May 8th 1945
Nine months and a year or so later....
FIRST BABY BOOMERS HIT PENSION-AGE TODAY

By Sarah O'Grady, Social Affairs Correspondent

HISTORY is being made today as the first baby boomers become old enough to retire.

Children conceived during the VE Day celebrations of May 8, 1945, are turning 65.

They were the start of the post-war baby boom, which saw thousands of soldiers returning home and having families.
More than 1,000,000 with dementia in the UK by 2050
More than £20 billion per year today
Economic costs of dementia per year

http://www.alzheimersresearchuk.org/dementia-statistics/
Alzheimer's disease: treatments and tests on the horizon
Prospects for disease modification therapies; and why we aren’t closer
Alzheimer and Auguste
Nov 26, 1901

She sits on the bed with a helpless expression. What is your name? **Auguste.** Last name? **Auguste.** What is your husband’s name? **Auguste, I think.** Your husband? **Ah, my husband.** She looks as if she didn’t understand the question. Are you married? **To Auguste.** Mrs D? **Yes, yes, Auguste D.** How long have you been here? She seems to be trying to remember. **Three weeks.** What is this? I show her a pencil. **A pen.** A purse and key, diary, cigar are identified correctly. At lunch she eats cauliflower and pork. Asked what she is eating she answers **spinach.**

*Lancet* **349** 1546-49
“In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability”

“Numerous small milary foci are found in the superior layers. They are determined by the storage of a peculiar material in the cortex.”

Lancet 349 1546-49
Plaques and Tangles
Plaques, amyloid and amyloid precursor protein
Metabolism of amyloid precursor protein
New treatments for AD – amyloid approaches
APP – mutations and secretases

- Swedish mutation 670/671
- Flemish mutation 692
- Dutch mutation 693
- London mutations 717
- Florida mutation 716
- $\beta$ secretase
- $\alpha$ secretase
- $\gamma$ secretase
New treatments for AD – amyloid approaches

Increased clearance

Anti-fibrillogensis

β secretase inhibitors

γ secretase inhibitors
The amyloid cascade hypothesis

Environment

Genes for late onset AD
…..it takes tau to tangle

Neurofibrillary tangles composed of aggregated, phosphorylated tau
Tau and the neuronal cytoskeleton
Tau phosphorylation and aggregation

normal

phosphorylation

Alzheimer’s disease
Genes

Environment

Genes


AT8

GSK-3 inhibitor
Modelling tauopathies

Motor neuron expression (UAS:GAL4)
Increased Tau
Active GSK3 (S9A-Sgg)

Larval phenotype
Larval phenotype
Adult phenotype

Proportion reaching top chamber vs. Days post occlusion for Wild-type and Tau transgenic groups.
GSK-3 inhibition rescues phenotype

GSK-3 dependent, tau induced phenotype
Disease modification therapies

Public health measures (e.g., diabetes, diet)

Environment

Genes for late onset AD

Anti-fibrillisation

Increased clearance

Immunisation

Secretase inhibitors

GSK3 inhibitors
## Progress towards new therapies

### Drugs in development for Neurodegenerative diseases June 2008:

<table>
<thead>
<tr>
<th></th>
<th>Company</th>
<th>Status</th>
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<tr>
<td>Phase II for Alzheimer’s</td>
<td>Elan/Wyeth</td>
<td>disease modification</td>
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<td>Elan/Wyeth</td>
<td>symptomatic/disease modification</td>
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<td>Voyager</td>
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<td>Wilmar Schwabe GmbH&amp;Co</td>
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<td>Mifepristone</td>
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<td>Tarenflurbil</td>
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<td>Xaliprodene</td>
<td>Sanofi-Aventis</td>
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<td>Gammagard</td>
<td>Baxter</td>
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<td>Semagacestat</td>
<td>Eli Lilly</td>
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<tr>
<td>Solanezumab</td>
<td>Eli Lilly</td>
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But the trials are failing!
The continuum of Alzheimer’s disease

Cognitive function

Preclinical

Aging

MCI

Dementia

Years
Biomarkers for dementia – CSF Aβ and tau; PET amyloid ligands
Biomarkers for dementia – alternative approaches
Automated regional analysis of structure

Atlas defined on template brain, in stereotaxic space

AD subjects, the color represents thickness in mm. Blue <1 mm and red=5 mm
Alzheimer’s versus controls

(Q2(Y) = 0.63)

Andy Simmons, Lars-Olof Wahlund, Christian Spenger
New system uses brain scans to spot early Alzheimer's

By Dominic Hughes
Health correspondent, BBC News

A new method using brain scans to spot the early signs of Alzheimer's Disease is being tested in NHS memory clinics.

An advanced computer programme compares a patient's brain scan with a database of 1,200 existing images of brains already affected by the disease.
Searching for a blood marker for Alzheimer’s disease

Correlation with cortical atrophy
Correlation with cognition (MMSE)
Correlation with speed of decline
Plasma Clusterin association with brain amyloid

In man....

Plasma clusterin *in life* correlates with brain clusterin in superior temporal gyrus

\[ R=0.47 \; ; \; p = 0.027 \; ; \; N=22 \]

In mouse....

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**In brain....**
Association of Plasma Clusterin Concentration With Severity, Pathology, and Progression in Alzheimer Disease

Madhav Thambisetty, MD, PhD; Andrew Simmons, PhD; Latha Velagapudi, DNB (Psychiatry); Abdul Hye, PhD; James Campbell, PhD; Yi Zhang, MD; Lars-Olof Wahlund, MD; Eric Westman, PhD; Anna Kinsey, PhD; Andreas Güntert, PhD; Petroula Potsi, PhD; John Powell, PhD; Miroslava Causevic, PhD; Richard Killick, PhD; Katie Lunn, PhD; Steven Lynham, MSC; Martin Broadstock, PhD; Fahad Choudhry, PhD; David R. Howett, PhD; Robert J. Williams, PhD; Sally L. Sharp, PhD; Cathy Mitchellmore, PhD; Catherine Tunnard, BSc; Rujina Leung, BSc; Catherine Fox, PhD; Daragh O’Brien, MSC; Gerome Breen, PhD; Simon J. Furey, PhD; Malcolm Ward, MSc; Iwona Klossowska, MD; Patricia Meccoci, MD; Hilinbba Sohninen, MD; Magda Tsolaki, MD; Bruno Vellas, MD; Angela Hodges, PhD; Declan G. M. Murphy, MB BCh, FRCPsych; Sue Parkins, PhD; Jill C. Richardson, PhD; Susan M. Resnick, PhD; Luigi Ferrucci, MD, PhD; Dean F. Wong, MD, PhD; Yun Zhou, PhD; Sebastian Muchilloch, MSC; Alan Evans, PhD; Paul T. Francis, PhD; Christian Spencer, PhD; Simon Lovestone, MRC Psych, PhD

**Context:** Blood-based analytes may be indicators of pathological processes in Alzheimer disease (AD).

**Objective:** To identify plasma proteins associated with AD pathology using a combined proteomic and neuroimaging approach.

**Design:** Discovery-phase proteomics to identify plasma proteins associated with correlates of AD pathology. Confirmation and validation using immunodetection in a replication set and an animal model.

**Setting:** A multicenter European study (AddNeuroMed) and the Baltimore Longitudinal Study of Aging.

**Participants:** Patients with AD, subjects with mild cognitive impairment, and healthy controls with standardized clinical assessments and structural neuroimaging.

**Main Outcome Measure:** Association of plasma proteins with brain atrophy, disease severity, and rate of clinical progression. Extension studies in humans and transgenic mice tested the association between plasma proteins and brain amyloid.

**Results:** Clusterin/apolipoprotein J was associated with atrophy of the entorhinal cortex, baseline disease severity, and rapid clinical progression in AD. Increased plasma concentration of clusterin was predictive of greater fibrillar amyloid-β burden in the medial temporal lobe. Subjects with AD had increased clusterin messenger RNA in blood, but there was no effect of single-nucleotide polymorphisms in the gene encoding clusterin with gene or protein expression. APP/PS1 transgenic mice showed increased plasma clusterin, age-dependent increase in brain clusterin, as well as amyloid and clusterin colocalization in plaques.

**Conclusions:** These results demonstrate an important role of clusterin in the pathogenesis of AD and suggest that alterations in amyloid chaperone proteins may be a biologically relevant peripheral signature of AD.

Arch Gen Psychiatry. 2010;67(7):739-748
Next steps – assay design for qualification

Intellectual property on ~30-protein panel protected by KCL/Proteome sciences. Licensed for research use to Millipore

Joint development with Proteome Sciences and Millipore

Funding from MRC

Luminex xMAP panel

- discovered biomarkers (n~30)
- complement pathways (n~15)

MS panel using Reaction Monitoring and isobaric tags
Genome-wide association study identifies variants at \textit{CLU} and \textit{CR1} associated with Alzheimer’s disease

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Genome-wide association study identifies variants at \textit{CLU} and \textit{PICALM} associated with Alzheimer’s disease

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100 years of progress
Annual government and charity investment in research

Government and charitable spending on dementia research is 12 times lower than on cancer research. £590 million is spent on cancer research each year, while just £50 million is invested in dementia research. Heart disease receives £169 million per year and stroke research £23 million.

http://www.alzheimersresearchuk.org/dementia-statistics/
100 km for dementia research!

http://uk.virginmoneygiving.com/team/KingsDementiaResearch

Maudsley Charity
Health in Mind

June 9th 2011
Acknowledgements

Current lab members

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<td>Joanna Riddoch-Contreras</td>
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<td>Chantal Bazenet</td>
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<td>Jennifer Bousfield</td>
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<td>Madhav Thambisetty (NIA)</td>
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<tr>
<td>Sarah Westwood</td>
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<td>Megan Pritchard</td>
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<td>Ana Bajo</td>
<td>Michaela Litchmore-Dunbar</td>
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...and many colleagues and collaborators
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MRC

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Alzheimer’s Research Trust and Alzheimer’s Society

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