Washington University: Setting the Stage for Secondary Prevention Trials in Alzheimer Disease

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Disclosure Statement (2011-2012)

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1. National Institute on Aging
   a) Alzheimer’s Disease Research Center (ADRC; P50 AG05681)
   b) Healthy Aging and Senile Dementia (HASD; P01 AG03991)
   c) Adult Children Study (ACS: P01 AG026276)
   d) Dominantly Inherited Alzheimer Network (DIAN; U19 AG032438)

2. Anonymous Foundation
3. Alzheimer’s Association
4. Industry-sponsored clinical trials (Eli Lilly; Janssen Alzheimer Immunotherapy Program; Pfizer)

Consulting Relationships

1. Eisai
2. Janssen Alzheimer Immunotherapy Program
3. GlaxoSmithKline
4. Novartis
5. Otsuka
6. Pfizer/Wyeth

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None

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None

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None

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Leonard Berg, MD
Founding Director, ADRC
The Story Begins with Normal Pressure Hydrocephalus

- Dramatic report in 1965 of improvement after ventriculo-atrial shunting in 3 cases with profound cognitive impairment

- Practicing neurologists initially excited about "treatable dementia" but soon find that shunting helps very few demented older adults

- At Washington University, Berg (a practicing neurologist) organized "Brown Bag Seminars" to discuss lack of response to shunting and consider other causes of dementia

The Special Clinical Problem of Symptomatic Hydrocephalus with Normal Cerebrospinal Fluid Pressure

Observations on Cerebrospinal Fluid Hydrodynamics

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Adult idiopathic communicating hydrocephalus with and without shunting

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From the Department of Neurology and Neurological Surgery and the Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, Missouri, USA
Origin of Washington University ADRC

- Tuesday Brown Bag Seminar group eventually decided to explore causes of “senile dementia” with a longitudinal study.

- After an unsuccessful first submission, “Mental Health in the Aged: Biomedical Factors” (R01 MH31054) awarded to Berg from 1979-1982:
  - Multidisciplinary; Botwinick and Storandt (Psychology) provide scientific rigor.
  - Use cognitive test performance as outcome measure; to avoid confounding when tests also were used to classify participants, developed the Clinical Dementia Rating (CDR; Hughes et al, Brit J Psychiatr 1982).
  - Memory and Aging Project (MAP) established as clinical research office; first participant enrolled in August 1979.
• NIMH does not fund renewal application in 1983

• Zaven Khachaturian asks Berg to submit a more comprehensive application to NIA, and it is successful: the Program Project “Healthy Aging and Senile Dementia” (L. Berg, PI) begins January 1, 1984
  – Now completing its 29th year of continuous funding

• In 1985, NIA also awards an ADRC grant to Berg; grant just began its 29th year of continuous funding
  – Original grant: 5 Cores, 7 R01-type Projects
  – Total DCs = $6,521,171  (in today’s dollars, $13,504,720)

• In 1983, Charles Hughes leaves Washington University for private practice; Berg recruits a new Instructor in Neurology
Develop Signature ADRC Principles

- CDR certification
  - Trainee Morris rated a control person as CDR 0.5 (Berg had rated CDR 0 as the person performed “normally” on testing)
  - Neuropathology examination showed histologic AD
  - Case report (Morris and Fulling 1988, Arch Neurol 45:345-349) introduces the concepts of:
    » Intra-individual decline as the salient feature of symptomatic AD
    » Informant history to capture this decline
    » Preclinical AD

- CDR 0.5
  - Previously denoted “questionable dementia”, now recast as earliest stage of symptomatic AD, or very mild dementia (Morris et al. 1991, Neurology 41:469-478)
Joseph L (Joel) Price, PhD
Tangles, CDR = 0

No Plaques

Age = 60

Age = 75

Age = 88

Plaques, CDR = 0

Age = 80

Age = 83

Age = 82

Age = 74

Orange = diffuse plaques
Green = neuritic plaques

Price and Morris, Ann Neurol 1999;45:358-368
Morphometric Evidence for Preclinical AD – I.

- Price JL et al. (Neurobiol Aging 1991; 12:295-312)
  - “Substantial pathological changes…in cases at the threshold for clinical dementia”

- Collaboration with Brad Hyman and colleagues (Gomez-Isla T et al., J Neurosci 1996; 16:4491-4500)
  - Case material from Washington University ADRC
  - Unbiased stereology shows neuronal number in EC is constant between ages 60-90 in CDR 0 cases, but decreases by 60% in layer II of EC in CDR 0.5 and by 90% in CDR 3 cases
  - Preservation of neurons distinguishes healthy aging from very mild symptomatic AD, which already has irreversible brain damage
Morphometric Evidence for Preclinical AD – II.

  - Plaques are absent in some CDR 0 brains (up to age 88) but NFTs in medial temporal structures are ubiquitous
  - ~30% of CDR 0 brains have full histopathological AD, or preclinical (asymptomatic) AD

- Price JL et al. (Arch Neurol 2001; 58:1395-1402)
  - Preservation of neuronal number distinguishes preclinical AD from even very mild symptomatic AD
### Hypothetical Relationships of Aging, Preclinical AD, and Symptomatic AD

<table>
<thead>
<tr>
<th></th>
<th>Aging</th>
<th>Preclinical AD</th>
<th>Very Mild AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaques in neocortex</td>
<td>None or a few diffuse plaques</td>
<td>Many neuritic &amp; diffuse plaques</td>
<td>Many neuritic &amp; diffuse plaques</td>
</tr>
<tr>
<td>Tangles in entorhinal cortex &amp; hippocampus/CA1</td>
<td>Few to many (increases w/age)</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td>Cell loss in entorhinal cortex &amp; hippocampus/CA1</td>
<td>None</td>
<td>Little to none</td>
<td>Substantial (30%-60%)</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>Normal, CDR 0</td>
<td>Normal, CDR 0</td>
<td>Very mild dementia or MCI, CDR 0.5</td>
</tr>
<tr>
<td>Pathological diagnosis</td>
<td>Normal</td>
<td>AD</td>
<td>AD</td>
</tr>
</tbody>
</table>

Models of Aβ Accumulation During Preclinical and Symptomatic AD

Possible models of Aβ growth:

- Inflammation
- Microglia
- Tau
- Oxidative stress
- Others

Neuronal and Synaptic Integrity

No AD | Preclinical AD | CDR 0.5→1→2→3 Clinical AD | Neuropathology

Onset of symptoms | Death

Years
Move to in vivo Detection of Preclinical AD – I.

- David Holtzman recruited to WUSM in 1994; he and colleague Anne Fagan in the ADRC establish a large and valuable repository of CSF and plasma in AD cases.

- At the 4th Leonard Berg Symposium in September 2003, William Klunk from University of Pittsburgh presents “Benzathiazole Amyloid Imaging Agents for PET” and begins collaboration with Mark Mintun, Morris, and other ADRC investigators.

- ADRC biomarker efforts expand under leadership of Morris as Director, Alison Goate, Eugene Johnson, Jr., and Holtzman as Associate Directors, and Virginia Buckles (joined later by Krista Moulder) as Executive Director.
Move to in vivo Detection of Preclinical AD – II.

- In 2005, “Antecedent Biomarkers for AD: The Adult Children Study” (P01 AG026276; JC Morris, PI) is awarded and combined with the HASD/ADRC cohorts allows examination of AD biomarkers in cognitively normal persons from age 45 y to 100+ y.

- In 2007, a supplement to the ACS is awarded to inaugurate the “Familial Adult Children Study”, led by Randy Bateman.

- In 2008, the ACS and its FACS serve as the infrastructure for a successful application to establish the Dominantly Inherited Alzheimer Network (DIAN; U19 AG032438; JC Morris, PI).
“Alzheimer disease” (AD) refers to the neurodegenerative brain disorder, regardless of clinical status, representing a continuous process of synaptic and neuronal deterioration.

AD has two major stages:
- Preclinical (presymptomatic; asymptomatic), undetectable by current clinical methods
- Symptomatic (clinical)

Symptomatic AD is defined by intraindividual cognitive decline, from subtle to severe, that interferes with daily function, and can be subclassified on symptom severity:
- Incipient (prodromal; mild cognitive impairment)
- Dementia

Preclinical AD is first detected at ~50 y and increases in frequency as a function of age and APOE4 status.

Preclinical AD is associated with development of symptomatic AD within ~5 y. – Fagan et al., Arch Neurol 2007; 64:343-349
– Morris et al., Arch Neurol 2009; 66:1469-1475

DIAN Validates AD Biomarkers

- Biomarkers are detected only in mutation carriers (MCs).
- Biomarker changes in asymptomatic MCs develop 20-25 years before estimated age of symptom onset.

The NEW ENGLAND JOURNAL of MEDICINE

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer’s Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghatti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network
Alzheimer Biomarker Pathochronology in Autosomal Dominant AD

Morris et al., Clin Invest 2012 (in press)
The Inaugural Berg Symposium

- Berg relinquishes leadership of the ADRC in 1997 (and becomes Emeritus Professor on retirement in 1998)
- To honor his seminal contributions, the 1st Leonard Berg Symposium was held on April 4th, 1997

Zaven Khachaturian
Robert Katzman
Donald L. Price

William A. Peck
William R. Markesbery
Dennis J. Selkoe
“Leonard Berg has been the motivating force in the University-wide program in dementia” - William Landau, MD

1927-2007