Alzheimer's Disease

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

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One Hundred Years of Solitude

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

Alois Alzheimer

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

insight: dementia is physical
DEGENERATION GENERATION

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

![Graph showing the increase in people with Alzheimer's disease from 2000 to 2050 with upper and lower estimates.](graph.png)
THE POPULATION IS AGING...
Millions of people aged 65 and older, living in the U.S.

... AND AGE IS THE BIGGEST RISK FACTOR FOR ALZHEIMER'S...
Risk of developing Alzheimer's at a given age over the next 10 years, for males and females.

... SO THE NUMBER OF CASES IS GROWING
Numbers of people diagnosed with Alzheimer's will increase by nearly 50 percent during the next 20 years.
1 dot represents 100,000 people diagnosed with Alzheimer's.

2000: 4.7 million
2010: 5.3 million
2030: 7.9 million
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
Over three centuries, many in this lineage of 5,000 people have inherited a single genetic mutation guaranteeing that they will develop Alzheimer's.
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.
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
- Early onset familial Alzheimer disease
- Dominant genetic trait
- One parent had eFAD
- Siblings: 50%
- eFAD and late-onset AD is essentially the same disease

(eFAD, family, same, mostly)
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; Malia Runbaugh, MS; GCC; Haydeh Payami, PhD; Gerard D. Schellenberg, PhD; Vivianna Van Deerlin, MD, PhD; Wuxing Yuan, MS; Thomas D. Bird, MD
### Autosomal Dominant Forms (eFAD)

<table>
<thead>
<tr>
<th>Protein/Gen</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid Precursor Protein (APP)</td>
<td>21</td>
</tr>
<tr>
<td>Presenilin-1 (PS1)</td>
<td>14</td>
</tr>
<tr>
<td>Presenilin-2 (PS2)</td>
<td>1</td>
</tr>
</tbody>
</table>

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.
12 to 15 fold increase risk for AD

Not autosomal dominant (ApoE)

ApoE4

ApoE4 is thought to lower the age of onset by a decade
lessons
- eFAD
- Test drugs before symptoms

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

memory
- 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.

lifestyle
- Preventative or delay strategies.
Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
Delay or stop
Assessing treatment by tracking AD specific biomarkers.

Administered 7 years before average age of diagnosis

Alzheimer’s Prevention Initiative
• 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.
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*
Disintegrating microtubule

Enzyme adding phosphate groups to tau

Microtubules held together by tau proteins

Toxic tangles formed by tau

Neuron
• Spinal tap
• Measures levels of tau protein
Alzheimer’s brain

Healthy brain

Hippocampus

Extreme shrinkage of hippocampus
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-β$_{1-42}$ forms.

Aβ-derived diffusible ligands

Fig. 1. Different assembled states of amyloid β$_{1-42}$ (Aβ$_{1-42}$). The assembled forms obtained from incubation of synthetic Aβ$_{1-42}$ are highly sensitive to preparation and incubation. Widely differing proportions of insoluble fibrils, soluble protofibrils (PFs) and oligomers are revealed by atomic force microscopy. Typical PF and fibril preparations contain varying levels of small globular molecules, putatively Aβ$_{1-42}$ oligomers; Aβ-derived diffusible ligand (ADDL) preparations initiated from monomeric dimethyl sulfoxide stock solutions are fibril- and PF-free, and (uniquely) comprise oligomers. Scale bar, 200 nm. Fibril, PF and ADDL preparations all show neurotoxicity in vitro. Courtesy of Brett Chomy and Blaine Stine.

Klein, W. L. et al (2001), TINS, Vol.24 No.4
(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.
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?
Sleep wake cycle is regulated by the circadian system.
Superchiasmatic Nucleus in the brain is the “master clock” used to coordinate and synchronize most of the body clocks in the periphery.
If the sleep wake cycle is disrupted it can cause metabolic dysregulation.

- Shift work
- Jet lag
- Sleep disorders
- Poor sleep hygiene
- "All-nighters"

- Metabolic disruption
- Weight gain, obesity
- Impaired immunity
- Cognitive malfunction
Cyanobacteria is a photoautotrophic organism that has a self-sustained circadian rhythm.
Our metabolic clocks are based on the diurnal rhythm - it is in our genes.
Shift workers are more prone to developing metabolic disorders

- 40% more likely to have cardiovascular disease
- Higher incidence of Diabetes Type II
- Higher risk of cancer – melatonin disruption

The Health Survey for England (2013);
Davis S, Mirick DK. Cancer Causes Control. 2006 May; 17(4):539-45.
SCN is not the only clock in the body.

Food can be a zeitgeber for the gut.

Intestinal activity and its ability to absorb nutrients are dependent on the time of day.
Time of eating has a huge effect on the liver and insulin efficacy.
Insulin stimulates the liver to remove glucose from the blood and stores it as glycogen.

Beta cells release INSULIN.

Tissues take up glucose from blood.

Lowers glucose levels in blood.

Figure adapted from Kaidanovich-Beilin, O. et al. 2012.
Glucagon stimulates the conversion of stored glycogen in the liver into glucose. Increases glucose levels in blood.

Alpha cells release GLUCAGON

glycogen  glucose

low  blood glucose

Figure adapted from Kaidanovich-Beilin, O. et al 2012
Glucose uptake in muscle is dependent on the circadian rhythm.

Insulin-sensitivity is dependent on the peripheral clock in muscle cells.
Insulin activates insulin receptors in the brain → affects feeding behaviors, reward, body metabolism, normal emotion & cognitive behaviors.

Insulin receptors are found throughout the brain - cortex, midbrain and hypothalamus.
Diabetes is a risk factor for dementia.

The risk of developing Alzheimer's disease is increased by 50 percent in people with diabetes.


Diabetes is a risk factor for dementia
Cerebral excess release of neurotransmitter amino acids subsequent to reduced cerebral glucose metabolism in early-onset dementia of Alzheimer type

Short Note

S. Hoyer and R. Nitsch

Department of Pathochemistry and General Neurochemistry, University of Heidelberg, Heidelberg, Federal Republic of Germany

Accepted November 2, 1988

Summary. A massive cerebral release of amino acids and ammonia was found in early-onset dementia of Alzheimer type. Aspartate and glycine were liberated in high concentrations, whereas glutamate remained rather unchanged. This excess cerebral protein catabolism is due to a 44% reduction in cerebral glucose metabolism. Whereas glutamate and other glucoplastic amino acids may substitute glucose, elevated aspartate may contribute to neuronal damage. The results are discussed with respect to a possible neuronal insulin/insulin receptor deficiency.
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
Articles

Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI

T. den Heijer¹,², S. E. Vermeer¹,², E. J. van Dijk¹,², N. D. Prins¹,², P. J. Koudstaal¹,², A. Hofman¹, M. M. B. Breteler¹

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DOI 10.1007/s00125-003-1235-0

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=465). Volumes are adjusted for age and sex and normalised to average head size.
Functional relationship between AD and type-2 diabetes (T2D)

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.
High carbohydrate intake worsens cognitive performance and behavior in patients with Alzheimer’s disease.
The circadian clock has a profound effect on the physiology and behavior of organisms.
The circadian clock has a profound effect on the physiology and behavior of organisms.
A Single Night of Partial Sleep Deprivation Induces Insulin Resistance in Multiple Metabolic Pathways in Healthy Subjects

Esther Donga, Marieke van Dijk, J. Gert van Dijk, Nienke R. Biermasz, Gert-Jan Lammers, Klaas W. van Kralingen, Eleonara P. M. Corssmit, and Johannes A. Romijn

Departments of Endocrinology and Metabolic Diseases (E.D., M.v.D., N.R.B., E.P.M.C., J.A.R.), Neurology (J.G.v.D., G.-J.L.), and Pulmonology (K.W.v.K.), Leiden University Medical Center, 2300 RC Leiden, The Netherlands

the effect of a single night of partial sleep on insulin sensitivity

This is what really happens in your brain when you sleep.
Glymphatic System

Throughout most of the body, a complex system of lymphatic vessels is responsible for cleansing the tissues of potentially harmful metabolic waste products, accumulations of soluble proteins and excess interstitial fluid. But astonishingly, the body’s most sensitive tissue—the central nervous system—lacks a lymphatic vasculature. What then accounts for the efficient waste clearance that must occur in order for the neural tissue of our brains to function properly?

This question has puzzled scientists for centuries. Our group believes that understanding how this process functions in the healthy nervous system holds the key to developing treatment options for a wide variety of neurological diseases, especially those characterized by the improper accumulation of misfolded proteins. The breakdown of the brain’s innate clearance system may in fact underlie the pathogenesis of neurodegenerative disorders such as Alzheimer’s, Parkinson’s, and Huntington’s disease, in addition to ALS and chronic traumatic encephalopathy. Past efforts to explain how the brain cleanses parenchymal tissue have suggested that solute and fluid exchange occurs between the interstitial fluid and the cerebrospinal fluid, and that this exchange is driven by diffusion. Yet as many have noted, the distances for diffusion in the brain are too great to explain the highly regulated interstitial environment.
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie, Hongyi Kang, Qiwu Xu, Michael J. Chen, Yonghong Liao, Meenakshisundaram Thiagarajan, John O’Donnell, Daniel J. Christensen, Charles Nicholson, Jeffrey J. Iliff, Takahiro Takano, Rashid Deane, Maiken Nedergaard

The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

https://www.youtube.com/watch?v=ci5NMscKJws
Average Number of Hours of Sleep per Night

Kripke, D et al (1979) Arch Gen Psychiatry;
Gallup Organization (1995), Sleep in America;

Are you getting enough sleep?
What would happen if you got one more hour of sleep?
Go to this website and read the article.