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Alzheimer's disease in the 100 years since Alzheimer's death

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It is 100 years since the death of Aloysius 'Alois' Alzheimer (1864–1915). In that time the disease that bears his name has gone from being considered a rare condition only affecting younger people to a major public health priority as Governments face ever-increasing numbers of people with dementia. Worldwide some 40 million people have dementia and Alzheimer's disease is the most important cause (Prince *et al.*, 2013). A recent UK poll identified Alzheimer's disease as the greatest concern about later life for British people over 60 years old, more feared even than cancer or the death of family and friends (https://yougov.co.uk/news/2015/07/26/alzheimers-greatest-concern-over-60s/). While Alzheimer's disease may now be at the forefront of the public imagination, it was not always thus. Over the past century, concepts of what Alzheimer's disease is, who it affects and how common it may be have undergone a number of dramatic shifts.

Alzheimer, Auguste D. and the defining of a disease

On 25 November 1901, a 51-year-old woman was admitted to the Municipal Asylum for Lunatics and Epileptics in Frankfurt. The patient was Auguste D. and the admitting psychiatrist Alois Alzheimer. Mislaid for years, the original file describing her case with her admission clerking handwritten by Alzheimer and four photographs was found in 1995 (Fig. 1). It contains a detailed description of her clinical presentation: she had been well until March 1901 when she developed unprovoked paranoia that her husband was having an affair with a neighbour. Soon after, she was noticed to have difficulty remembering things and was making mistakes preparing meals and dealing with money. She became progressively disoriented to time and place and paranoid that people were talking about her. Alzheimer gives examples of the deficits he observes on cognitive assessment, including severely impaired recall memory of objects she has just seen and correctly named. On reading, she omits sentences, and she is unable to progress with writing, repeating 'I have lost myself'. Her spontaneous speech is 'full of paraphrasic derailments and perseverations'. Later in her admission, he notes 'she behaves as if blind, touching other patients on their faces while they fight her.' Auguste D. remained in the institution until her death in 1904. By this time, Alzheimer had moved to Munich to continue his medical and scientific work at the Royal Psychiatric Clinic, under the directorship of Emil Kraepelin. Alzheimer headed the neuroanatomic laboratory and requested that Auguste D.'s file and brain be sent to him so that he could study the neuropathological features of her disease. As a physician–researcher, he believed that clinical practice and laboratory research complemented each other in the quest to understand the diseases that afflicted his patients, once writing 'Why should not the physician improve his competence by enlarging scientific knowledge of psychiatry besides doing his daily clinical practice?' (Whitehouse *et al.*, 2000).

Alzheimer presented the clinical and pathological findings from Auguste D.'s case at the meeting of Southwest German Psychiatrists held in Tübingen, in 1906 and his lecture was published under the title 'A Characteristic

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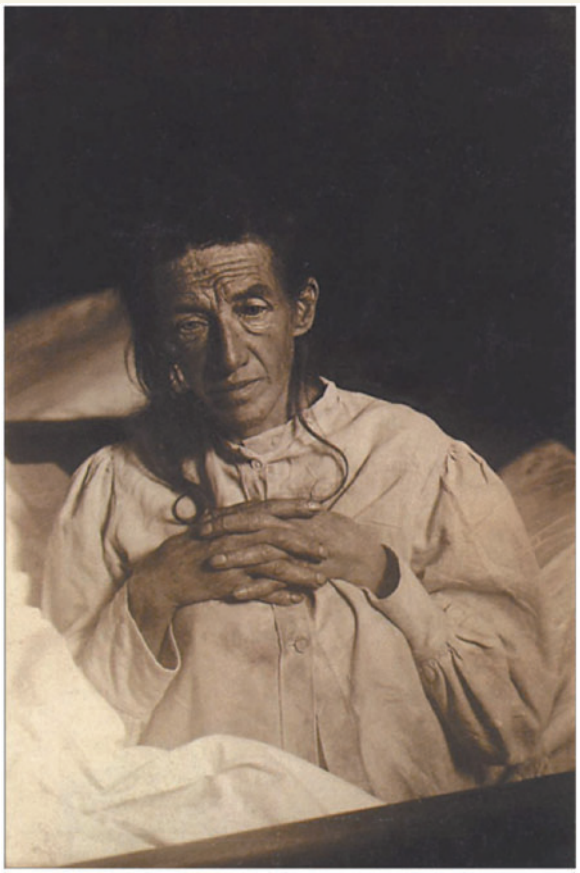

Figure 1 Photograph of Auguste D., dated November 1902. Reprinted from The Lancet, 349(9064), Maurer et al., Auguste D and Alzheimer's disease, 1546-9, 1997, with permission from Elsevier.

Disease of the Cerebral Cortex' the following year. He described and beautifully recorded (Fig. 2) characteristic changes in the neurofibrils revealed by the Bielschowsky silver stain at autopsy. Thick fibrils accumulated in apparently normal-appearing cells until 'eventually, the nucleus and cytoplasm disappeared, and only a tangled bundle of fibrils indicated the site where once the neuron had been located'. Severe neuronal loss was observed and '...over the entire cortex, and in large numbers especially in the upper layers, miliary foci could be found which represented the sites of deposition of a peculiar substance'. Many years later, hyperphosphorylated tau (encoded by *MAPT*) was found to be the key component of the tangles and amyloid-β the 'peculiar substance' that formed the core of the plaques. Psychoanalytic studies presented at the meeting received more attention than Alzheimer's paper and were the ones to get reported in the local press. However, in 1910 Kraepelin coined the term 'Alzheimer's disease' in the eighth edition of his *Handbook of Psychiatry*, declaring it to be a specific clinical-pathological disease entity.

Examining the historical context in which these events occurred reveals a number of disparate factors that enabled the observations to be made by Alzheimer and may have influenced Kraepelin in defining them soon after as an eponymous disease. As often is the case, technological advances laid the ground for novel insights: the growth of German industry in the second half of the 19th century was revolutionizing histology. Improved microscopes had been developed and the creation of the aniline dye industry brought a plethora of new dyes and advances in staining methods, some of which found applications in histopathology. Alzheimer had worked closely with the neurologist and histopathologist Franz Nissl and could not have made his observations without the silver staining techniques developed by Bielschowsky in 1902, which allowed alterations to the neuronal cytoskeleton to be seen in such remarkable detail. Another important factor was the evolution of concepts around psychiatric disease. For Kraepelin, the explanation for mental disorders lay in organic changes in the brain, and clinical delineation of distinct disease entities was the route to understanding the relationship between mind and brain. The clinical–pathological syndrome described by Alzheimer provided Kraepelin with a strong example of his approach; naming it a 'disease' after a colleague who shared his belief in an organic basis for psychiatric illness can perhaps be seen as putting down a marker for his theory over rival psychoanalytic ideologies.

There was, however, a fundamental issue with Kraepelin's concept of Alzheimer's disease, which was evident when he defined it and has remained a source of ambiguity and contention ever since. This was the relationship with senile dementia and normal ageing. Plaques and tangles had both been described previously, but in the brains of elderly patients with dementia. Extraneuronal plaques had been observed by Beljahow (1887), Redlich (1898) and Fischer (1907) and were renamed 'senile plaques' in 1910 by Simchowitz when he found they could also be present in non-demented elderly people, but in lower numbers. In 1906, 'destruction of the neurofibrillae' and 'neurofibrillary bundles' were noted in senile dementia patients by Bianchi and Fuller, respectively (Huppert *et al.*, 1994). However, the prevailing notion at the time was that senile dementia was an inevitable consequence of ageing. 'Senile dementia is that mental impairment which is a direct result of cerebral deterioration from old age,' wrote the psychiatrist William Pickett in 1904. Over 30 years later, there had been little change to this view of ageing. British neurologist MacDonald Critchley commented in 1939 that 'frontiers between healthy and abnormal old age—between senescence and senility—[are] so ill-defined as to be scarcely recognizable'.

A key feature that allowed Kraepelin to define Alzheimer's disease as a discrete disease entity was the young age of the patients. In his 1910 *Handbook of Psychiatry*, he drew on Alzheimer's original description of Auguste D., a subsequent case report by Bonfiglio (1908) of a 60 year old Italian patient with similar clinical and histopathological findings and a case series (at the time unpublished) by his colleague Perusini (1910), which added two further young onset patients. Kraepelin felt that there were clinical features in addition to age that also distinguished these patients from those with senile dementia, including rapid progression, language

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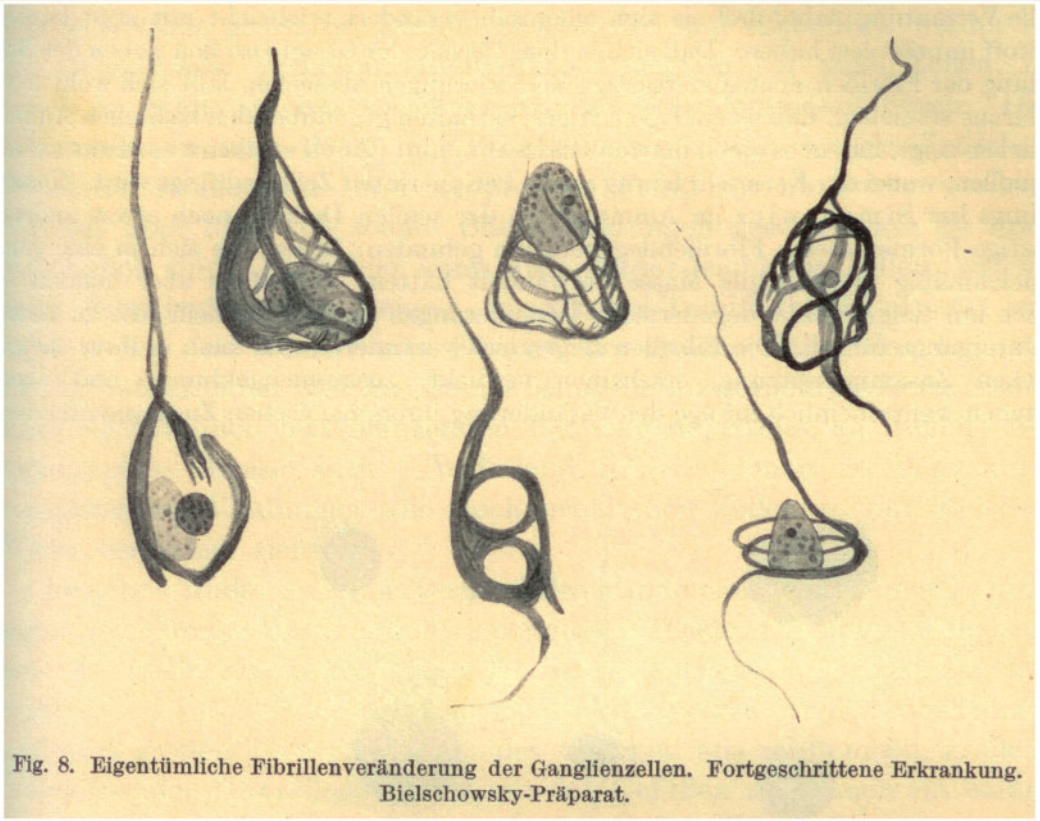

Figure 2 Neurofibrillary tangles drawn by Alzheimer above the caption 'Peculiar fibrillary changes of the nerve cells. Progressed stage of disease'. From Alzheimer (1910-1911). Reprinted with permission from Bernard Becker Medical Library, Washington University School of Medicine.

disturbance, seizures and focal signs. Kraepelin, however, acknowledged that 'The clinical interpretation of this Alzheimer's disease is still confused. Whilst the anatomical findings suggest that we are dealing with a particularly serious form of senile dementia, the fact that this disease sometimes starts already around the age of 40 does not allow this supposition'. Age was therefore such a central parameter in Kraepelin's classification system and the idea that senile dementia was related to ageing so entrenched in the thinking of the time that young patients were, by definition, precluded from being categorized together with senile dementia. Being so closely tied to normal ageing, it was unclear whether senile dementia was a disease at all. Alzheimer's disease as defined by Kraepelin, on the other hand, clearly fell within the realm of psychiatry and the dominant view in the decades that followed was that it represented a rare 'presenile' condition.

Alzheimer's disease redefined as a 'major killer'

It was not until the second half of the 20th century that Alzheimer's disease become redefined as affecting late as well as early onset patients. This shift in thinking accompanied a transformation in the conceptualization of senile dementia and normal ageing. The British psychiatrist Martin Roth made a seminal contribution with his 1955 study, in which he argued that mental disorders in the elderly could be split into distinct categories, which carried very different prognoses (Roth, 1955). With senile dementia increasingly viewed as a pathological condition and distinguished from other psychiatric disorders of the elderly it could be studied in its own right, and it soon became apparent that the historical distinction from Alzheimer's disease no longer seemed valid. In the late 1960s, Roth and his colleagues Blessed and Tomlinson demonstrated that the majority of cases of senile dementia had neurofibrillary tangles and amyloid plaques and the latter correlated with severity of cognitive impairment (Blessed *et al.*, 1968). Roth concluded in 1970 that:

> 'Traditionally the distinction between Alzheimer's disease and Senile dementia was a clear one. It rested on the occurrence in Alzheimer's disease of focal phenomena: the Parietal lobe group of features, the characteristic mixture of apraxia, agnosia, spatial disorientation and so on. In Senile dementia, on the other hand, a simple amnestic dementia was held to be the principal ingredient of the clinical picture . . . . . German workers have recently called this distinction into question. Lauter and Meyer claim to have

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demonstrated focal phenomena in the senile cases. In the light of these is the distinction (between Alzheimer's disease and Senile dementia) valid clinically or pathologically, or are we left with age criteria alone?' (Whitehouse *et al.*, 2000).

With Alzheimer's disease and senile dementia unified in a single disease concept, a line was now drawn between dementia and normal ageing and it was increasingly appreciated that major cognitive impairment was not an inevitable outcome of ageing. Although Glennerstedt had reported plaques in 84% of non-demented elderly people in 1933, observations that pathological features of Alzheimer's disease may occur without dementia could be incorporated into the new framework. The work by Blessed and colleagues had demonstrated that the severity of pathology was worse in patients with dementia and, according to the psychodynamic model that was prominent among some psychiatrists working on senile dementia at the time, an individual's ability to withstand organic damage depended on a variety of personality factors, stress and life crises, as well as the underlying pathology. Once the separation between Alzheimer's disease and senile dementia was eliminated, it was realized that Alzheimer's disease was in fact responsible for the majority of dementia and was very common. In an editorial published in *Archives of Neurology* in 1976 entitled 'The prevalence and malignancy of Alzheimer's disease: A major killer', Robert Katzman argued for a unifying concept of Alzheimer's disease and senile dementia and estimated that the disease may rank as the fourth or fifth most common cause of death in the United States (Katzman, 1976). It took some time for the distinction to be completely abandoned, with the terms 'Alzheimer's disease' and 'senile dementia of the Alzheimer type' recommended initially. However, the new conceptualization of Alzheimer's disease had a profound impact on public attitudes. It represented the start of Alzheimer's disease becoming redefined as a major social and public health issue and concern for public policy.

Insights into the biology and genetics underlying Alzheimer's disease

Alongside the changing public perception of Alzheimer's disease, scientific understanding of the biological basis of the disease began to grow. In the late 1970s, the cholinergic deficit in Alzheimer's disease was identified and linked to selective degeneration of cells in the nucleus basalis of Meynert, paving the way for the subsequent development of cholinesterase inhibitors as symptomatic treatments. In 1984, George Glenner identified the amyloid-β protein in angiopathic blood vessels from patients with Alzheimer's disease and Down's syndrome, highlighting an important possible clue to the genetic aetiology of Alzheimer's disease. It had been recognized as early as the 1930s that there were some rare families in which multiple individuals developed Alzheimer's disease with a pattern suggesting autosomal dominant inheritance. The finding that individuals with Alzheimer's disease and those with trisomy 21, who invariably develop dementia with plaques and tangles at autopsy if they live to middle age, have the same amyloid-β pathology, put chromosome 21 in the spotlight. Amyloid-β was subsequently identified in plaques and in 1987 the amyloid precursor protein (*APP*) gene was cloned and found to localize, as predicted, to chromosome 21. In 1991, direct sequencing of *APP* in a large family from Nottinghamshire with early onset Alzheimer's disease identified a mutation at codon 717, which co-segregated with disease. Chromosome 21 linkage was not, however, identified in many of the other kindreds that were studied and it soon became clear that Alzheimer's disease was genetically heterogeneous. Four years later, presenilin 1 (*PSEN1*) on chromosome 14 was identified as the major locus for autosomal dominant familial Alzheimer's disease and presenilin 2 (*PSEN2*) on chromosome 1 as the locus for a minority of cases. Just the previous year, it had been found that the apolipoprotein E4 allele was a major risk factor for sporadic early and late onset forms of Alzheimer's disease.

After the identification of *APOE*4 as a major risk factor for Alzheimer's disease, almost 15 years passed before another gene was found to be conclusively associated with the disease. However, the past 6 years have witnessed some major developments in our understanding of genetic risk factors for sporadic Alzheimer's disease. Genome-wide association studies have identified multiple genetic loci with low risk effects for Alzheimer's disease, including *CLU*, *PICALM*, *CR1*, *BIN1*, *MS4A6A*, *ABCA7*, *SORL1*, *PTK2B*, *EPHA1* and *HLA-DRB5–HLA-DRB1* (Guerreiro and Hardy, 2014). The biological processes that these loci are involved in: immune and inflammatory responses, cholesterol and lipid metabolism and endosomal vesicle recycling, have therefore been highlighted as potentially important pathways in Alzheimer's disease pathogenesis. The role of the innate immune system was brought further to the forefront by the discovery in 2013 that rare variants in *TREM2*, a microglial surface receptor, are associated with a significantly increased risk of Alzheimer's disease. The current symptomatic treatments for Alzheimer's disease involve regulating neurotransmitters, with the acetylcholinesterase inhibitors donepezil, rivastigmine and galantamine and the NMDA-receptor antagonist memantine. Many of the therapies undergoing development and assessment in clinical trials target amyloid-β or tau. The biological pathways illuminated by recent genetic studies now open up further potential therapeutic avenues for drug discovery efforts in Alzheimer's disease.

Although autosomal dominant mutations account for a very small proportion of cases of Alzheimer's disease, the discoveries from these young onset families had, and continue to have, profound implications. The amyloid cascade hypothesis was proposed, which posits that accumulation of amyloid-β is the initiating event in Alzheimer's disease

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pathogenesis (Hardy and Higgins, 1992). This hypothesis has had a major influence on research and motivated the development of therapies that aim to reduce production of amyloid-β or increase its clearance from the brain. Identification of familial Alzheimer's disease mutations also provided the information necessary to make transgenic animals in which these therapies could be tested, some with dramatic effect, before going in to a series of trials in humans. Ironically, these initial clinical trials tended to exclude the familial patients that had contributed to the ideas and models on the basis of their young age.

Young onset and familial Alzheimer's disease return to the spotlight

More recently, there has been a refocus on young onset Alzheimer's disease and in particular familial Alzheimer's disease, with clinical trials belatedly turning their attention towards individuals with autosomal dominantly inherited mutations. This was largely because of changes in the view of when the disease first develops in the brain, when it is first detectable *in vivo*, and when it may be most effective to intervene. This new perspective has been driven by a realization that Alzheimer's disease has a long presymptomatic period, partly informed by the prospective study of asymptomatic individuals including those at risk of familial Alzheimer's disease. The potential for early identification and intervention has been enhanced by the development of new CSF markers and brain PET imaging measures of amyloid and tau. More recent research diagnostic criteria for Alzheimer's disease incorporate biomarkers and preclinical states of disease into the framework (Dubois *et al.*, 2014). Just as technological developments at the turn of the 20th century, in the form of new histological staining methods and microscopes, facilitated the original definition of Alzheimer's disease, advances in biomarker and imaging technology over the past decade have supported this latest conceptualization of the disease. Molecular imaging with PET tracers that bind amyloid and tau now allow us to see what Alzheimer couldn't see: the 'plaques and tangles' during life. The increasing recognition of the long preclinical period to Alzheimer's disease coincided with a series of failures of treatment trials that included patients with mild to moderately severe dementia. The concern that emerged is that if the disease has a 10–15 year presymptomatic period when plaques and tangles become established and widely distributed in the brain, it may be too late or at least more difficult to a slow a process that has already gathered momentum by the time a patient has established dementia. If it is possible to detect and track the extent of amyloid and tau pathology *in vivo* as well as more downstream effects such as atrophy and cognitive impairment, then presymptomatic treatment trials become more feasible; offering the prospect of interventions when there has been the minimum of irreversible neuronal damage and when there is most to save in terms of function.

Hence we enter the era of presymptomatic secondary prevention trials, with studies underway to test treatments in asymptomatic individuals at risk for Alzheimer's disease by virtue of genetics, familial Alzheimer's disease or *APOE*4, or because of imaging evidence of prodromal cerebral amyloid accumulation. The effects of therapy will be tracked with MRI, PET and CSF as well as sensitive cognitive measures, aiming to delay the onset of the symptoms that led to Auguste D's institutionalization and that are so devastating to millions globally. Alzheimer and Auguste's contributions and the debates that surrounded them remain as relevant as ever. Observations that around a third of cognitively normal older people have positive amyloid scans have resurrected some of the century-old discussions about the relationship between dementia and normal ageing, and the question of how generalizable early onset (and particularly familial) Alzheimer's disease is to late onset disease has never been so timely. In this context, with the discovery in 2013 that Auguste D. had a *PSEN1* mutation it seemed that perhaps a full circle had been reached, with treatments being tested in families that may have been her distant relatives. However, in a follow-up report last year the mutation in Auguste D. was not validated, nor were mutations in *APP* or *PSEN2* identified (Rupp *et al.*, 2014). The rediscovery of Auguste D.'s brain sections in 1997 had allowed the pathological diagnosis of Alzheimer's disease to be confirmed by modern immunohistochemical methods but any genetic basis for her disease (she was *APOE*3 homozygous) remains, as with so many other early onset Alzheimer's disease patients, a mystery.

The past century has seen a number of transformations in the conceptualization of Alzheimer's disease. The 2013 G8 dementia summit recognized Alzheimer's disease as a growing global health and economic problem, requiring serious action in terms of investment in research and development of disease-modifying therapies but also that alongside the search for prevention and treatment strategies we must invest in enabling people to live well with dementia—ensuring that patients and their families have access to early diagnosis and support that is all too often lacking. A hundred years on Alzheimer's legacy is more relevant than ever—in fact the question of how tractable is this disease and how we care for those with it is perhaps one of the key challenges for the coming century.

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