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# THE MYSTERY AND HISTORY OF ALZHEIMER'S DISEASE

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**ABSTRACT:** Even though the malady of dementia has existed for thousands of years, the correlated neurodegenerative alterations taking place in certain regions of the human brain were detected in recent times. Today, we are aware that dementia is a primary manifestation of Alzheimer's disease (AD). In 1907, Alöis Alzheimer described the symptoms of a 51-year-old woman, Auguste Deter, who was under his observation at the state Asylum in Frankfurt (Germany). Alois Alzheimer noticed the existence of unusual accumulations in the brain (described as amyloid plaques today) and a massive loss of neurons while examining the brain of his first patient that suffered from memory failure, bizarre behavior and abnormal personality before death. With the enhanced lifespan, direct and indirect health expenditures of patients suffering from AD have increased exponentially. There is neither an appropriate experimental model for testing the memory of animals akin to human memory nor any cure for AD. It is important to investigate the past events resulting in AD to comprehend the present scenario and gain insight into the future. The authors have described in this review article the risk factors, symptoms, and the historical milieu of Alzheimer's disease comprehensively so that meaningful conclusions could be drawn from past experiences, thereby speeding up the progress of the fabrication of a suitable experimental model that would be useful in identifying new anti-Alzheimer agents, thus facilitating the unearthing of safe medicines, which in turn would rescue the entire mankind from this deadly disease.

**INTRODUCTION:** Alzheimer's disease is a complex irreversible neurodegenerative disorder, which progressively impairs the cognitive abilities of the patient and adversely affects different regions of the brain including the medial temporal lobe, hippocampus, cerebral cortex, and neocortical structures. The major clinical signs of AD are marked by dementia, aphasia, apraxia, agnosia, agraphia, dyslexia, anomia, loss of executive functions, abnormal personality, difficulties in performing day-to-day tasks, and bizarre behavior.

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Alzheimer's disease is distinguished by the deposition of β-amyloid peptides in the extracellular surface of neurons and the formation of neurofibrillary tangles arising from the intracellular accumulation of excess phosphor-rylation of Tau protein [1-8]. AD forms the top-most primary basis of dementia, affecting around 50 million individuals worldwide, and is ranked as the fifth chief reason for death globally.

In the US alone, more than 6 million individuals live with AD today, which is expected to rise to 14 million by 2050. Similarly, in Western Europe, dementia affects ~2.5% of people within the age group of 65–69 years, escalating to about 40% of those aged between 90–94 years and by 2050, there would likely be 18.9 million patients suffering from dementia in Europe and 36.5 million in East Asian countries [9].

The life expectancy in developing countries like India has almost doubled from 37 years in 1950–1960 to 69 years in 2015–2020 [10, 11, 12]. The enhanced lifespan of the human race around the globe in general, Indians and Japanese in particular has resulted in a huge number of Alzheimer patients. AD is one such disease, which has made the German physician, Alois Alzheimer (the discoverer of this disease) world-famous after more than a century after his death. The authors have made a humble attempt to narrate the life story of Dr. Alzheimer along with the biography of the first Alzheimer's patient in this review article to unravel the mystery of Alzheimer's disease. The authors have comprehensively described the chronological events of Alzheimer's disease so that lessons are learned from experience and meaningful inferences could be arrived at thereby facilitating the discovery of safe therapeutic remedies useful in AD for the benefit of mankind as a whole.

**Life-Story of Dr. Alzheimer and the Earliest Patient of Alzheimer's disease:**

**Alois Alzheimer (Well known for Alzheimer's disease):** Alois Alzheimer took birth in a Christian (Catholic) family on June 14, 1864, in the township of Marktbreit in Lower Frankonia close to Würzburg along the river Main. Mr. Edward, father of Alois was a royal notary in the Bavaria Kingdom, whose first wife passed away due to puerperal fever after the delivery of their first son. Alzheimer's father (Edward) then got married to Alois's maternal aunt and had six more children with her; the eldest child was Alois Alzheimer. Alois Alzheimer had his school training initially in Marktbreit and shortly in Aschaffenburg. Alzheimer completed his college studies in Berlin, Freiburg, and Würzburg (1883–1885).

During his graduate course, Alzheimer developed a great interest in the subject of anatomy and enjoyed working with microscopes. He completed his studies at Würzburg with the submission of a dissertation in anatomy and successfully obtained the official diploma in medicine. Then, there were no clues that Alzheimer would take up a career in psychiatry, the field in which he did not have much interest. However, an accidental episode occurred soon after his studies in medicine that changed the direction of his entire life. In Germany during those days, rich German families used to engage young physicians for taking care of mentally ill relatives. Alzheimer, who was not well financially in those days accepted one such proposal and voyaged for 5 months (May to October 1888) accompanied by a mentally ill female. Unfortunately, no information is available concerning this patient's psychological sickness or individuality**.** But this episode transformed the life of young Alzheimer, who developed a taste for psychiatric disorders and empathy for mentally ill patients. Alzheimer at 24 years of age received his initial official placement as an assistant house officer in December 1888 at the Community Hospital for Mental and Epileptic Patients in Frankfurt, whose director was Emil Sioli. He developed an intense curiosity in different areas of psychiatry during his 15 years period in this institute and developed a good rapport as a skilled clinician.

Here he came across Franz Nissl in 1884, with whom he built up a secured companionship and learned new methods for the fixation and staining of microscopic preparations of different brain parts. Alzheimer decided to marry a rich widow Cecilia Geisenheimer in 1895 attracted by her wealth and to pursue his research work in the field of brain disorders smoothly without any hardship. Thus, he soon became financially sound and independent. He desired to be the clinical director of a psychiatric sanatorium to pursue his research passion without any obstacles. The appointment of Dr. Alzheimer as the hospital's deputy director marked an important step toward his dream professional target. Dr. Alzheimer thus had become comfortable professionally, and financially and also had harmonious family life with his spouse and three children born between 1895 and 1900.

However, the year 1901 was very tough for Dr. Alzheimer when his 41-year-old wife left for a heavenly abode while the third child was only a few months old. Alzheimer was now a widower and had to pay attention to three children. Fortunately, his unmarried sibling consented to shift to Frankfurt to watch out for the household chores so that Alzheimer could pursue his professional ambitions. To trounce the sorrow of his wife's demise, Alzheimer worked more intensively at the sanatorium than ever before. He investigated thoroughly all newly admitted psychologically ill patients and made detailed and

extensive documentation of his findings. On November 26, 1901, he came across a newly admitted 51- year old lady patient named Auguste Deter. He observed her behavior and all the symptoms. When he obtained her detailed history and carried out preface investigations, Dr. Alzheimer developed a notion that this lady had been suffering from an unknown deadly disease. He by no means anticipated for one moment that the clinical investigations of this patient would sow the seeds for the breakthrough of a new disease that would make him famous worldwide. Soon, in 1903, he shifted to the Royal Psychiatric Clinic of the University; where he headed the Anatomical Laboratory until 1912.

He was invited by the well-known and influential German psychiatrist Emil Kraepelin of Heidelberg. Despite lots of explanations in favor of Heidelberg, Alzheimer declined Kraepelin's incitement and applied unsuccessfully for an important position in a Hessian state hospital. When Alzheimer's intimate friend Nissl learned about this, he swayed Kraepelin to reiterate his proffer of a decent position at the Heidelberg Hospital to Alzheimer's and requested his friend Dr. Alzheimer to favorably consider the proposal. Alzheimer rose to the occasion and proved himself as a meticulous dedicated worker at Heidelberg hospital working ceaselessly taking no holidays. In 1904, Alzheimer satisfactorily defended his postdoctoral thesis on ''Histological studies about the differential diagnosis of progressive paralysis'' based on 170 postmortems. In November, Alois was employed as a university lecturer in the Faculty of Medicine at the Ludwig Maximilian University.

The Medical Faculty of Munich promoted him to assistant professor in 1908. Three years later in July 1912, he became a full-fledged Professor of Psychiatry and Director at the Neurologic and Psychiatric Institute of the Silesian Friederich-Wilhelm University in Breslau (now Wroclaw in Poland) [13]. During these 8 years, numerous young scientists from many countries were trained by Dr. Alzheimer, who later became a famous neuro-pathologist or clinical psychiatrist. During his move to Breslau, Alzheimer suffered from a severe cold that was complicated by a bacterial infection, which afterward developed into sub-acute endocarditis. In February 1913, Alois was admitted to a private clinic but his health progressively deteriorated with the failure of both the kidneys and lungs. Dr. Alzheimer left the planet earth at 51 years of age, on December 19, 1915 [14, 15]. But, his work is highly admired even after a century after his death and Alzheimer's disease has become a familiar household name.

**The First Patient of Alzheimer's disease: Auguste Deter:** Auguste Deter was born into a working-class family of Kassel on May 16, 1850, in a medieval city in Germany. She attended school for being a literate lady and completed simple mathematical tests. At the tender age of 14 years, Auguste began to work as a seamstress assistant. At the age of 23, she married Karl, a railway clerk, and moved 180 km south to Frankfurt. Her last home address was an apartment on the south side of the river Main. Dr. Alzheimer first encountered his now-famous patient, Mrs. Deter, on November 26, 1901. She had been admitted to a municipal mental asylum in Frankfurt the day before with a feeble look. Her husband narrated that the duo had been pleasantly married since 1873.

In March 1901, when his wife was 51years old, she exhibited untreatable paranoid symptoms and dementia. The patient's health deteriorated fast and Auguste Deter suffered from sleep disorders, intense memory loss, aggressiveness, abnormal behavior, progressive confusion, and frequent crying episodes. Her personality progressively deteriorated in less than 8 months. She showed envy towards her spouse and pronounced psychosocial impairment. She felt that somebody wanted to slay her and used to shout wildly. She often dragged a bed sheet outside, wandered around wildly, and cried for hours at midnight. Ms. Deter became restlessly boisterous, threatened fellow citizens with a horrifying scream, and started to doubt each movement of strangers for no cause [16, 17]. Dr. Alzheimer observed her and obtained her detailed clinical history. Despite her reasonably fair ability to remember and speak out her husband's name in the initial stage of the illness, she was not able to write (agraphia) her name in a notebook upon repeated requests. She could recognize and name kinds of stuff such as pencils, keys, and cigarettes. However, she did not remember the food items she ate a few minutes before. She had lost the track of time, place, and things around her and

displayed utter confusion. Soon, her speech became incoherent, her expression was flat and she spent most of the time in bed with her legs pulled up. When she understood that she could not answer Dr. Alzheimer's simple questions, she felt sad, depressed and lost [15]. Auguste Deter was declared dead on April 8, 1906, five weeks short of her 56th birthday, from septicemia due to a decubitus ulcer in the sacral and left trochanteric region [14]. Postmortem investigations of her brain by Dr. Alzheimer revealed that she had been suffering from an unknown mental disease now well known as Alzheimer's disease.

**Discovery of Alzheimer's disease (AD):** Dr. Emil Sioli, the director of the Community Hospital for Mental and Epileptic Patients, Frankfurt, informed his former colleague, Dr. Alzheimer, about the demise of the patient Auguste Deter in April 1906. He further arranged for an autopsy and provided the brain material of the late Ms. Auguste Deter for post-mortem investigations to Dr. Alzheimer as requested. Dr. Alzheimer carried out both morphological and histological investigations on the brain of Auguste Deter. Dr. Alzheimer discovered for the first time the histological aberrations developed and the presence of abnormal deposits inside the brain tissue of Deter (now known as beta-amyloid plaques and tangles of neurofibrils).

He presented this interesting data before Kraepelin and other researchers persuading them that these histopathological irregularities found in the brain during postmortem investigations were unique and could account for the abnormal clinical symptoms and explain the unusual behavior of the patient seen while suffering the unexplored illness before the actual death. Kraepelin supported Dr. Alzheimer to present the case study of Auguste D. at the subsequent scientific congress of German psychiatrists in the month of autumn 1906 in Tubingen. Alfred Hoche, a prominent psychiatrist from the University of Freiburg, (1865–1943) and a professional competitor of Kraepelin, (who had recommended the case of Dr. Alzheimer) was the Chairman of the technical session. Dr. Hoche had his nosological notion and categorization of psychiatric ailments. It so happened that Kraepelin was not present in the auditorium (among the audience) during Alzheimer's presentation.

After Alois Alzheimer's talk, Dr. Hoche neither made any comment nor encouraged any discussion on Alois's presentation, deviating from the typical job of a good Chairman. The lack of appreciative compliments and the absence of healthy discussion on this unique finding of a new mental disorder during the scientific assembly were disappointing and unacceptable to Dr. Alzheimer. Only a very short abstract was printed in the official proceedings of the meeting and Tübingen's public press covered extensively the psychoanalytical lectures delivered during the scientific congress giving no importance to Alzheimer's presentation. Yet, Dr. Alois Alzheimer did not give up and continued his further research in similar cases. Such was the initial fate of Alzheimer's disease, which is so popular today. In the subsequent year, in 1907, Alzheimer delivered his next lecture entitled "A characteristic serious disease of the cerebral cortex". In his publication, Alzheimer explained the pathological picture of Auguste D's illness. He mentioned the occurrence of abnormal deposits and peculiar fibrils in the cells of the cerebral cortex corresponding to the well-accepted present concept of beta-amyloid plaques along with neurofibrillary tangles. He further declared that "All in all, we have to face an altogether new peculiar disease. Dr. Alzheimer and Dr. Perusini thereafter scrutinized three other cases analogous to that of Auguste D., and Perusini published the history of all four cases, in addition to histopathological details in 1909.

Kraepelin planned printing the 8th edition of his renowned manual Psychiatrie during the years 1906-1910. As he was convinced and had documented the original work of Alzheimer's findings, he included a report on the case history of patient D. Auguste in the written text of 1908 and proposed naming this particular illness as "Alzheimer's disease" in the new edition of Kraepelin's textbook. In 1911, Alois Alzheimer himself published once more in a wider context the details of pre-senile and senile forgetful progressions. He portrayed the whole reason for the death of the male patient, Josef F., after 3 years of hospitalization in Munich in 1910. Kraepelin diagnosed Josef F. as suffering from Alzheimer's disease before death and mentioned the case of Josef F. in his textbook [30].

The histological investigation authenticated the clinical diagnosis, but there was one important difference. Alzheimer noticed that there were only plaques and no neurofibrillary tangles in the slide preparations of Josef's brain. Therefore, doubts were raised in those days whether "plaques-only" cases belonged to the same disease category as cases with the occurrence of both plaques as well as the neurofibrillary tangles. The material of both cases (Auguste Deter and Josef F.) was re-investigated with modern neurohistochemical techniques in recent times. The results of these investigations, jointly with the published literature reports and conceptual interpretations were published by H-J. Möller and M. B. Graeber. Today, we appreciate that the patients with the incidence of beta-amyloid plaques only inside the brain tissue and individuals with both plaques plus neurofibrillary tangles in the brain represent simply different stages of the same disease (Alzheimer's disease) [18]. There is neither an appropriate experimental model for testing the memory of animals akin to human memory nor a radical therapy for AD. The FDA-approved medicaments that are presently prescribed for this chronic irreversible disease are either choline-esterase inhibitors such as donepezil, rivastigmine, *etc*., or nootropic agents like piracetam. Regrettably, all the medications target only the symptoms of the ailment to a certain extent but do not arrest the disease progression. Indian scientists [19, 20, 21, 22, 23] have been focusing on such therapeutic herbs and plant constituents, which exhibit the potential to prevent Alzheimer's disease and show promising memory-enhancing properties. The authors have described the history of AD in detail so that the lessons are learned from past experience and that meaningful inference could be drawn, leading to the development of pragmatic experimental models that might prove realistic for screening new anti-Alzheimer agents. The discovery of safe anti-Alzheimer medicines would benefit mankind as a whole.

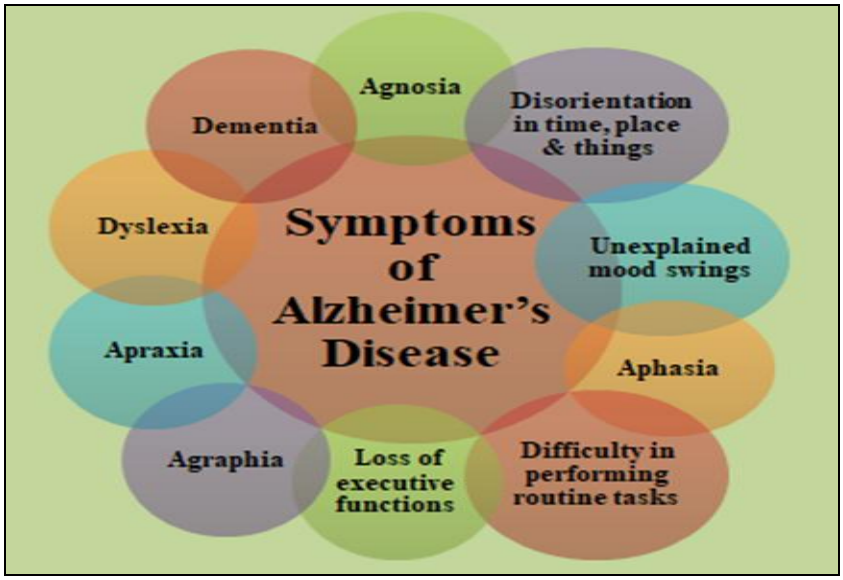


**FIG. 1: CLINICAL SIGNS OF AD**

**CONCLUSION:** It's now a well-established fact that Alzheimer's disease is the foremost leading cause of the impairment of learning ability and memory among the aging population all around the globe. Although the exact causative factors of the ailment have not been identified, several hypotheses are available to explain the pathogenesis of AD. The patients surviving till the cruel stage of AD experience long-faced difficulties in routine daily activities such as wearing clothes, bathing, swallowing, and visiting the washroom, even if we ignore the escalating costs of caregivers. In the severest form of the illness, AD patients are not able to perform even the simplest physical tasks of day-to-day life. They depend on caregivers until the very last breath, thereby making the life of close family members miserable. In recent years, translational and multi-disciplinary approaches from genetic, biological and biomarker-based clinical investigations have contributed to unveiling

the biochemical, physiological in addition to pathophysiological features of the Aβ pathway. Usually, the obvious memory mutilations crop up in AD patients after about five years of initiation of deposition of Aβ plaques. Therefore, when one is suspected to have AD, most of the time, one has by now encountered serious neuronal damage. Therefore, an early diagnosis of AD becomes crucial. Currently, no radical cure for AD is established. The consensus medicines that are prescribed for AD patients target only the symptoms to some extent without altering the deteriorating internal sequence of events.

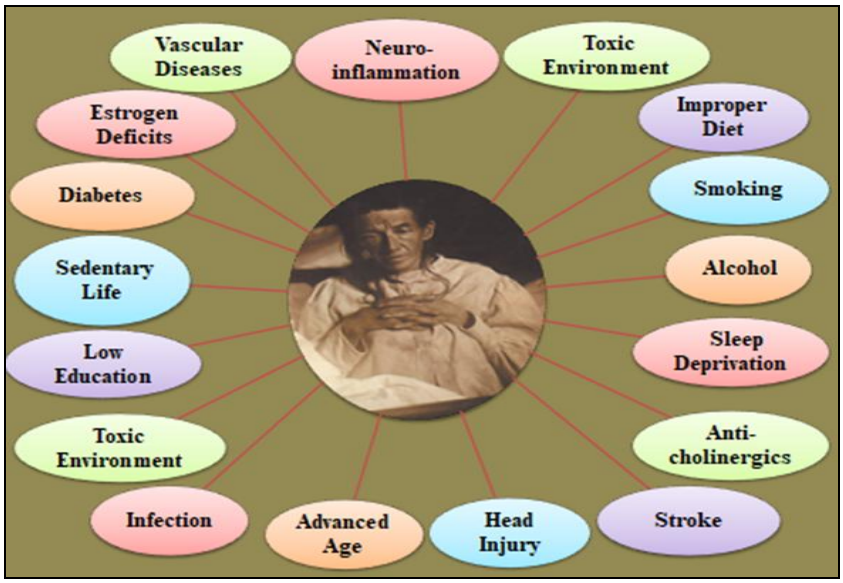


**FIG. 2: RISK FACTORS RESPONSIBLE FOR CAUSING ALZHEIMER'S DISEASE**

These drugs in no way halt the process of disease progression. When considering the need and the major healthcare burden, AD has a very small number of therapeutic agents n the pipeline participating in the drug development phases. This is a huge drawback when comparing the number of affected people and the cost of patient care. The current hypotheses point towards the agents that can either selectively inhibit β or γ secretases responsible for the formation of Aβ plaques, drugs that can selectively inhibit aggregation of Aβ, or drugs that can dissolve Aβ plaques. Although the beta-amyloid pathway is considered the most prominent, the ROS, tau and AChE levels are equally important.

Furthermore, neuroprotective drugs, neuro-regenerative agents, tau phosphorylation inhibiting drugs, and tau aggregation inhibiting drugs might also be effective, provided they cross blood-brain-barrier, have reasonably good bio-availability, considerably longer half-life, and have a high therapeutic index. The authors have described the historical account of Alzheimer's disease comprehensively so that meaningful implications can be drawn from past experiences to speed up the progress of the fabrication of a suitable experimental model that could be useful in identifying new anti-Alzheimer agents, thus facilitating the breakthrough yielding safe medicines, which in turn would rescue the entire mankind from this deadly disease.

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