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
Why study the damaged brain?

- Increases understanding of healthy brains
- Basis for development of new treatments
Recall

Time of eating has a huge effect on the liver and insulin efficacy.

Cellular response to INSULIN is dependent on the circadian cycle.

Insulin-sensitivity is dependent on the peripheral clock in muscle cells.

Glucose uptake in muscle is dependent on the circadian rhythm.
Recall

When you eat sugar determines how your body will respond

Eating sugar at night → higher blood sugar
The risk of developing Alzheimer's disease is increased by 50 percent in people with diabetes.

Craft, S. Nat. Rev. Neurol. 8, 360–362 (2012);

Diabetes is a risk factor for dementia
Recall

- Circadian rhythm disruption
- Metabolic dysfunction
- Insulin resistance
- Alzheimer’s Disease

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.

Auguste showed signs of dementia such as:
- Loss of memory
- Delusions
- Temporary vegetative states

Sleep disturbances:
- Trouble sleeping
  “drag sheets across the house and scream for hours in the middle of the night.”

http://en.wikipedia.org/wiki/Auguste_Deter

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

- Alzheimer examined Auguste D.’s brain.
- Discovered plaques and tangles.
- At the time it was thought that dementia was normal aging.
The prevalence of Alzheimer’s disease is expected to rise sharply in the United States as its population ages.
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.

Scientific American (June 2010) Alzheimer’s: Forestalling the Darkness
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.

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

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

Maria Eloy, 81 (his sister) 48 at onset.

Darío, 55 (his brother) 47 at onset.

Odiros, 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 lapses.

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
Francisco Lopera
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.
Amyloid accretion
- 5 – 20 years before diagnosis of Alzheimer’s dementia
- damages synapses

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

Brain shinkage
- 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

Disintegrating microtubule

Enzyme adding phosphate groups to tau

Microtubules held together by tau proteins

Toxic tangles formed by tau
Healthy brain

Alzheimer’s brain

Hippocampus

Extreme shrinkage of hippocampus

Scientific American (June 2010)

Alzheimer’s: Forestalling the Darkness
What’s sleep got to do with it?

Sleep disruption leads to metabolic disruption

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

Figures: Elko Otaka, NYT
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,1* Hongyi Kang,1* Qiwu Xu,2 Michael J. Chen,2 Yonghong Liao,2 Meenakshisundaram Thiagarajan,3 John O'Donnell,2 Daniel J. Christensen,1 Charles Nicholson,2 Jeffrey J. Iliff,1 Takahiro Takano,1 Rashid Deane,2 Maiken Nedergaard1†

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 fluid. 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.
Average Number of Hours of Sleep per Night

1960: 8+  
1995: 7  
2004: 6

Are you getting enough sleep?

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