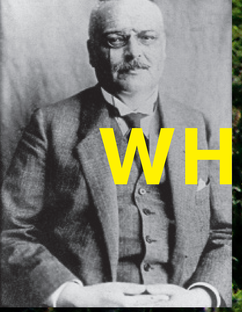

Aloysius "Alois" Alzheimer 1864-1915

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WHAT IF ALZHEIMER DEMENTIA IS A SYSTEMIC DISEASE?

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Family history of dementia, advanced or old age, are the only significant risk factors of developing Alzheimer dementia. These are the risks we cannot do anything about. Other risks include head trauma, stroke, cerebrovascular and cardiovascular events, neuropsychiatric conditions, obesity, diabetes, and the APOE4 gene. Some rare inherited forms of Alzheimer dementia are caused by APP, PS1 or PS2 gene mutations.

We argue Alzheimer dementia is not brain autonomous but a systemic disease. Long before any mind and memory problems appear there are signs and symptoms in the body. We can find out what they are, where they do come from, and how they cause and contribute to Alzheimer dementia progression. Such signs and symptoms present novel targets to prevent, delay and treat Alzheimer dementia.

THE AMYLOID HYPOTHESIS IS TOO GOOD TO BE TRUE

The amyloid hypothesis says Alzheimer dementia begins in the brain with Aß peptides accumulation and amyloid formation. The amyloid hypothesis has dominated Alzheimer research and clinical trials 25 years. However, 30% of people without Alzheimer have at careful autopsy examination typical amyloid pathology in the brain. Also, PET imaging of brain amyloid of mentally normal old people often looks like brain amyloid of Alzheimer people. These data say brain amyloid is not the cause of Alzheimer dementia.

WHAT A DRAG IT IS GETTING OLD

In the US 1900, there were 10,000 people at the age 100 years and over. In 2050, there are 1,000,000 people over 100 years. In the US today, 85 and over make the fastest growing group of people.

In the US 2014, Alzheimer research was funded with $750 million, while $1 billion a day was spent looking after 5.5 million people living with Alzheimer dementia, at homes and nursing homes.

In the US 2010-2050, Alzheimer dementia care will cost $20 trillion. We don't have that kind of money.

TIME AFTER TIME

One by one, every clinical trial of Alzheimer dementia treatment has failed. Did the trials fail because of what was done was too little too late, or did the trials simply fail perhaps because of our ideas about Alzheimer dementia etiology are wrong?

Too many trials had to be stopped early because the investigational drugs showed no efficacy, only made the Alzheimer people do worse. This gives Alzheimer research a bad name.

WHY ALZHEIMER DRUG DISCOVERY AND DEVELOPMENT IS FAILING?

According to the Pharmaceutical Research and Manufacturers of America (phrma.org), in 13 years between 1998-2011, clinical research and development of 101 drugs for Alzheimer dementia treatment were discontinued or canceled.

We know how to manage high blood pressure, high glucose and high cholesterol. Alzheimer mind is not like high blood pressure, high glucose, or high cholesterol. Mind is what the brain does. Mind is such a big target that whatever happens in the brain cannot miss it. Aß lowering drugs do not help prevent, delay, or treat Alzheimer dementia.

PREVENTION IS THE ONLY CURE

Alzheimer dementia does not happen overnight. A lifetime goes by before the mind and memory problems appear.

As an alternative for cure, we must look for prevention, and find ways to delay the onset, slow the progression, and stop Alzheimer dementia ever happening. A 5-year onset delay would reduce health care costs by 50%. Today that would mean savings of $0.5 billion a day.

Dementia is what or how it is diagnosed and measured. Can we discover and develop sensitive, predictive and differential psychometric measures associated with robust biomarkers and genomic signatures for the asymptomatic stage of dementia progression? Can we diagnose and measure something that is not there? In short, can we find the people at large at risk of developing Alzheimer dementia? Then what do we do next?

Preventive Alzheimer trials are large, take years to complete and yes, are very expensive and yet, insignificant in cost compared to the cost we spend the day after tomorrow for Alzheimer people.

Current trials include Alzheimer's Prevention Initiative (clinicaltrials.gov NCT01998841), Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (NCT02008357), and two DIAN trials (NCT00869817 and NCT01760005). All these trials use anti-Aß antibodies made by Genentech, Lilly or Roche, and aim to prevent or reduce brain amyloid formation in people genetically predisposed for Alzheimer dementia with the APOE4 gene, or in the unfortunate people in Medellin, Colombia, who are genetically determined for Alzheimer dementia with the PS1 gene mutation E280A. The trials may last till 2020.

December 19, 2014, one of the first preventive Alzheimer trials (NCT01224106) failed and was discontinued. This was a phase 3 trial on 360 people in 100 centers in 15 countries. This trial used *gantenerumab*, a novel fully humanized IgG1 mouse monoclonal antibody made by Roche that had been optimized for binding to a conformational Aß epitope in brain amyloid.

To improve the outcome of Alzheimer trials we need to recruit the right people and design the right "individualized" treatments for everybody.

BIOMARKERS AND GENOMIC SIGNATURES OF ALZHEIMER DEMENTIA

Why we have to discover and study biomarkers in the blood or cerebrospinal fluid, why we need to look for genomic signatures, to predict the risk of developing Alzheimer dementia?

We already know one in ten over 65, and one in two over 85 years is diagnosed with Alzheimer dementia. We already know, since 1993, two APOE4 genes increase Alzheimer dementia risk 12-fold. We already know 1% Alzheimer dementia is inherited and caused by dominant mutations in APP, PS1 or PS2 genes, in 0.5 million people in 517 families.

It is highly unlikely any biomarker or genome-wide association studies will ever find anything like APOE4, APP, PS1 or PS2.

We already have the data to develop targets for novel therapeutic interventions and disease-modifying treatments, if we care about cure of Alzheimer dementia.

DOES ANYBODY REALLY KNOW WHAT TIME IT IS?

USAgainstAlzheimers.org is committed to achieving the bold and attainable goal of ending Alzheimer's by 2020. Five years later in 2025, National Alzheimer's Project Act (napa.alz.org), from Act to Action has prevented Alzheimer's. Today alz.org has a vision of a world without Alzheimer's. In 2050, there are 160 million Alzheimer people. Is Alzheimer dementia the price we pay for the evolution of human mind half-million years ago?

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READ MORE

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