Alzheimer's Disease

A mind in darkness awaiting the drink of a gentle color.

Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD
Gabriel García Márquez

One Hundred Years of Solitude
Alois Alzheimer

- Case of Auguste D., 50 year old woman in Germany - 1906
- Her disruptive behavior prompted her husband to see Dr. Alzheimer.

Insight: Dementia is physical

- Alzheimer examined Auguste D.’s brain.
- Discovered plaques and tangles.
- At the time it was thought that dementia was normal aging.
DEGENERATION GENERATION

The prevalence of Alzheimer’s disease is expected to rise sharply in the United States as its population ages.

[Graph showing increasing trend of people with Alzheimer’s disease from 2000 to 2050, with upper and lower estimates indicated.]
EARLY ONSET:

Memories begin failing in one’s 40s, occasionally as early as 32.

By 47, on average, full-blown Alzheimer’s develops.

New York Times, The Vanishing Mind 2010
A Clouded Inheritance

A group of 25 families in Colombia has inherited a genetic mutation from common ancestors, making members prone to early-onset Alzheimer’s.

At right, Alzheimer’s cases among the founding members of the clan and some of their early descendants, who number in the thousands today.

KEY

- No Alzheimer’s
- Suspected cases
- Known cases

PAISA MUTATION

The inherited disease is caused by a mutation of the presenilin 1 gene on chromosome 14.

Note: the chart has been simplified and does not show all children or descendants.

**TODAY** Carlos Alberto Villegas, his wife and their siblings descend from a common ancestor, circled above, who had the Paisa mutation.

Carlos Alberto, 53. Onset of memory problems at 41.

María Elsy, 61 (his sister) 48 at onset.

Darío, 55 (his brother) 47 at onset.

Oderis, 50 (his brother) 46 at onset.

Blanca Nelly, 41 (his wife) Currently no symptoms.

William, 48 (her brother) 45 at onset.

Gladys, 36 (her sister) Too afraid to have children.

Liliana, 29 (her sister) Terrified of any memory lapse.

Two sisters show early symptoms but deny it.

Source: University of Antioquia

New York Times, The Vanishing Mind 2010
The Vanishing Mind

In the mountains of northwest Colombia, many members of a sprawling extended family suffer from a genetic mutation that makes them begin to forget in their early 40s. | Related Article
eFAD

- Early onset familial Alzheimer disease

family

- Dominant genetic trait
- One parent had eFAD
- Siblings: 50%

same, (mostly)

- eFAD and late-onset AD is essentially the same disease
Early-Onset Alzheimer Disease in Families With Late-Onset Alzheimer Disease

A Potential Important Subtype of Familial Alzheimer Disease

Kiri L. Brickell, MBChB; Ellen J. Steinbart, RN, MA; Melia Rumbaugh, MS, CGC; Haydeh Payami, PhD; Gerard D. Schellenberg, PhD; Viviana Van Deerlin, MD, PhD; Wuxing Yuan, MS; Thomas D. Bird, MD
autosomal dominant forms (eFAD)

- amyloid precursor protein (APP) on Chromosome 21
- presenilin-1 (PS1) on Chromosome 14
- presenilin-2 (PS2) on Chromosome 1

Accounts for most eFAD
Members of 25 extended families, with 5,000 members, develop early-onset Alzheimer’s, usually before the age of 50, if they harbor an aberrant version of a particular gene.

**PAISA MUTATION**
The inherited disease is caused by a mutation of the presenilin 1 gene on chromosome 14.
<table>
<thead>
<tr>
<th>12 to 15 fold increase risk for AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not autosomal dominant (ApoE)</strong></td>
</tr>
<tr>
<td>ApoE4</td>
</tr>
<tr>
<td><strong>ApoE4 is thought to lower the age of onset by a decade</strong></td>
</tr>
</tbody>
</table>
- eFAD
- Test drugs before symptoms

- Many recent drug candidates have failed in trials.
- Perhaps because the drugs were given too late.

- When a person loses their memory – it is too late.
- The disease has been present for a long time by the time there are symptoms.

- Preventative or delay strategies.
<table>
<thead>
<tr>
<th>Delay or stop</th>
<th>Administered 7 years before average age of diagnosis</th>
<th>Alzheimer’s Prevention Initiative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessing treatment by tracking AD specific biomarkers.</td>
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</table>
• 5 – 20 years before diagnosis of Alzheimer’s dementia
• damages synapses

• 1 – 5 years before diagnosis
• Tau protein detaches from the microtubules.

• 1 – 3 years before diagnosis
• Cell death shrinks the brain.
Amyloid Accretion 5–20 years before diagnosis of Alzheimer’s dementia

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
Amyloid-beta blocks neurotransmitters from reaching the post-synaptic receptors.
PET scans show increasing retention in the brain’s frontal lobes of the amyloid-beta tracer Pittsburg imaging compound-B (PIB) over the course of two years in a 74-year-old, even while the subject remained cognitively normal.

Scientific American (June 2010)

*Alzheimer’s: Forestalling the Darkness*
Neuron

Disintegrating microtubule

Enzyme adding phosphate groups to tau

Microtubules held together by tau proteins

Toxic tangles formed by tau

Alzheimer’s: Forestalling the Darkness
• Spinal tap
• Measures levels of tau protein
Healthy brain

Alzheimer’s brain

Hippocampus

Extreme shrinkage of hippocampus

Scientific American (June 2010)

Alzheimer’s: Forestalling the Darkness
Computer graphic of slices through a normal brain and an Alzheimer’s brain, derived from volumetric magnetic resonance imaging, shows considerable shrinkage (right) from degeneration and death of nerve cells.
Does changing amyloid beta levels really improve cognition?

One needs to apply a cognitive test along with a biomarker measure in order to make sure that the treatments are helping.
Inhibitors of enzymes that produce amyloid-beta

Enzymes are involved in precursor steps

Vaccines/Antibodies

Vaccines induce the body to produce antibodies that bind to amyloid and clear them from the brain.
Amyloid-beta aggregation blockers

Agents that prevent amyloid fragments from clumping could prevent damage to neurons

Anti-tau compounds

Blocking production of the toxic form of the tau protein

Or

Impeding its aggregation into tangles
Targeting small Aβ oligomers: the solution to an Alzheimer’s disease conundrum?

William L. Klein, Grant A. Krafft and Caleb E. Finch

Amyloid β (Aβ) is a small self-aggregating peptide produced at low levels by normal brain metabolism. In Alzheimer’s disease (AD), self-aggregation of Aβ becomes rampant, manifested most strikingly as the amyloid fibrils of senile plaques. Because fibrils can kill neurons in culture, it has been argued that fibrils initiate the neurodegenerative cascades of AD. An emerging and different view, however, is that fibrils are not the only toxic form of Aβ, and perhaps not the neurotoxin that is most relevant to AD: small oligomers and protofibrils also have potent neurological activity. Immuno-neutralization of soluble Aβ-derived toxins might be the key to optimizing AD vaccines that are now on the horizon.

Klein, W. L. et al (2001), TINS, Vol.24 No.4
Atomic force microscopy of amyloid-\(\beta_{1-42}\) forms.

A\(\beta\)-derived diffusible ligands

Fig. 1. Different assembled states of amyloid \(\beta_{1-42}\) (A\(\beta_{1-42}\)). The assembled forms obtained from incubation of synthetic A\(\beta_{1-42}\) are highly sensitive to preparation and incubation\(^{10}\). Widely differing proportions of insoluble fibrils, soluble protofibrils (PFs) and oligomers are revealed by atomic force microscopy\(^{11}\). Typical PF and fibril preparations contain varying levels of small globular molecules, putatively A\(\beta_{1-42}\) oligomers; A\(\beta\)-derived diffusible ligand (ADDL) preparations initiated from monomeric dimethyl sulphoxide stock solutions are fibril- and PF-free, and (uniquely) comprise oligomers. Scale bar, 200 nm. Fibril, PF and ADDL preparations all show neurotoxicity \textit{in vitro}.

Courtesy of Brett Chromy and Blaine Stine.
(a) ADDLs are potent neurotoxins that slowly kill hippocampal neurons in mature brain slice preparations. With the live–dead dual fluorescence assay, **ADDLs selectively induce death in hippocampal CA1 neurons**, whereas a subpopulation of CA3 neurons and cerebellar neurons are resistant.

(b) **ADDLs block LTP** in hippocampal slice within 1 hr. In vivo stereotaxic injections give similar results. As seen here, ADDLs do not block pre-tetanic population spikes, nor do they inhibit EPSPs or LTD.

Klein, W. L. et al (2001), TINS, Vol.24 No.4
What Causes Alzheimer's?

- Scientists are still not certain.
- Age and family history have been identified as potential risk factors.
- Researchers are exploring the role of genetics.
- Diabetes?
- Sleep problems?
What's insulin got to do with it?

It is not just in the pancreas!

- **insulin**
  - Hormone helps store sugar and fat for energy – produced in pancreas.

- **Type 1 diabetes**
  - When body cannot produce enough insulin

- **Type 2 diabetes**
  - When body has inadequate insulin response

- **Type 3 diabetes?**
  - Neurodegenerative diseases? Alzheimer’s, Parkinson’s & Huntington’s
Insulin receptors in the brain!

- Learning and memory
- Snort insulin → better recall
- Memory tasks → increases insulin levels

Suzanne de la Monte
@ Brown University

- Does insulin have a part in Alzheimer’s disease?
- Postmortem study – compare insulin receptors in AD and healthy control brains.

Healthy brains had more insulin...

- Healthy brains had on average 4x higher insulin levels and 10x as many insulin receptors in the learning and memory regions of the brain

Diabetics are...

- 2x more likely to develop AD
- 7x more likely to develop Huntington’s disease
- 50% of Parkinson’s patients have glucose metabolism dysfunction.
AD and T2D share:

- Demographic profiles
- Risk factors
- Clinical features
- Biochemical features
Type 2 Diabetes – metabolic disorder

- > 30 years of age
- 7% global population

Characterized by a relative insulin deficiency

Risk factors – high blood glucose, obesity, vascular disease, insulin resistance

All of these factors, individually and collectively, increase the risk of AD and vascular dementia
We observed that people with Type 2 diabetes had more hippocampal and amygdalar atrophy on MRI than people without diabetes. Moreover, in persons without diabetes mellitus, insulin resistance was associated to amygdalar atrophy on MRI. The presence of atherosclerosis or cerebrovascular disease did not explain the associations.

The strengths of our study are its population-based design and the large sample with volumetric MRI. The prevalence of diabetes mellitus in our study was comparable to another Dutch population study [27], leading to a moderate number of people with diabetes mellitus studied in the sample. However, the associa-

Fig 2. Hippocampal volumes and amygdalar volumes (standard error) on brain MRI in participants with diabetes (n=41) and without diabetes (n=65). Volumes are adjusted for age and sex and normalised to average head size.
Elevated levels of insulin → Cross blood brain barrier → Compete with amyloid-β for IDE insulin-degrading enzyme.

The insulin-degrading enzyme (IDE) has a major role in clearance of both insulin and amyloid-β peptide.
Metabolic Alterations Induced by Sucrose Intake and Alzheimer’s Disease Promote Similar Brain Mitochondrial Abnormalities

Cristina Carvalho,¹,² Susana Cardoso,¹,² Sónia C. Correia,¹,² Renato X. Santos,¹,² Maria S. Santos,¹,² Inês Baldeiras,¹,³ Catarina R. Oliveira,¹,⁴ and Paula I. Moreira¹,⁵
Neuropathological studies of patients with Parkinson's disease have shown that insulin receptors are densely represented on the dopaminergic neurons of the substantia nigra pars compacta (Unger et al., 1991) and loss of insulin receptor immunoreactivity and messenger RNA in the substantia nigra pars compacta of patients with Parkinson's disease coincides with loss of tyrosine hydroxylase messenger RNA (the rate-limiting enzyme in dopamine synthesis) (Moroo et al., 1994; Takahashi et al., 1996).
Neuroprotective agents

Boost natural brain chemicals

Enhance health of neurons
Disrupted Sleep?

- Diabetes
- Heart Disease
- Memory problems
- AD biomarker increase with disrupted sleep
  - 8h in bed → only 6.5h of sleep
Alzheimer’s Disease: The Challenge of the Second Century

David M. Holtzman,1,2,3,4,5 John C. Morris,1,3,4,5 Alison M. Goate1,3,4,6

Alzheimer’s disease (AD) was first described a little more than 100 years ago. It is the most common cause of dementia with an estimated prevalence of 30 million people worldwide, a number that is expected to quadruple in 40 years. There currently is no effective treatment that delays the onset or slows the progression of AD. However, major scientific advances in the areas of genetics, biochemistry, cell biology, and neuroscience over the past 25 years have changed the way we think about AD. This review discusses some of the challenges to translating these basic molecular and cellular discoveries into clinical therapies. Current information suggests that if the disease is detected before the onset of overt symptoms, it is possible that treatments based on knowledge of underlying pathogenesis can and will be effective.
http://www.pbs.org/theforgetting/