

REMEMBERING ALZHEIMER'S LEGACY: 110 YEARS SINCE THE PASSING OF ALOIS ALZHEIMER

Motto: "A peculiar disease of the cerebral cortex has captured my attention, one that reveals itself through profound memory loss, confusion, and a progressive erosion of the mind."

Alzheimer's disease, a devastating neurodegenerative condition, was first brought to the world's attention in 1906 by the German psychiatrist and neuropathologist Alois Alzheimer (1).

His ground-breaking work began with the study of a 51-year-old patient, Auguste Deter, who exhibited unusual symptoms of progressive memory loss, confusion, and hallucinations—an alarming decline that could not be classified within the known medical conditions of the time (2). After her passing, Alzheimer meticulously examined her brain and discovered the presence of amyloid plaques and neurofibrillary tangles, marking the first recorded case of what would later bear his name (3).

While Alzheimer's contributions were pivotal, he did not work in isolation. His mentor, Emil Kraepelin, one of the most influential psychiatrists of his era, played a crucial role in formally recognizing the disease.

In the 1910 edition of his Textbook of Psychiatry, Kraepelin classified this newly identified disorder as a distinct form of dementia, differentiating it from other types of cognitive decline that typically appeared in old age (4).

At the same time, Czech psychiatrist Oskar Fischer was independently investigating dementia and arrived at remarkably similar conclusions. In 1907, Fischer conducted a meticulous postmortem analysis of

16 elderly patients suffering from cognitive decline. He documented the accumulation of abnormal protein formations in their brains—structures he named Sphaerotrachia cerebri multiplex, which closely resemble what we now call amyloid plaques (5).

Meanwhile, Romanian neurologist Gheorghe Marinescu made crucial discoveries that predated both Alzheimer and Fischer. Collaborating with French pathologist Paul Blocq in 1892, Marinescu was among the first to describe peculiar plaque-like formations in the brain's grey matter, which he termed "nodules of neuroglial sclerosis" (6).

Each of these brilliant minds played a vital role in shaping our understanding of Alzheimer's disease. Their collective efforts laid the foundation for modern neuropathology, offering early insights into the biological mechanisms that underpin dementia. Their discoveries, once confined to the pages of medical journals, have since fueled over a century of research, bringing us closer to unravelling one of the greatest medical mysteries of our time.

Our comprehensive analysis explores the evolution of Alzheimer's disease (AD) research, highlighting the key scientific breakthroughs that have shaped our understanding of its neuropathology, clinical presentation, imaging advancements, treatments, and future directions from the early 20th century to today.

EARLY 20TH CENTURY DISCOVERIES

- 1906 – Alois Alzheimer’s Landmark Case: Alzheimer detailed the case of Auguste Deter, a 51-year-old woman with severe memory loss, confusion, and hallucinations. His post-mortem analysis revealed amyloid plaques and neurofibrillary tangles, establishing the foundation for AD pathology (1).

- 1910 – Emil Kraepelin defines AD: Kraepelin, a renowned psychiatrist and mentor to Alzheimer, formally named the disease in his *Textbook of Psychiatry*, distinguishing it from other dementias and cementing its place in medical literature (4).

- 1907 – Oskar Fischer’s Parallel Discoveries: Fischer independently described amyloid plaques in dementia patients, analyzing 16 postmortem brains and identifying protein aggregates he termed "Sphaerotrichia cerebri multiplex." Despite the significance of his findings, they were overshadowed by Alzheimer’s work (5).

- 1892 – Gheorghe Marinescu’s Early Observations: Marinescu and Paul Blocq were among the first researchers to describe grey matter plaques, referring to them as "nodules of neuroglial sclerosis." Their work laid the groundwork for the later recognition of amyloid pathology in AD (7).

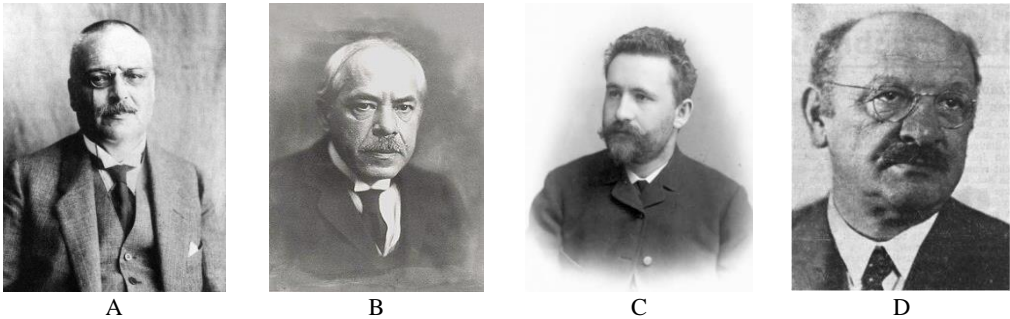


Fig. 1. A – Alois Alzheimer, the German psychiatrist and neuropathologist who first identified Alzheimer’s disease in 1906; B – Gheorghe Marinescu, the Romanian neurologist whose early work on senile plaques contributed to the understanding of neurodegeneration; C – Emil Kraepelin, the psychiatrist who formally classified Alzheimer’s disease in 1910; D – Oskar Fischer, the Czech psychiatrist who independently described amyloid plaques in dementia patients in 1907.

The recognition and understanding of Alzheimer’s disease emerged through the collective efforts of distinguished researchers, whose contributions, though shaped by different times and places, converged to define one of the most complex neurodegenerative disorders (fig. 1).

MID TO LATE 20TH CENTURY PROGRESS

- 1968 – Plaques Linked to Dementia:

A quantitative neuropathological study confirmed that the density of senile plaques correlated with cognitive decline, solidifying the amyloid hypothesis (8).

- 1984 – Beta-Amyloid Identified: Scientists successfully isolated and characterized beta-amyloid as the primary component of AD plaques, marking a turning point in molecular research (10).

- 1986 – Tau Protein’s Role Confirmed: Researchers discovered tau protein as a key

Remembering Alzheimer's legacy: 110 years since the passing of Alois Alzheimer

element of neurofibrillary tangles, reinforcing the dual-pathology model of amyloid and tau accumulation in AD (10).

- The pathological hallmarks of Alzheimer's disease (AD) include the accumulation of beta-amyloid plaques and neurofibrillary tangles, which contribute to neuronal dysfunction and degeneration. Beta-amyloid plaques form due to the abnormal aggregation of amyloid-beta peptides, dis-

rupting synaptic communication and triggering neuroinflammation. Meanwhile, tau protein abnormalities lead to the formation of neurofibrillary tangles, destabilizing the microtubule network essential for intracellular transport. The progressive accumulation of these pathological structures results in widespread neuronal loss, cortical atrophy, and cognitive decline, characteristic of AD (fig. 2).

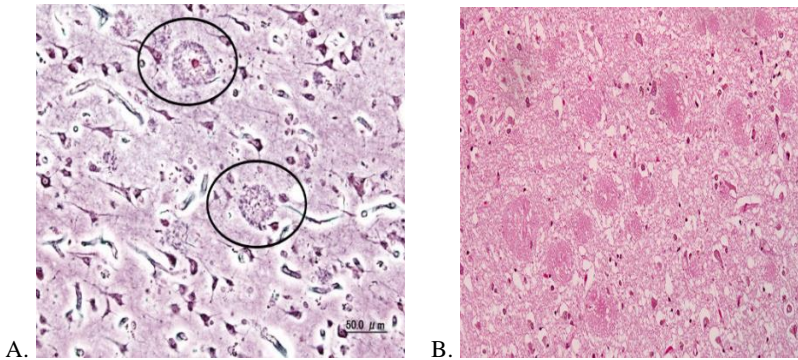


Fig. 2. A – Beta-amyloid plaques and tau pathology in Alzheimer's disease (Source: National Institutes of Health (NIH). Beta-Amyloid and Tau Pathology in Alzheimer's Disease. NIH; 2024); B – Neuronal degeneration in Alzheimer's disease, showing the widespread cellular damage caused by beta-amyloid accumulation and tau pathology (Source: Getty Images. Neuronal Degeneration in Alzheimer's Disease. Getty Images, 2024).

21ST CENTURY ADVANCEMENTS

- 2000s – Imaging Revolution: Advanced MRI and PET (fig. 3) scans transformed the ability to visualize AD-related brain changes, confirming that atrophy often begins in the medial temporal lobes, particularly in the hippocampus, before spreading to parietal and frontal regions (11).

- 2024 – Breakthrough in Blood-Based Diagnostics: A new blood test demonstrated 90% accuracy in detecting AD pathology, paving the way for early diagnosis and intervention (12).

Regional Brain Atrophy in AD

Research has mapped the progression of atrophy in AD, revealing a distinct pattern

of neurodegeneration:

- Temporal Lobes: Early and severe atrophy (up to 30%) impairs sensory processing, language comprehension, and memory formation (13).

- Hippocampus: As a key structure for memory consolidation, its progressive shrinking correlates with the severity of cognitive decline (14).

- Frontal Lobes: As the disease advances, the executive function centers responsible for decision-making, planning, and social behavior deteriorate (15).

- Parietal Lobes: Spatial orientation and navigation abilities decline, contributing to disorientation, apraxia, and visuospatial deficits (16).

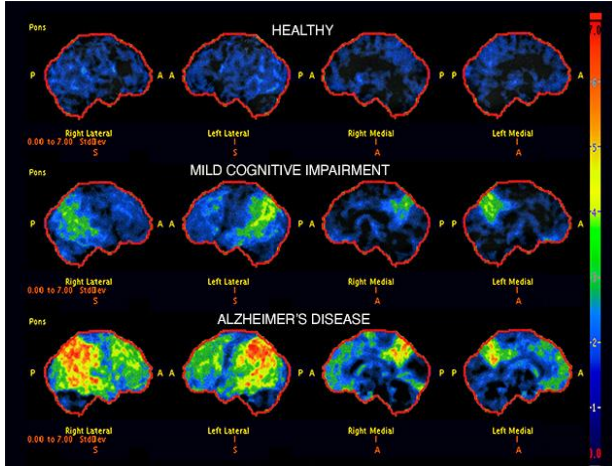


Fig. 3. PET scans illustrating progressive glucose hypometabolism from a healthy brain (top) to mild cognitive impairment (middle) and Alzheimer’s disease (bottom), highlighting neurodegeneration in key brain regions (Source: Mayo Clinic. Brain scan images for diagnosis of Alzheimer's disease. Available at: <https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/multimedia/img-20543518>)

TREATMENT DEVELOPMENTS

Over the years, Alzheimer’s disease treatments have evolved from symptomatic management with cholinesterase inhibitors in the 1990s to disease-modifying therapies targeting

amyloid pathology, such as Aducanumab (2021) and Lecanemab (2023). These advancements reflect a shift toward addressing the underlying neurodegenerative mechanisms rather than just symptom relief (tab. I).

TABLE I.

Major Treatment Milestones in Alzheimer’s Disease

| Year | Treatment | Mechanism | Impact |
|-------|---|---|--|
| 1990s | Cholinesterase Inhibitors (Donepezil, Rivastigmine) | Enhances acetylcholine levels to improve cognition | Modest symptom relief in mild to moderate AD (17) |
| 2003 | Memantine | Regulates glutamate activity to prevent excitotoxicity | Approved for moderate to severe AD (18) |
| 2021 | Aducanumab | First disease-modifying therapy targeting amyloid plaques | Controversial, but approved under accelerated pathway (19, 21) |
| 2023 | Lecanemab | Anti-amyloid therapy with confirmed efficacy in slowing cognitive decline | First fully FDA-approved disease-modifying therapy (20, 21) |

FUTURE PERSPECTIVES

The next frontier in AD research focuses on early detection, precision medicine, and novel therapeutic targets:

- **Targeting Tau Aggregation:** Therapies are being developed to prevent or reverse tau pathology, a key driver of neurodegeneration (22).

rodegeneration (22).

- **Neuroinflammation Modulation:** Investigations into microglial activation and inflammatory pathways may lead to immunotherapies that slow disease progression (23).
- **Synaptic Protection Strategies:** Scientists are exploring ways to enhance neuro-

plasticity and synaptic resilience, aiming to preserve cognitive function despite disease pathology (24).

In conclusion, the evolution of Alzheimer's disease (AD) research is a testament to the contributions of pioneering scientists who shaped our understanding of this devastating neurodegenerative disorder. From Alois Alzheimer's meticulous observations in 1906, which first linked cognitive decline to amyloid plaques and neurofibrillary tangles, to Emil Kraepelin's formal classification of the disease in 1910, their foundational work paved the way for modern neurology and psychiatry.

At the same time, Oskar Fischer independently described amyloid pathology in dementia patients, yet his findings were largely overshadowed by historical circumstances. Similarly, Gheorghe Marinescu's early recognition of neuroglial nodules in the brain was a key, yet underappreciated, milestone in AD research. These early scientists, each working in different parts of Europe, laid the groundwork for the neuropathological discoveries that still define AD today.

Over the past century, technological advancements have dramatically expanded our ability to study and diagnose AD. Im-

aging techniques like MRI and PET scans now allow for early detection, while biomarker research in cerebrospinal fluid (CSF) and blood has revolutionized diagnostic accuracy. What once required a post-mortem brain analysis can now be identified decades before symptoms appear, offering hope for earlier intervention.

Therapeutic advancements have also reflected a shift from symptomatic treatment to disease modification. The introduction of cholinesterase inhibitors in the 1990s, followed by memantine in 2003, provided temporary relief but failed to halt disease progression. More recently, Aducanumab (2021) and Lecanemab (2023) have opened a new chapter in AD treatment, focusing on amyloid clearance, though their long-term efficacy remains debated.

Despite a century of research, AD remains an incurable condition, with millions worldwide facing its relentless progression. The future of AD research lies in targeting not just amyloid and tau pathology, but also neuroinflammation, synaptic dysfunction, and genetic risk factors. As we move forward, the contributions of early pioneers like Alzheimer, Kraepelin, Fischer, and Marinescu serve as a reminder that scientific discovery is built on the perseverance of those who dare to question, observe, and innovate.

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