Overview of Alzheimer's Disease and Mixed-Dementia from a Scientific Perspective

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Social Security Administration s
Compassionate Allowance Outreach Hearing on
Early Onset Alzheimer s and Related Dementias
July 29, 2009

Overview

- Clinical manifestations of Alzheimer's disease
- Pathological manifestations of Alzheimer's disease
- Common conditions that Coexist with Alzheimer's disease
- Differential diagnosis of Alzheimer's disease
- Genetic risk factors
- Prognosis of Alzheimer s disease
- Differences with late onset disease

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NINCDS/ADRDA Definition of Dementia

- Acquired intellectual deterioration in an adult
- At least 6 month's duration
- At least two spheres of mental activity (eg, orientation, attention, memory, language, spatial abilities, etc) compromised
- Impairs the ability to function optimally in the community

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McKhann et al. *Neurology* 1984;34:939-944.

NINCDS-ADRDA criteria for Alzheimer's disease

- Progressive decline of memory and other cognitive abilities
- Cannot be entirely explained by another condition
- Definite AD requires pathologic confirmation by biopsy or autopsy

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McKhann et al. *Neurology* 1984;34:939-944.

Memory

- The recording, retention, and retrieval of information
  memory accounts for all knowledge gained through experience
  - specific events
  - knowledge of facts
  - acquisition of skills

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Memory Systems Affected by Alzheimer's Disease

- Episodic Memory
- Semantic Memory
- Working Memory
- Spatial Memory
- Implicit Memory
- Perceptual Speed

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Clinical Manifestations of Alzheimer's Disease

- Cognitive impairment
  - Memory, language, attention, processing speed, spatial ability
- Behavioral disturbances
  - Hallucinations, misperceptions, delusions; agitation, aggression
- Affective disturbances
  - Depression
- Motor impairment
  - Parkinsonian (extra-pyramidal) signs
    - Gait disturbance, bradykinesia, rigidity, tremor
  - Weakness and physical frailty
- Other signs
  - Weight loss
  - Sleep disturbance
  - Incontinence

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Pathological Manifestations of Alzheimer's Disease

- Atrophy
  - Hippocampal and generalized
- Plaques and tangles
  - Amyloid deposition
  - phosphorylation of tau proteins
- Amyloid angiopathy
- Neuronal loss (neurodegeneration)

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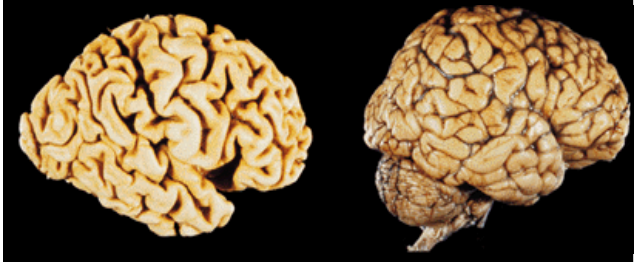
Alzheimer's disease | Normal brain



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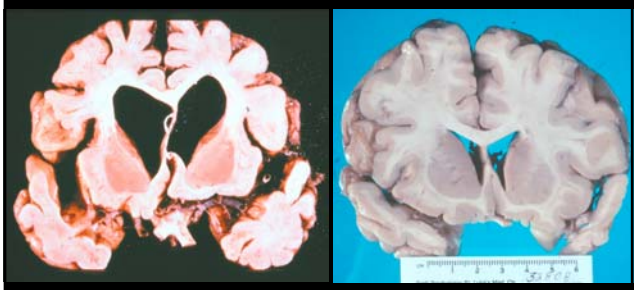
Alzheimer's disease | Normal brain



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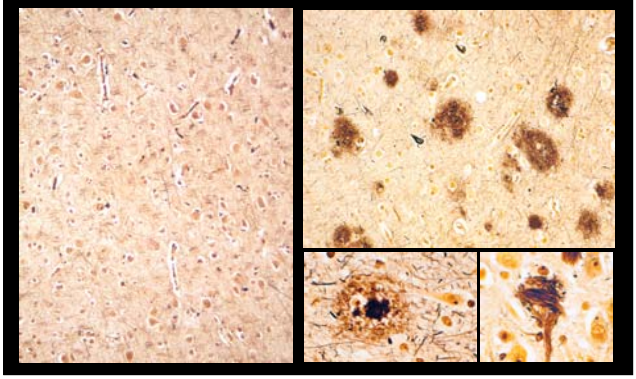
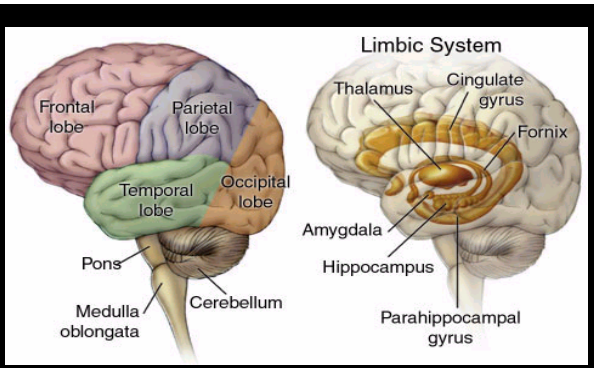
Normal brain | Alzheimer's disease



Limbic System



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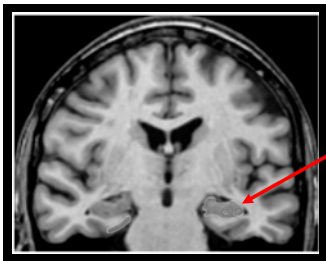

Hippocampus

Hippocampal formation: Brain region critical to laying down new episodic memories.

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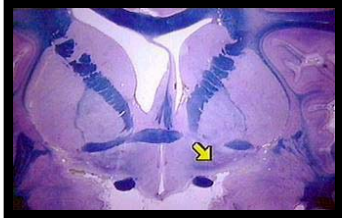
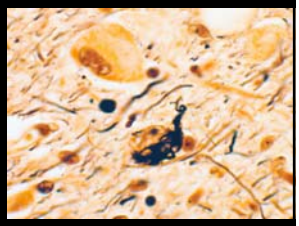
Cholinergic basal forebrain neurons (Nucleus basalis of Meynert)





Nucleus basalis of Meynert: Source of cholinergic projection neurons to hippocampus and neocortex.

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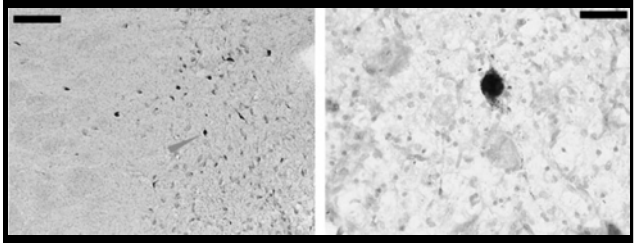
Tangles in the Substantia Nigra



Substantia Nigra: Part of brain affected by Parkinson's disease and involved in motor function.

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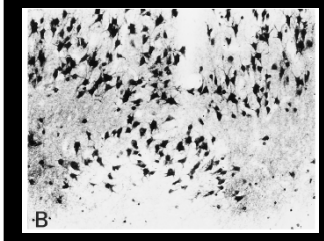
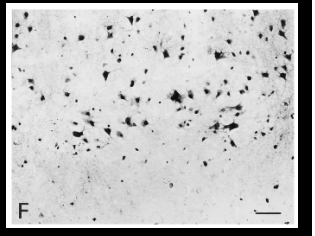
Hippocampal Neurons





Many

Few

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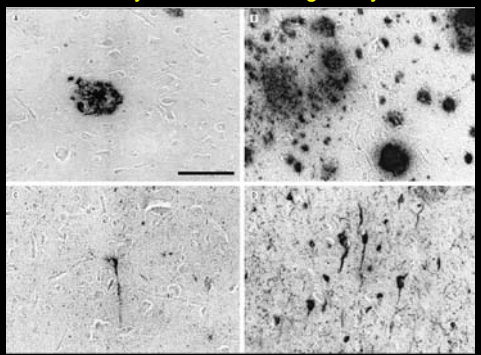
Low Amyloid

High Amyloid



Low Tangles

High Tangles

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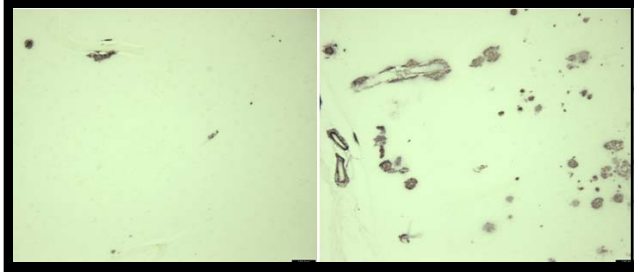
cerebral amyloid angiopathy



Low

High

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Common Conditions that Coexist with Alzheimer's Disease

- Cerebral infarctions
  - Macroscopic
  - Microscopic
- Parkinson's/Lewy Body Disease
  - Nigral
  - Limbic
  - Neocortical

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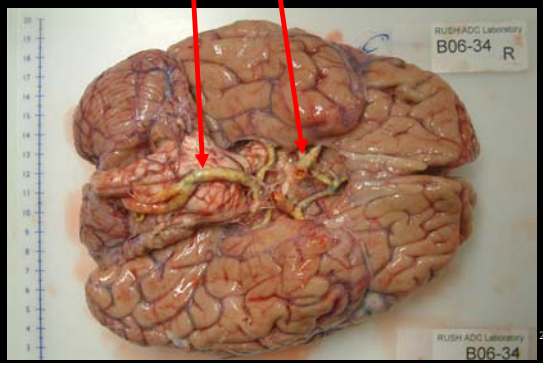
Cerebral Atherosclerosis



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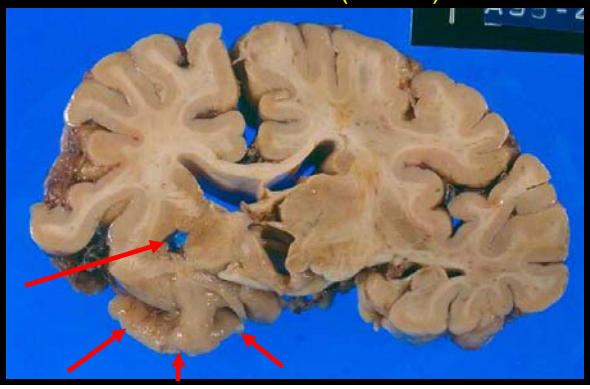
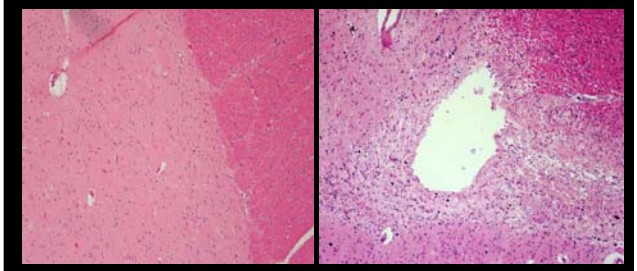
Cerebral Infarctions (Stroke)



Subcortical macroscopic infarct



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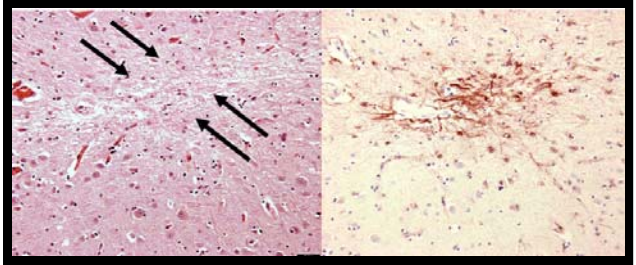
Cortical Microinfarct



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Parkinson's disease

Normal brain

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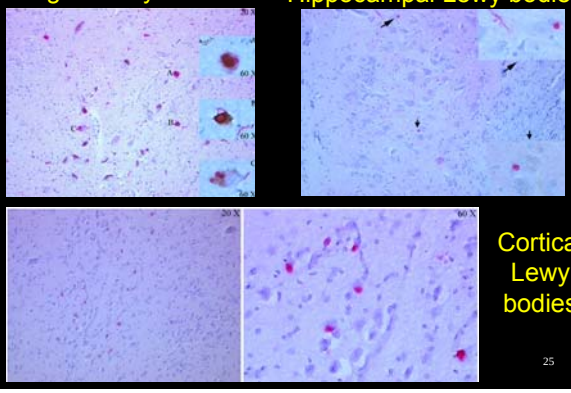
Nigral Lewy bodies

Hippocampal Lewy bodies



Cortical Lewy bodies

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Diagnosis of Alzheimer's disease

- Progressive decline of memory and other cognitive abilities relative to a previous level of performance
  - History of decline obtained from a knowledgeable surrogate
    - Usually sufficient
  - Repeat neuropsychological testing
    - Needed occasionally
  - Inferred from knowledge of premorbid function
    - Sometimes unavoidable
- Documented by formal mental status testing
  - Cognitive Screening Tests
  - Full Neuropsychological Battery
    - Helpful in early disease when dementia is not clear
- Other tests primarily used to identify coexisting conditions

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Differential Diagnosis of Alzheimer's disease

- Other less common causes of progressive dementia
  - e.g., fronto-temporal lobar degeneration
- Conditions that may mimic dementia
  - Depression and other Psychiatric Conditions
  - Malingering
- Other tests that may aid in the identification of these conditions
  - Formal neuropsychological testing
  - MRI
  - PET
  - EEG

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- There are no good estimates of the number of persons with early onset AD in the US, but it likely about 100,000 or more.
- There is no evidence of differences by gender, race or ethnicity.
- There is no evidence that environmental, experiential, or psychological factors known to be associated with late-onset AD are also associated with early onset AD.
- A variety of genetic factors are associated with risk of early onset AD.

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Genetic Risk Factors for Alzheimer's Disease

Increase Risk

- Genetic mutations
  - Amyloid precursor protein (*APP*, 21q)
  - Presenilin 1 (*PSEN1*, 14q)
  - Presenilin 2 (*PSEN2*, 1q)
- Genetic polymorphisms
  - Apolipoprotein E ε4 allele

Decrease Risk

- Genetic polymorphisms
  - Apolipoprotein E ε2 allele

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Prognosis of Alzheimer's disease

- Cognitive decline inexorably progressive until death
- Plateaus may occur but patients do not improve (in the absence of a reversible coexisting condition)
- Rate of decline variable; factors associated with decline:
  - Younger age
  - Parkinsonian signs
  - Hallucinations
  - Weight loss and frailty
  - More educational attainment
- Disability virtually by definition
  - Clinical Dementia Rating Scale
- Death in 8-10 years, but highly variable

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Staging of Dementia—Clinical Dementia Rating

- 0 = no dementia
- 0.5 = questionable dementia
  mild forgetfulness
- 1 = mild dementia
  moderate memory loss, mild disorientation and impairment of social/occupational functioning
- 2 = moderate dementia
  severe memory loss, requires assistance in activities of daily living and personal hygiene
- 3 = severe dementia
  help with care and personal hygiene
- 4 = profound dementia
  speech unintelligible, does not follow simple commands, barely ambulatory with assistance
- 5 = terminal dementia
  no response or recognition

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Compared to persons with late onset AD, persons with early onset are more likely to:

- Be gainfully employed and present at an earlier stage of illness
- Progress more rapidly
- Survive to experience terminal disease
- Have a genetic cause
  - Especially those with very early onset (< age 35)
- Have AD without a co-morbid condition.

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