) : Neuropathology

Cerebral atrophy

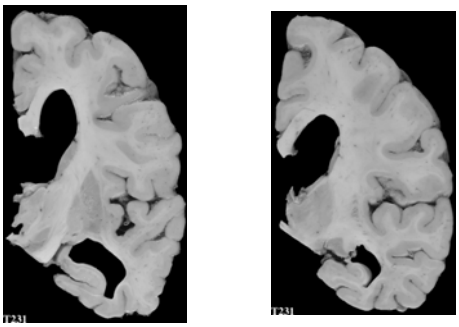


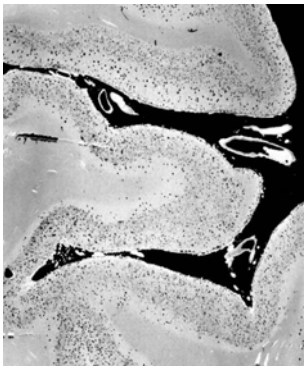
Atrophy = Widening of sulci + Narrowing of gyri

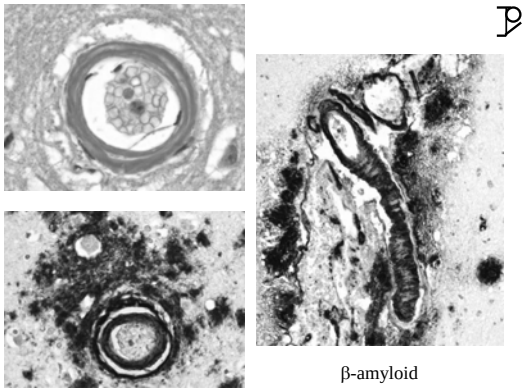
Permanent loss of predominantly glutamatergic, pyramidal neurons of neocortex



Basal nucleus of Meynert (cholinergic system)

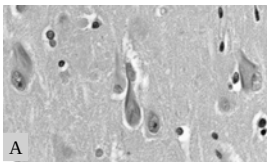


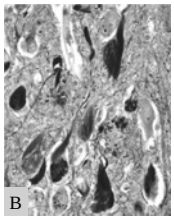


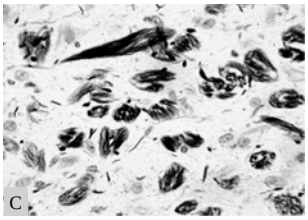


Neurofibrillary tangles

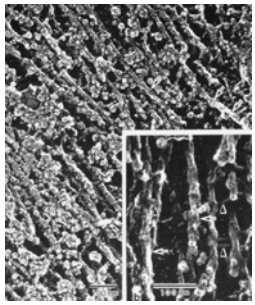
A: Early stage
B: Intermediate stage
C: End stage (ghost)
A: HE, B & C: Silver







Neurofibrillary tangles: ultrastructure

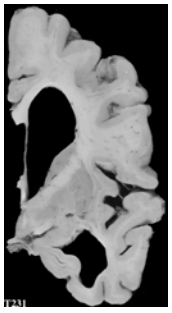


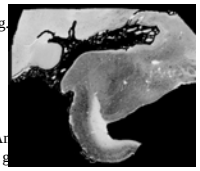
Paired helical filaments
8 - 12 nm, helically wound
Insoluble
React with silver stains

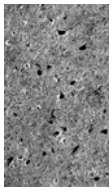
Hyperphosphorylated Tau
? Abnormal kinase or phosphatase activities

Tau: normal neuronal proteins, bind to microtubules regulate their assembly.

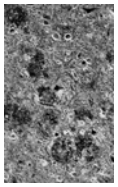
Uncus (rostral) = Ambient g. + semilunar g.





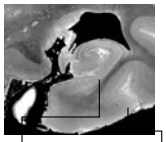


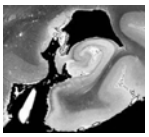
Biel schowsky

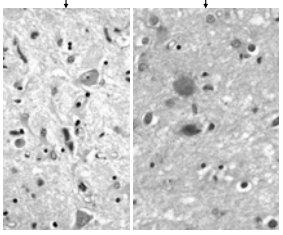


Cortical n.

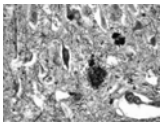
Basal n.



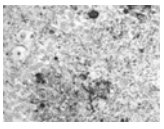




CA1

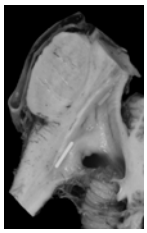


CA4



St. gr.

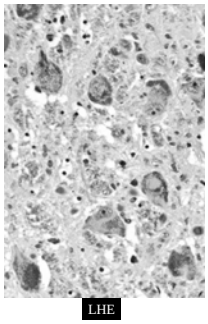
Substantia nigra pars reticulata (SNr), & compacta (SNc)



Coeruleus
Norepinephrine

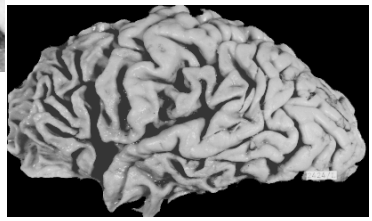
Paradoxical sleep
Cortical activation

Dorsal n. X



LHE

Pick disease



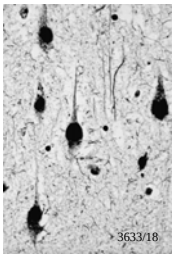
Pick body

Cytoplasmic, round, argyrophilic,
tau positive, ubiquitin positive,
10 - 15 µm across
α–synuclein negative

Pick bodies usually involve
- **neocortical, pyramidal neurons**
- **hippocampal, pyramidal neurons**
- **stratum granulosum of dentate gyrus**
- **amygdala**
- **striatum**
- **brainstem**

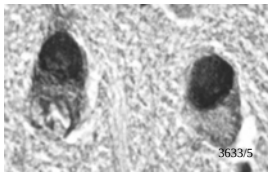
Pick body

Bielschowsky



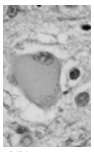
3633/18

Tau



3633/5

Tau positive
Ubiquitin positive
α-synuclein negative



2424

Ballooned neurons

Pick disease

Primary progressive aphasia

Chromosome 17-linked dementia

Corticobasal degeneration

Alzheimer disease

Progressive supranuclear palsy

Creutzfeldt-Jakob disease

Parkinson disease

And

Dementia with Lewy bodies

Parkinson disease

1919: Trétiakoff, C.

50,000 Americans / year -> diagnosed with PD

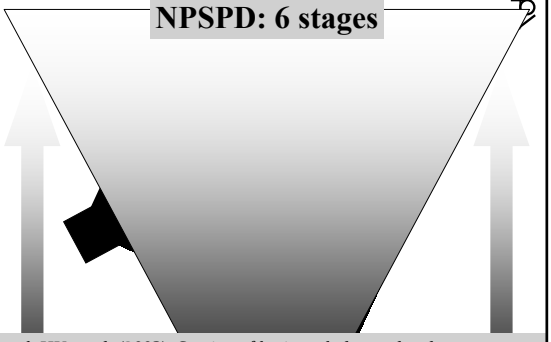
Parkinson disease (PD)

Bradykinesia
Rigidity
Resting tremor
Postural instability

Neuronal loss
Cytoplasmic inclusion: Lewy body

Pars compacta of substantia nigra
Nucleus coeruleus
Substantia innominata
Hypothalamus
Dorsal nucleus of vagus

NPSPD: 6 stages



Braak HK, et al. (2003). Staging of brain pathology related to Sporadic Parkinson's disease. Neurobiology of Aging 24:197-211

Neuronal loss
Cytoplasmic inclusion: Lewy body

Dorsal nucleus of vagus
Nucleus coeruleus
Pars compacta of substantia nigra
Hypothalamus
Substantia innominata -> Mesolimbic cortex

Parkinson disease

If, in addition,
neurons with Lewy body in
cerebral neocortex (-> dementia)

Diffuse Lewy body disease

If, in addition,
neuritic plaques or neurofibrillary tangles or both in cerebral cortex
(as seen in Alzheimer disease)

Alzheimer Disease Lewy body variant

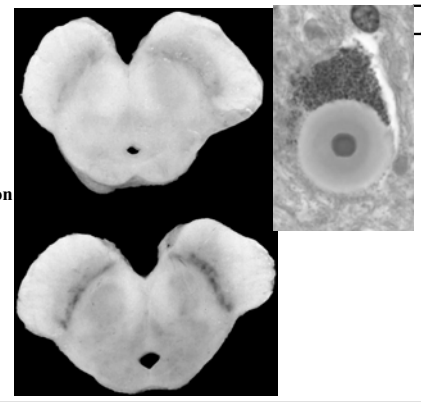
Lewy body

Cytoplasmic inclusion, round, 8 - 30 µm

Brainstem type, discrete
Cortical type, ill-defined

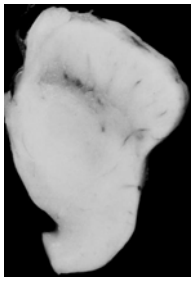
Found in

5% of asymptomatic, elderly subjects
100% of patients with Parkinson disease
or with Lewy body dementia

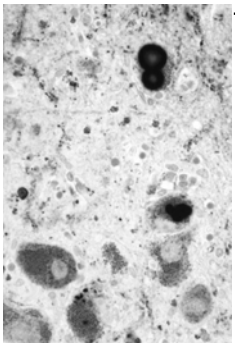


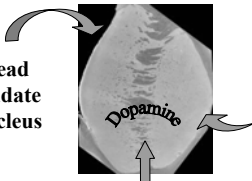
Parkinson

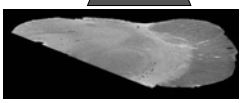
Control



2120



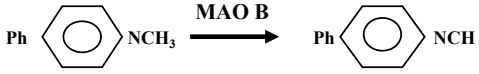




VIDEO

QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.

MPTP



MPTP

1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydropyridine

Not toxic

MPP$^+$

1-Methyl-4-Phenylpyridinium ion

Toxic

=

Or

≠

VIDEO

QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.

VIDEO

QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.

VIDEO

QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.

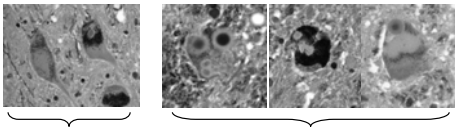
Dementia with Lewy body (LB) = Diffuse LB disease

Lewy bodies

Neocortex, hypothalamus, substantia innominata, substantia nigra (compacta), coeruleus, dorsal nucleus of vagus

Lewy neurites

Hypothalamus, substantia innominata, CA3-2 of hippocampus (minimal) substantia nigra (compacta)



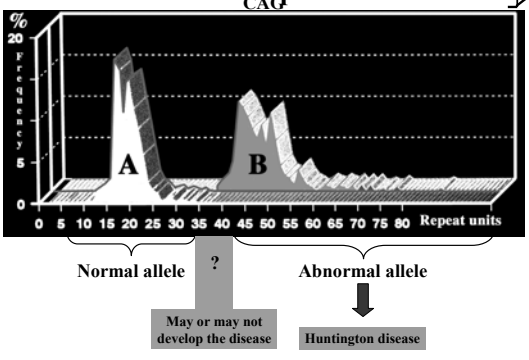
Substantia nigra Nucleus coeruleus

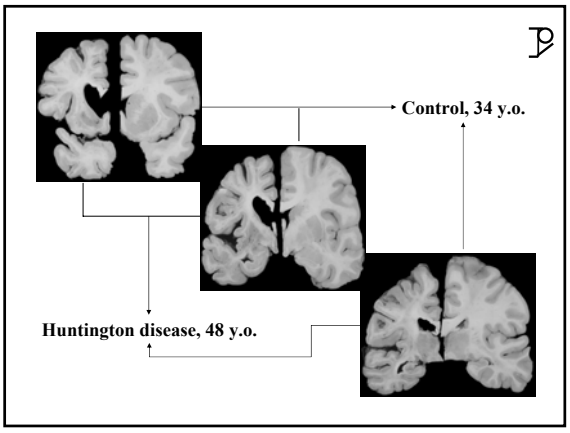
Huntington disease

Huntington disease

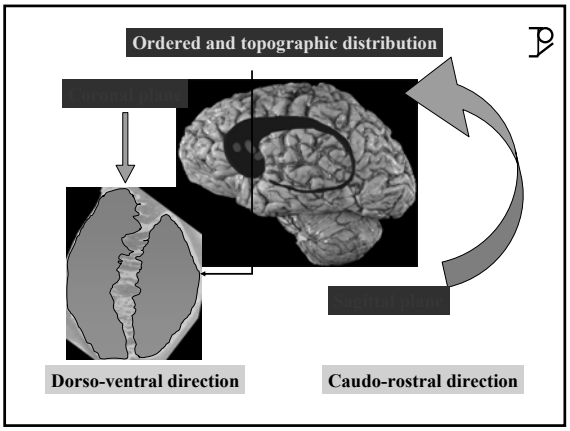
Early stage

CAG repeats





QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.



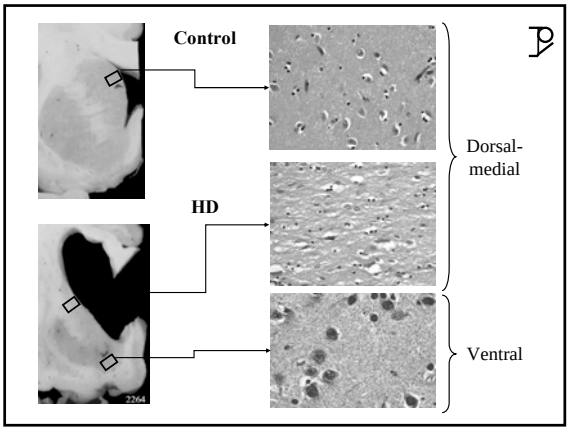
Huntington disease
Late stage

QuickTime™ and a
DV/DVCPRO - NTSC decompressor
are needed to see this picture.

VIDEO

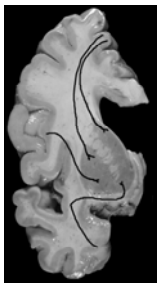
Huntington disease
Juvenile onset
End-stage (Grade 4/4)

VIDEO



Excitotoxicity

Glutamate

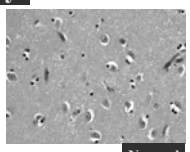


Receptors

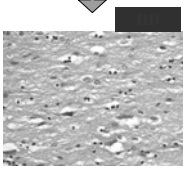
NMDA
AMPA
Kainate
Metabotropic

+

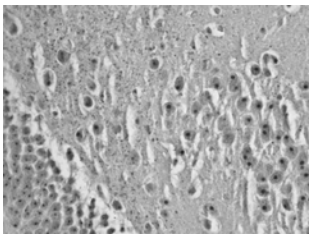
HDIT15
PolyQ



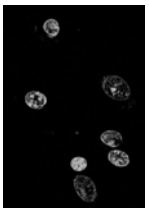
Normal



Nuclear inclusions



Mouse R6/2
145 CAG



14 y.o. w
82/12 CAG

Huntington disease
Late onset
Relatively early stage
Slow progression