

**UNC Chapel Hill School of Social Work
Clinical Lecture Series**
presents

**Where Do We Draw the Line?
The Ethics of Diagnosing Dementia
(Alzheimer's Disease)**

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The Discovery of Alzheimer's Disease

Alois Alzheimer, in 1906, described a middle-aged female patient who experienced progressive dementia that affected language, memory, and behavior. After her death, he described neuritic plaques and neurofibrillary tangles in the neocortex and other brain regions.

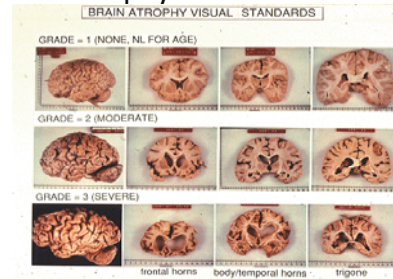


**But When Did Alzheimer's Disease
"Really" Become Alzheimer's
Disease?**

1977

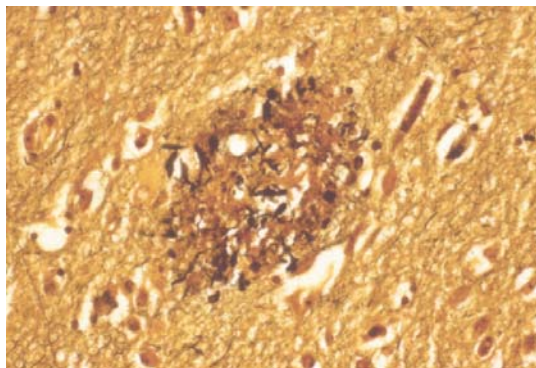
And I was present at the creation.

Brain Atrophy in Alzheimer's Disease

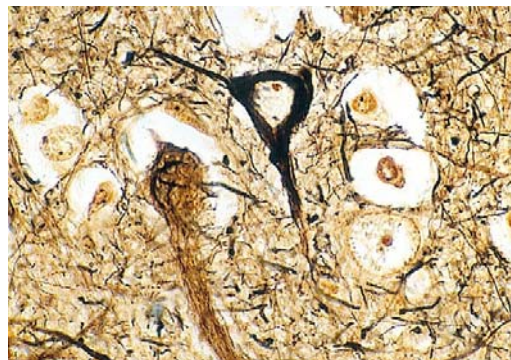


Controversy as to whether whole brain atrophy is as predictive as atrophy of the hippocampus and entorhinal cortex (mesotemporal lobe)

Neuritic Plaques



Tangles



Diagnostic Criteria for Dementia of the Alzheimer's Type (DSM-IV)

- The development of **multiple cognitive deficits** manifested by both
 - Memory impairment (impaired ability to learn new information or recall previously learned information)
 - One (or more) of the following domains of cognitive function:
 - **Aphasia**
 - **Apraxia** (inability to carry out motor activities, despite intact motor function)
 - **Agnosia** (failure to recognize or identify objects, despite intact sensory function)
 - **Disturbance in executive function** (e.g., planning, organizing)

Diagnostic Criteria for Dementia of the Alzheimer's Type (cont.)

- Cognitive deficits above cause significant **impairment in social or occupational function and represent a significant decline** from previous levels of function.
- The course is characterized by **gradual onset** and continuing cognitive decline.
- Other conditions are ruled out (such as vascular dementia and brain tumor)

Alzheimer's Disease – Demographics and Trends

- An estimated **4.5 million Americans** have Alzheimer's Disease.
- The number will continue to grow – between 11 and 16 million people by 2050.
- A person with AD will live an **average of eight years** and as many as 20 years or more from the onset of symptoms.
- From the time of diagnosis, people with **AD survive about ½ as long** as those of similar age without AD.
- The **annual cost** of caring for AD patients in the US is approximately **\$100 billion dollars**.

Alzheimer's Disease – Demographics and Trends

- More than **7 in 10 people with AD live at home**, where almost **75% of their care is provided by family and friends**. The remainder of personal care is paid care, averaging \$19,000 per year (families pay almost all of that out of pocket).
- **One-half of nursing home residents have AD** or a related disorder.
- The **average lifetime cost** of care for an individual with AD is **\$174,000**.

Alzheimer's Disease – Demographics and Trends

- **Medicare costs** for beneficiaries with AD are expected to increase 75% from \$91 billion in 2005 to **\$160 billion in 2010**.
- **Medicaid** expenditures on residential dementia care will increase 14% from \$21 billion in 2005 to **\$24 billion in 2010**.
- Finding a treatment that delayed onset by five years could reduce number of people with AD by nearly 50% after 50 years.

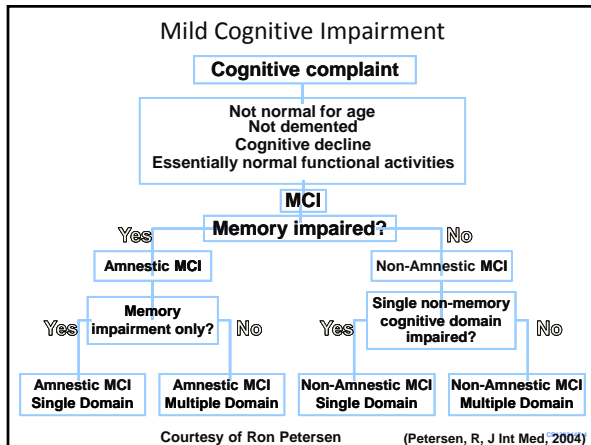
So What is Happening in DSM-5?

Background

- ▣ Increasingly, individuals are seeking care for cognitive impairment that is not severe or disabling enough to be called “dementia” (e.g., they notice a subjective change in their memory).
- ▣ **Evolving clinical, epidemiological, radiological, pathological, and biomarker research data** suggest that it is possible to identify the subgroup of individuals with elevated risk of progression to dementia.
- ▣ The relative size of this subgroup depends on the setting and heterogeneity of the population.

Mild Cognitive Impairment (MCI)

- The concept of MCI has become very popular with investigators.
- It is unclear whether the concept is of clinical value (though it probably will be part of DSM-V. It’s included in the Appendix of DSM-IV-TR as “mild neurocognitive disorder.”)
- The public has little understanding of the concept



What is the Incidence of MCI?

- Individuals in the Mayo Clinic Study of Aging (a study launched in 2004 that is following 1,786 who were 70- 89 year-olds from Olmsted County, Minnesota) developed mild cognitive impairment at a rate of about **5.3% per year.**

The older the person, the higher the rate

(Peterson et al, International Conference on Alzheimer’s Disease 2008, oral presentation)

Neurocognitive Disorders and DSM-5:

What Has Happened to Dementia?

A Digression...

Neurocognitive Disorder Work Group Members:

Dilip V. Jeste, MD	(Chair, UCSD)	Recused
Dan G. Blazer MD, PhD	(Chair, Duke)	Acting chair
Ronald C. Petersen MD, PhD	(Mayo Clinic)	Acting co-chair

Deborah Blacker, MD, ScD (Harvard)
 Mary Ganguli, MD, MPH (Pittsburgh)
 Igor Grant, MD, PhD (UCSD)
 Jane S. Paulsen, PhD (Iowa)
 Perminder S. Sachdev, MD, PhD (University of New South Wales)

Disclaimer

- I speak for myself, not the work group or the APA
- These are criteria that have been posted publically but are still in progress.

How the Work Gets Done

- The Neurocognitive Disorders Work Group of the American Psychiatric Association's (APA) DSM-5 Task Force
 - Began work: April 2008
 - Task: proposing revisions to criteria for disorders referred to in DSM-IV as Delirium, Dementia, Amnesic and Other Cognitive Disorders.
 - One of many groups on general areas of psychopathology (e.g., "Psychoses Work Group"); also cross-cutting groups (e.g., life cycle factors)

How the Work Gets Done

- Over the past three years we have, among ourselves and with input from outside consultants and advisors, worked to develop a working draft that was posted on the APA's website www.dsm5.org in February 2010.
- This draft contained both an overview / rationale for the approach we have taken to date and preliminary criteria for the broadly defined disorders.

How the Work Gets Done

- We have met five times in person.
- We have conference calls about every other month.
- We have been in almost daily e-mail discussion (especially with the issues around new proposed diagnostic criteria).
- We have come to know one another VERY well (a potential for inbreeding).

Background (1)



Previous iterations of DSM directly or indirectly recognize the syndrome of **Dementia**:

- Decline, **from a previously higher level**, in cognitive function;
- Decline must be seen in **two or more** cognitive domains, one of which is **memory**;
- Decline must be sufficient to interfere with social and occupational **functioning**.
- Decline must not be solely attributable to delirium and other mental disorders.

Background (2)

- ☐ Dementia is a **syndrome**.
- ☐ The syndrome is **caused** by one or more **underlying diseases/conditions** that affect the brain.
- ☐ Causes of the syndrome can be degenerative (AD), vascular, traumatic, infectious, metabolic/toxic.
- ☐ Progressive diseases (like AD) underlying the dementia syndrome develop gradually over years before the threshold of functional impairment is reached.
- ☐ It is somewhat disingenuous to claim that the disease only begins at the onset of functional impairment, and the individual is normal/healthy until that time.

Broad Criteria of Mild Cognitive Impairment as of February 2010

- A. Evidence of mild decline from a previous level of performance in one or more cognitive "DOMAINS."
- B. Cognitive deficits are insufficient to interfere with independent everyday functioning.
- C. Cognitive deficits do not occur exclusively in the context of a delirium.
- D. Cognitive deficits are not wholly or primarily attributable to another psychiatric disorder.



- The syndromes are on a continuum (*the underlying cause may not be*).
- Divisions along the continuum are by nature arbitrary.
- The lines are drawn based on change within the individual: experienced/ reported, measured or inferred.
- There will be variability related to:
 - Individuals' premorbid ability, cognitive demand of everyday life, insights, comorbid conditions.
 - Clinicians' experience, skill, judgment, available tools.

Mild NCD in Alzheimer's Disease

- ☐ Meets criteria for Mild NCD;
- ☐ Memory domain is usually impaired; (exceptions recognized)
- ☐ Other domain(s) may or may not be impaired;
- ☐ Gradual onset and progressive course;
- ☐ Not wholly attributable to other disorders;
- ☐ *Supportive evidence*: AD biomarkers present / positive
- ☐ *Recognize comorbid disease* (especially cerebrovascular) and mixed etiology.

This lowers the bar!

Objective

1. To name and define:

- ☐ a syndrome of acquired cognitive impairment;
- ☐ that is in excess of that expected for age (in older adults);
- ☐ does not rise to the threshold of "major" impairment (aka dementia);
- ☐ can be an early stage of a progressive dementing disease OR
- ☐ a state that is static, transient or reversible, depending on etiology.

What's in a Name?

"Mild Neurocognitive Disorder."

"Mild" - challenged on grounds that it trivializes the entity and may lead to denial of services.

"Neuro" - challenged on grounds that all cognition is neural.

"Cognitive" - not yet been challenged.

Overview of Proposed Characteristics

A state of:

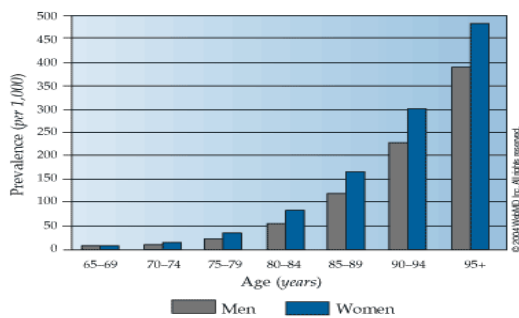
- recognizable (objective/subjective) state of cognitive decline, *with*
- everyday functioning still independent but associated with:
 - more errors;
 - greater effort; and/or
 - more compensatory strategies than previously.

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Frequency and Clinical Course

Prevalence of Alzheimer's Disease by Age and Sex



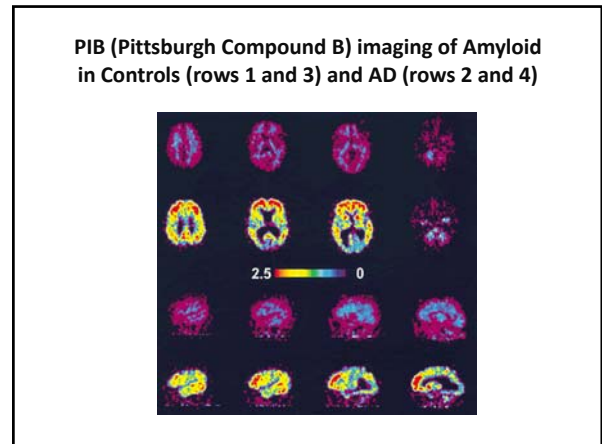
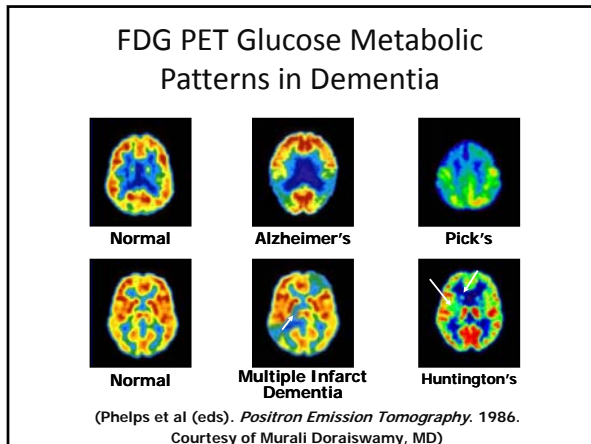
Stages of Alzheimer's Disease

No Impairment (? neuropathological findings)
Very mild symptoms with no appreciable impairment (cannot distinguish from normal changes with aging)
Mild decline
Moderate decline (clear but early AD)
Moderately severe decline (clear functional impairment)
Severe decline (can no longer care for self)
Very severe decline (around the clock care or institutional care)
... Death
Each Stage often lasts about 3-4 years

Can We Identify Alzheimer's Disease Before the Appearance of Symptoms?

How early can the signs of AD be identified? The Nun Study

- Study of 678 Catholic sisters, initially 75 to 102 years of age
- Begun in 1992
- Evaluated annually for dementia
- Had agreed to brain donation at the time of their deaths
- Finding: Alzheimer's disease with onset in old age **could be predicted accurately from characteristics of autobiographical essays written at an average age of 22** (Snowdon et al, 1996).



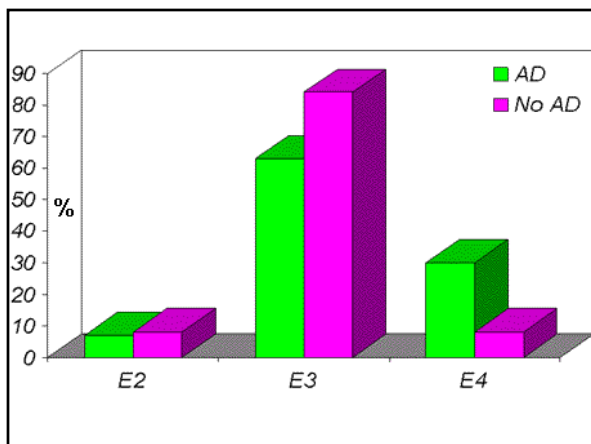
Inherited Alzheimer's Disease

- Researchers have identified three genes that cause early-onset AD – mutations in the:
 - amyloid precursor protein (APP) gene
 - presenilin 1 (PSEN1) gene, and
 - presenilin 2 (PSEN2) gene.

Mutations in any of these genes result in the production of large amounts of a toxic protein fragment called amyloid beta peptide.

APOE and Alzheimer's Disease

- The gene for Apolipoprotein e is a susceptibility gene for AD. The gene comes in three common alleles (2, 3, and 4). The e3 allele is the most common.
- The e4 allele of the APOE (Apolipoprotein E) gene has been found to increase the risk for AD. The e2 allele has been found to be protective.



APOE and Risk for AD

- Study from Cache County, Utah (over 3,000 subjects provided DNA in a community follow-up study as well as detailed family history.
- Over an average of seven and a half years of observation, the people who experienced the most significant cognitive decline had a family history of the disease, and one or more copies of APOE E4

(Hayden and Welsh-Bohmer, International Conference on Alzheimer's Disease 2008, oral presentation)

The TOMM40 polymorphism

- TOMM40 codes for a protein that is embedded into outer membranes of mitochondria and is required for the [movement of proteins](#) into [mitochondria](#).
- Individuals with a large number of extra copies of the long repeat version) of TOMM40 coupled with APOE3 develop Alzheimer’s an average of seven years earlier (about age 70) compared with APOE individuals with the short repeat version and may account for 90% of cases.

(Roses et al, 2009)

The TOMM40 polymorphism

- Actos (pioglitazone) is currently in clinical trials to determine if taking the drug can delay onset of AD (predicted by TOMM40).
- The drug works differently than other approved drugs (by reducing inflammatory reaction, amyloid plaques).
- The drug, currently used for diabetes, is relatively free of side effects.

TBI and Alzheimer’s Disease

Methods

In this study the incidence of AD pathology was explored in:

- 1.58 consecutive patients (mean age 77) with residual closed TBI lesions, and
- 2.57 age-matched autopsy proven AD cases.

(Jellinger KA, Paulus W, Wrocklage C, Litvan I, 2001)

TBI and Alzheimer’s Disease

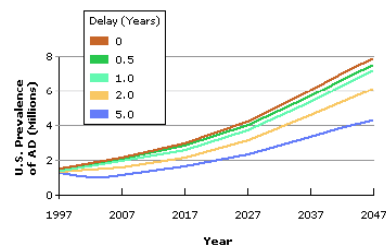
- **CONCLUSIONS:** The results confirm clinical studies suggesting severe TBI to be a risk factor for the development AD. The risk is higher in subjects lacking ApoEepsilon4 alleles. Further studies in larger autopsy series are needed to elucidate the relationship between TBI, genetic predisposition, and AD.

This finding has received much attention from the military and the sports industries

What are the Currently Accepted Treatments?

Can these “Treatments” Prevent the Onset of Symptoms

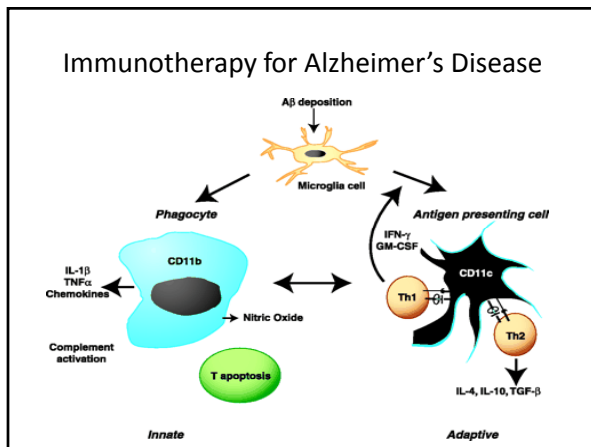
Impact of Delay in Progression of AD Secondary to Medication



- ### Treatment of Alzheimer's Disease
- **Medications to treat or perhaps prevent neurocognitive decline**
 - Medications to treat behavioral abnormalities
 - Attention to the Environment
 - Family intervention

Medications used to Treat (and Prevent) AD

Type	Examples
Cholinesterase inhibitors	Tacrine (Cognex) – rarely used these days Donepezil (Aricept); Rivastigmine (Exelon); Galantamine (Razadyne)
N-methyl-D-aspartate receptor antagonist	Memantine (Namenda)
Antioxidants	Vitamin E – usually not recommended
Hormones	Conjugated estrogens – usually not recommended
Other potential neuroprotective factors	Nonsteroidal anti-inflammatory drugs (NSAIDs); Ginkgo Biloba; Statins



- ### Can AD be prevented with Statins?
- **Data:** A population-based cohort study comprising 1,789 older Mexican Americans with cognitive impairment. (A total of 1,674 participants free of dementia.)
 - **Results:** Overall, 452 of 1,674 participants (27%) took statins during the study. Over the 5-year follow-up period, 130 participants developed dementia.
 - (A Cox proportional hazards model was adjusted for education, smoking status, presence of at least one APOE 4 allele, and history of stroke or diabetes at baseline.)
 - **Persons who had used statins were about half as likely as those who did not use statins to develop dementia.**
- (Cramer et al, International Conference on Alzheimer's Disease 2008, oral presentation)

- ### Exercise and the Prevention of Alzheimer's Disease Progression
- Patients in the early stages of Alzheimer's disease who performed better on a treadmill test had less atrophy in the areas of the brain that control memory as determined by magnetic resonance imaging to examine.
 - Half of the participants were healthy older adults, and half were in the early stages of Alzheimer's.
 - Physically fit Alzheimer's patients had larger hippocampuses.
- (International Conference on Alzheimer's Disease in Chicago. Robyn A. Honea, Ph.D)

- ### Exercise and Alzheimer's Disease
- Volunteers who reported memory problems but did not meet criteria for dementia were recruited. A total of 170 participants were randomized and 138 participants completed the 18-month assessment.
 - **Intervention** Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity.
 - **Conclusions** In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.
- (Lautenschlager et al, 2008, JAMA)

Conclusions

- At what point do we first label an individual with the diagnosis of “Neurocognitive Impairment”?
 - Genetic and pathological signs before the onset of symptoms
 - The first onset of symptoms
 - The first onset of significant impairment

None of these are obvious and exact decision points

Conclusions

- We have at least three broadly competing needs:
 - 1) The needs for the research community to explore early diagnosis and potential preventative interventions (e.g., do we obtain PET scans on everyone after the age of 50?)

Conclusions

- 2) The needs of practicing clinicians to accurately identify the their patients/clients to insure appropriate care. (Early identification of neurocognitive impairment may assist families in using advanced directives regarding future decision making.)

Conclusions

- 3) The needs of third party payers to appropriately reimburse for evidence based care as well as care desired by the patient/client and family

So Where Do We Draw the Line?