The changing nosology of Alzheimer disease over more than 100 years: a historical review

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ABSTRACT

Introduction. This review article differentiates between naturalistic disease (infections, stroke) and normative, socio-medical diseases. Alzheimer disease (AD) is a normative disorder first described by Kraepelin in 1910, based on histological features reported by Alzheimer, as an infrequent presenile dementia.

Development. The first nosological change occurred in the 1970s-1980s, encouraged by sociological factors and American neurologists (Kaztman, Terry). They established a new frequent clinical-pathological entity, combining presenile and senile dementia into Alzheimer-type dementia with a definite diagnosis (McKhann criteria, 1984). This nosological classification was soon accepted internationally.

By the late 20th century, AD was divided into genetic AD (1%, three causal genes) and sporadic AD (99%). Recent genetic and molecular advances in the 21st century favour the redefinition of the disease (Dubois, Jack) as a biological entity (with no initial pathological findings or clinical manifestations), using biomarkers (amyloid, tau) and neuroimaging studies, based on the amyloid cascade hypothesis (the protein is presumably toxic for the brain). This made AD a more frequent disease than in the previous nosological classifications.

The pathological confirmation that the majority of dementias in the elderly are of a mixed type, the failure of vaccines, and of anti-amyloid drugs, and the decrease in the risk of dementia in wealthy countries lead to a conceptual crisis of AD. Some authors consider AD a (heterogeneous, multicausal) syndrome whereas others see it as a condition linked to ageing, or even a myth.

Conclusion. The concept of AD has changed significantly over more than 100 years, and although the medical paradigm persists, the need for a conceptual readjustment is beginning to be considered.

KEYWORDS

Dementia, presenile, senile, history, Alzheimer disease, nosology, syndrome, neurodegenerative disease

Et très peu d'histoire... vaut mieux que pas d'histoire du tout
Claude Lévi-Strauss

1. Introduction

In general, there are two types of diseases: some have existed since time immemorial (eg, certain infections, stroke [apoplexy]) and are considered "natural" according to Aristotelian criteria (this is the naturalistic perspective of diseases, which currently may be considered under the Boorse biostatistical model)[1]; whereas others were created due to medical or normative advances or socio-cultural standards that comply with Nordenfelt's holistic theory of health.[2] An example of the latter may be arterial hypertension, whose status as a disease was established in the second decade of the 20th century, when health insurance companies confirmed the risk of

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cardiovascular diseases and early death in their actuarial studies. The ancient Egyptians already took the pulse, and blood pressure began to be measured in the 19th century, but it was not until the early 20th century that it began to be considered a disease or risk factor, thanks to a scientific discovery.[3]

Dementia in the elderly has always been seen as a natural disease linked to ageing or senility, and it has been considered a natural disorder since ancient Rome.[4] Its history may be analysed from different points of view,[4,5] which are not the subject of this review. In the 19th century, dementia in the elderly was known as senile dementia (SD), a term of Latin origin ("mindless") that appeared for the first time in *Etymologiae* by Isidore of Seville.[A] However, the term Alzheimer disease (AD) was coined by the all-powerful German psychiatrist Emil Kraepelin in 1910,[6] after a discovery by Alois Alzheimer, one of his collaborators. In 1906, Alzheimer reported the presence of neurofibrillary tangles (later known as neurofibrillary degeneration [NFD]) in a case of presenile dementia (PSD) published in 1907.[5,7-9] This term was used to refer to dementia with onset before "senium" (60 years). Based on this case and another three described by his team, Kraepelin designated the condition AD and considered it a new type of PSD due to its histological characteristics.[6] The emergence of AD was controversial, as many contemporary authors did not accept this new entity. In academia, AD was conceived as a rare presenile disease.[5,9]

The large population of wealthy elderly people in the United States after the Second World War,[10] and later in the 1970s and 1980s, favoured a changing view, promoted by the American neurologist Robert Katzman. He believed that presenile and senile dementia were the same entity: Alzheimer-type dementia (ATD).[11] This new nosology of AD was successful, and gained international recognition as a clinical-pathological entity according to the McKhann diagnostic criteria.[9]

With the introduction of genetics and molecular biology (late 20th century), the familial form of AD was divided into genetic AD (gAD), due to three causal genes and of early onset, and sporadic AD (sAD), which lacked a clear cause and particularly affected individuals aged 80-85 years. Thanks to genetics, a new pathophysiology of both forms of AD emerged: the amyloid cascade hypothesis (ACH).[12] The majority of the research on AD since 1992 has revolved around this hypothesis.[7,9] In the 21st century, scientific and medical advances have been vertiginous. Molecular biology has favoured the identification of AD (amyloid and tau) and neuroimaging biomarkers that led to another changing view, with many researchers seeing AD (with or without dementia) as a biological entity.[13,14] However, this Copernican change in the nosology of AD has not enjoyed the same universal acceptance as the previous one, for several reasons: *a)* new histological (immunological) stains have favoured the appearance of new pathological entities in the dementia of the elderly[9,15] with confirmation that the majority are caused by mixed pathologies[16]; *b)* the failure of the drugs developed according to the ACH[17,18]; and *c)* the decreased incidence of dementia in wealthy countries.[19] All these reasons have determined the nosological crisis of AD and its uniqueness. Currently, many authors view AD as a heterogeneous syndrome,[20] whereas others consider it an entity linked to ageing.[9] Some have even dared to characterise it as a myth.[21]

The aim of this study is to perform a historical review of the nosology of AD, whose development has very rapidly advanced in the last three decades.

2. Development of a long historical sketch

2.1. The controversial beginning of Alzheimer disease

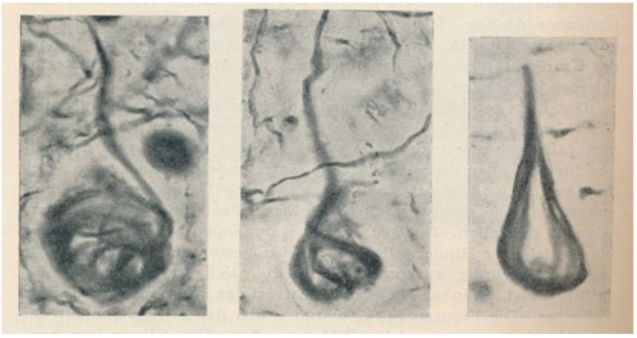
The new disease was described by Kraepelin in 1910,[6] from a case reported by Alzheimer and three cases from his pupils (Perusini and Bonfiglio) who presented intraneuronal neurofibrillary tangles (later known as NFD) and senile plaques (SP), known at the time as miliary plaques. The entity seemed to be questionable, even by Alois Alzheimer himself, as mentioned in his 1911 article.[22] The designation AD by Kraepelin raised considerable debate, which is beyond the scope of this article; however, it should be mentioned that the creation of AD was born more of contextual criteria (he rewarded Alzheimer for his unpaid work in his laboratory and won prestige for his school in Munich)[5,9] than a medical reality. However, there were clinical criteria separating AD from SD: in addition to its presenile onset, the focal cortical signs (aphasia, apraxia, agnosia) and faster progression contrasted with SD, which presented later onset, slower progression, and less obvious cortical signs. Nonetheless, the separation of the two entities was questionable for several reasons.

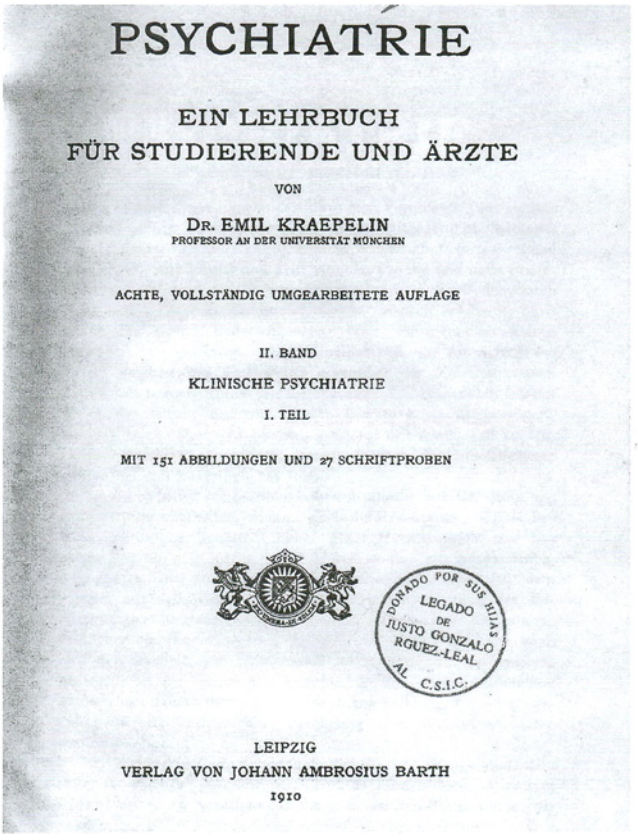
[A]See https://es.wikipedia.org/wiki/Etimolog%C3%ADas_(Isidoro_de_Sevilla).

Firstly, we should note the pathological reasons. NFD and SP were described in AD, but Fisher, Kraepelin's rival from the Prague neuropathological school, had precisely characterised SP (a lesion of increased pathogenic potential) in a type of SD that he designated presbyophrenia. He also rejected AD as a new entity.[5,9] Figures 1-3[23] illustrate SP and NFD.

The controversy around SP and AD lasted decades, with supporters and detractors of its importance, especially because many authors considered SP a non-specific pathology associated with ageing (the words of the Spanish neurologist Pérez-Trullén[24] on this subject are interesting). Table 1 includes a brief summary of the opinions of many authors (psychiatrists, neurologists, and pathologists) from the first 50 years after the birth of AD. The main controversies questioned whether SP and NFD were a non-specific cerebral manifestation of brain ageing or a specific manifestation of SD[24]; authors seemed to side with the former hypothesis, as they were detected in elderly people without dementia (and in other neurodegenerative diseases [ND]) and even in experimental animals as a result of the injection of toxic substances.[9,25] As shown in Table 1, the main nosological problems of AD were already present: the majority of authors believed that AD was an early form of SD, that lesions were non-specific and associated with ageing, that AD may be a syndrome, and even that clinical manifestations of ND may be avoided due to the "power of the brain reserve." An age limit of 40 years was established in order that juvenile cases not be classified as AD. It is also worth mentioning the scarcity of cases published up to the time of the First World War; the cases described and reviewed by Fuller,[26] an African-American neurologist from Kraepelin's team, were minimal (Table 1). This number increased later; the majority of authors considered AD a special form of SD, of non-vascular origin, which was associated with SP, NFD, neuronal loss, brain atrophy, and other rarer but non-specific histological manifestations.[9] An eminent neurologist, R.D. Newton, already noted the difficulty of separating AD from SD in 1948.[27]

We should also mention that many important American psychiatrists (eg, Rothschild) subscribed to Freud's theories of psychoanalysis, which highlighted many psychological aspects in the development and manifestations of dementia[9]; for the psychoanalytic school, dementia was not only caused by brain injuries (as mentioned by Kraepelin and his school), but




PSYCHIATRIE

EIN LEHRBUCH
FÜR STUDIERENDE UND ÄRZTE

VON

DR. EMIL KRAEPELIN
PROFESSOR AN DER UNIVERSITÄT MÜNCHEN

ACHTE, VOLLSTÄNDIG UMGEARBEITETE AUFLAGE

II. BAND

KLINISCHE PSYCHIATRIE

I. TEIL

MIT 151 ABBILDUNGEN UND 27 SCHRIFTPROBEN

LEIPZIG
VERLAG VON JOHANN AMBROSIUS BARTH
1910

Figure 1. Top: neurofibrillary tangles (neurofibrillary degeneration) in the upper part of the image, as shown in Kraepelin's book.[6] Bottom: first page of the book. Images taken from the copy preserved at the library of the Cajal Institute in Madrid.

psychological and personal factors were also significant in its appearance and development. This psychoanalytic position somewhat overshadowed the initial controversy on the entity of AD.[9,28] More data were obtained during the 1960s. Specifically, in 1963, the English neurologist McMenemey[29] published a work on the concept of AD,

Table 1. The early years of Alzheimer disease. Comments of the main authors on its nosology and characteristics (1906-1970).

Main author/Year	Comments
Alzheimer[8]/1906-7	Description of neurofibrillary tangles (NFD) in a case of PSD
Kraepelin[6]/1910	Definition of AD in 4 cases described by his pupils. AD as an entity
Fischer[110]/1907	Description of SP in SD. AD was not considered a distinct entity from SD in his article from 1912*
Fuller[111]/1907	Description of NFD in several neurological diseases and SD
Alzheimer[22]/1911	Report of 2 cases of EA. Questioning of AD as a distinct entity from SD
Fuller[112]/1912	Case report and review. AD is an atypical form of SD
Perusini[113]/1911	AD is considered an atypical form of SD
Simchowicz[114]/1911	Description of granulovacuolar degeneration. Shares Kraepelin's opinion of AD
Barrett[115]/1913	Possible AD with motor deficit. Review of the 14 cases of AD described
Lambert[116]/1916	Report of 5 cases of EA. AD and SD are the same entity
Simchowicz[117]/1924	Change of opinion. AD is a severe form of SD
Malamud[118]/1929	AD must be considered a syndrome with multiple causal factors
Hernderson[119]/1930	Report of 4 cases of AD. Cases of AD must be > 40 years old
Lowenberg[120]/1931	Description of a juvenile case (< 40 years). AD is a heterogeneous entity
Gellerstedt[53]/1933	SP and NFD are associated with ageing. They are non-specific
Rothschild[38]/1934	Report of 5 cases of AD and review of the cases reported (90). Clinical variability Pathological findings are similar in AD and SD. SP and NFD are non-specific Psychosocial component
Rothschild[121]/1936	AD results from an exogenous component (syndrome) plus ageing
Jervis[122]/1936	Description of a juvenile case (2 previous). AD is a clinical-pathological entity
Rothschild[123]/1937	No clear relationship between SP and cognitive decline in 24 cases of SD
Hannah[124]/1936	AD and SD are clinically distinct entities
McMenemey[125]/1940	Report of 6 cases of AD. Constitutional and toxic-infectious causes of AD Introduction of the "reserve power of the brain"
Newton[27]/1948	AD and SD are the same entity and are associated with ageing
Goodman[126]/1953	Report of 23 cases of AD. Causal factor: microglia insufficiency
Schenk[127]/1954	Description of a series and review of Pick's articles on AD. AD is a syndrome
Roth[128]/1955	Differentiates vascular SD and degenerative SD and their progression
Corsellis[129]/1962	Analysis of 300 elderly patients with a mental disease, 96 autopsy studies SP and NFD are more frequent in cases of SD
Larsson[130]/1963	Study of 377 probands with SD and their families in Stockholm Increased genetic risk (4 times greater) in SD vs controls
Terry[33]/1964	Description of the ultrastructure of SP and NFD
Blessed[131]/1968	Study of SD pathological cases and controls. Clear correlation between SP and psychometric tests, but poor correlation with SD
Margolis[132]/1969	Detailed histological analysis of lesions in PSD and SD

AD: Alzheimer disease; NFD: neurofibrillary degeneration; PSD: presenile dementia; SD: senile dementia; SP: senile plaques.

*Fischer O. Bemerkungen zur phlogetischen (Leukozytose)-Therapie und über ein neues Mittel für die Therapie der Metalues. Med Klinik 1922;28:1-11.

Figure 2. Drawings of neurofibrillary tangles by Gaetano Perusini.[23] In early 20th century, pathologists drew their microscopy findings by hand due to the prohibitive cost of photomicrographs.

describing it as a clinical-pathological entity, unrelated to cerebral arteriosclerosis and associated with ageing, like SD. By the end of the decade, the English school had produced relevant pathological works, including those by Corsellis, and Roth, Tomlinson, and Blessed, who performed a quantitative and qualitative study of the characteristic lesions of patients with AD and SD and healthy subjects, distinguishing several mainly quantitative thresholds for SP, but with a high percentage (close to 50%). However, a significant number of cognitively normal elderly subjects exceeded this threshold without clinical manifestations of dementia. SP were clearly associated with cognitive decline, but the association with dementia was much weaker.

It would be a disservice to history if we failed to mention that in 1996, the Italian neurologist Luigi Amaducci[30] shook up the initial history of AD, when he suggested that the first case of AD (1907) was in fact dementia due to metachromatic leukodystrophy. The claim, published first in Italian journals, was accepted by the journal *Science*. This commotion continued with a re-evaluation of Alois Alzheimer's cases of AD by German psychiatrists after searching in the archives of several hospitals.[9] This matter is still to be definitively clarified; as it has no relevance to our study on nosology, I encourage readers to refer to a recent study analysing it in detail.[9]

2.2. The conceptual change in the 1970s. Alzheimer disease as the most frequent cause of dementia

As pointed out by the historian Ballenguer,[10] among others,[31,32] the social change that occurred in the United States after the Second World War led to an increased life expectancy of elderly people and an increase in the admissions to nursing homes. Little by little, their financial situation also began to improve. These social changes promoted a new vision of old age and dementia, and a different conception of these issues among the population, but also a new scientific view of dementia and ageing. It was finally Robert Katzman,[11] following the steps of R.D. Newton,[27] who argued that there was

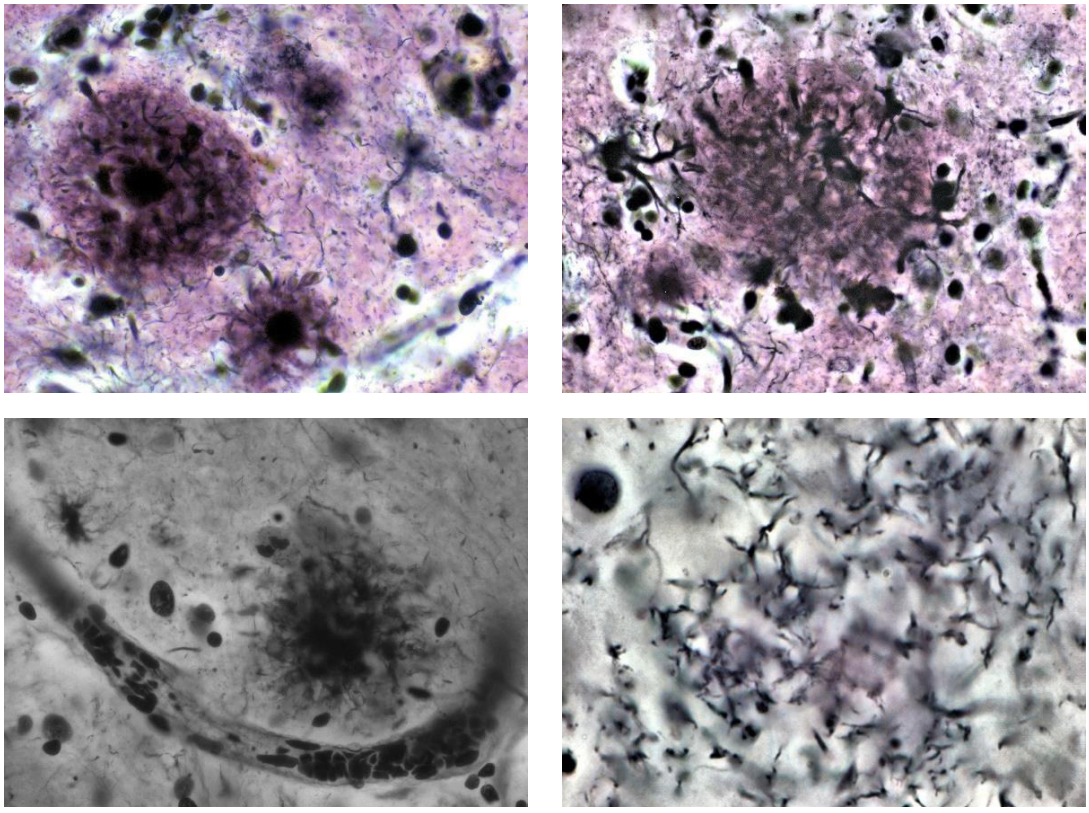


Figure 3. Images of senile plaques by S. Ramón y Cajal (courtesy of Dr R. Martínez, former director of the Cajal Institute in Madrid). Top: detail of two senile plaques with different staining techniques; bottom: detail of a senile plaque and a blood vessel (left) and dystrophic neurites in the plaques (silver nitrate staining).

no difference between the pathological lesions of AD and SD (Terry et al.[33] had shown that they shared a similar ultrastructure) and they both, with several studies, supported the idea that AD was the major killer of American elderly adults. This conceptual change, narrated by Katzman,[11] was made possible because AD and SD were joined together (clinical signs and pathological hallmarks: neuronal loss, SP, and NFD) and they were considered to be one and the same, as agreed in a meeting of dementia experts in 1978[34] (this conception contradicted the separation of AD and SD proposed by Kraepelin). However, the political and social leadership and the relationship with the National Institutes of Health fell on Robert Butler, an eminent psychiatrist and gerontologist, as well as an active advocate of human rights, detractor of ageism, and first director of the National Institute of Aging (NIA) (1975-1981).[9] One essential objective was to study AD in depth (already applied to all patients older than 60 years) and to try to find a cure. Unfortunately, providing long-term care to patients with AD and supporting their families was not a main objective for the NIA nor for the Alzheimer disease associations.[31,32] It is worth mentioning the role of Zaven Khachaturian in the objectives of the NIA, for his position as director of the "exterior" studies and organiser of the Centres of Excellence for dementia (United Sates), and his expertise in the directorship of the journal *Alzheimer's & Dementia* until 2022.[9]

Patrick Fox[28] suggested that the change in the nosology of AD was not merely scientific, but rather a true paradigm shift in the Khunian sense,[35] and was accompanied by a social movement, with a medicalisation of ageing,

which was transformed into a medical entity, AD, and led to legal and social changes and a growing investment in research resources (analogous to the fight against cancer). The NIA's budget for funding AD research went from 0.8 million dollars in 1976 to 80 million in 1989, growing by 100 times in 13 years.[29] This was the first nosological change in AD, which became a broad clinical-pathological entity that could be diagnosed using the first McKhann criteria from 1984,[36] which were pathologically validated in numerous studies. The criteria presented good diagnostic sensitivity but moderate specificity, with misdiagnosis of Lewy body dementia (LBD) and cerebrovascular disease.[9] The new concept of AD *medicalised* SD, which until then had been considered an inherent part of ageing,[10,31,32] and also supplanted vascular pathology, which had traditionally been a "popular" cause of dementia (some authors still consider it as such[37]). For the hope of elderly patients, a cure was expected thanks to the significant financial resources allocated for its study.

2.2.1. The internationalisation of the new nosology of Alzheimer disease

The medical relevance of the scientific, professional, and financial machinery of the United States was and is enormous; it is no surprise that this leadership was achieved with the new nosology of AD and its diffusion. Worldwide medicine accepted the new conception of AD (Figure 4), as observed in MEDLINE citations. Up to 1934, 90 cases had been described,[38] and until the 1970s very few reports were published, and with an increase beginning in the 1980s and 1990s. In that decade, 3000 articles were published per year. From 2020, more than 14 000 articles per year were published. In 2024, more than 18 000 studies were published, and more than 225 000 references had been registered on MEDLINE by January 2025.

A recent article[9] comments on bibliometric studies in the literature that quantify the number of publications, clinical trials, patents, and different scientific indexes, and how the contributions from different countries have changed over the period analysed, with the United States always being the leader in terms of these publications. In the most recent period, a 35-year period (1983-2017) analysed by Robert at al.,[39] the order of countries with the most published studies was: United States, United Kingdom, China, Germany, Italy, Japan, France, Canada, Spain, and, in tenth position, Australia.

Several texts analyse the significant implications of AD for the general populations of different countries,[31,32] but this topic is not relevant in this review.

2.3. The 21st century and the third nosological change in Alzheimer disease: a biological entity

2.3.1. The basis for the change

The new century brought numerous advances in the nosology of ND, including AD, promoted by the development of genetics (information in the DNA) and molecular biology (DNA-associated biochemistry, protein synthesis, and metabolism), and the huge scientific and socio-economic infrastructure that it involved and still requires.[39] In the field of AD, genetic advances determined two subtypes: sAD and gAD (typically presenile, familial, and with autosomal dominant inheritance). Anomalies in the amyloid precursor protein (*APP*) gene were discovered, leading to the description of more than 50 pathogenic variants to date, followed by other alterations in the genes encoding presenilin-1 (*PSEN1*, the most frequent gAD, accounting for 55%-70% of cases) and presenilin-2 (*PSEN2*).[40,41] All forms of gAD amount to less than 1% of cases of AD; the majority of cases (> 99%) are sporadic. Another relevant genetic finding (from 1993) is the apolipoprotein E (*APOE*) gene, whose alleles are relevant risk factors for dementia (and other diseases). One allele of this gene, ε4 (and especially the combination ε4/ε4), is a genetic risk factor for both types of AD.[40,41] In 2000, the introduction of genome-wide association studies (GWAS) marked the start of a fascinating race to detect new risk alleles for sAD. Currently, more than 70 alleles (risk and protective) have been described for sAD, a polygenic disorder.[9,41] These genetic discoveries would be relevant for the proposal of the ACH as a pathophysiological explanation for AD (1992),[12] as the three genes described in the gAD forms are associated with APP metabolism, leading to overproduction of beta-amyloid (Aβ), the main protein present in SP.[7]

2.3.2. The amyloid cascade hypothesis as the origin of Alzheimer disease

The ACH[12] replaced the traditional conception of AD as a disease linked to ageing, or abiotrophy or ND if we may. This is a more "modern and attractive" hypothesis and originates from several sources:

1) It started when the SP core was confirmed to contain a 40–amino acid protein misfolded into fibrils (Aβ), whose

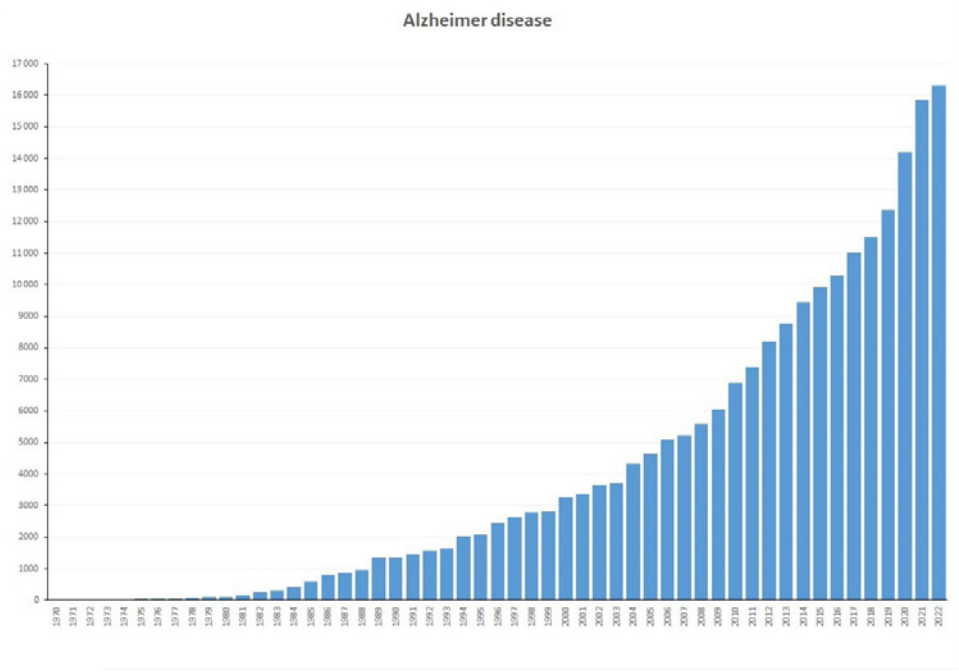


Figure 4. Number of MEDLINE publications on Alzheimer disease. Very few articles were published up to 1980. Subsequently, a quasi-exponential increase may be observed. In 2024, more than 24 000 references were published. Data were obtained from MEDLINE using the MeSH term "Alzheimer disease."

structure and sequence were discovered by Glenner et al.[42] in 1984 (Table 2).[7,9]

2) The discovery of the APP protein and its formation as a protein of the neuronal membrane, which contains Aβ, and its role in the genesis of the different familial forms of gAD (the three previously mentioned genes) through complex, well-studied mechanisms[43] that lead to Aβ accumulation in the brain (increased production or decreased clearance) in the form of SP.[7,9]

3) Several studies included in the 2001 review by Selkoe,[44] who cultured cells from patients with AD in his huge laboratory at Harvard, concluded that Aβ was toxic for brain tissue by multicellular actions and a cascade of events that may cause dystrophic neurites, microgliosis, astrocytosis, synaptic dysfunction, and neuronal death. They also described its clinical correlation with cognitive decline and dementia. In SP, we observe an accumulation of Aβ (and, to a lesser extent, of other proteins), and excessive Aβ production has been reported in gAD; in terms of disease mechanism, both forms of AD (gAD and sAD) were assumed to involve the same pathogenic process. In the 21st century, the brain toxicity of Aβ has been questioned; some authors support an inverse role, that is, a protective action for the brain.[7,45]

From a historical perspective, it is true that gAD and Down syndrome are associated with an excessive amount of Aβ in the brain, that SP contain Aβ, and that the protein may be toxic for the nervous system. With this theoretical background, the English geneticists Hardy and Higgins[12] argued in 1992 that the ACH was the pathophysiological explanation for AD: excess Aβ triggered a cascade of events that generated the rest of the characteristic pathological processes in AD (as mentioned in the previous paragraph), finally resulting in dementia. For more than 30 years, the ACH has been the paradigm (in the Khunian sense) in the pathogenesis of AD, and has guided the development of anti-AD vaccines and drugs.[21,46] This development has been immense, highly sophisticated, and has been funded with billions upon billions of dollars.[7,46]

Table 2. Main historical milestones in Alzheimer disease/dementia of the elderly.

Year/Main author	Description
1907/Alzheimer[8]	Description of NFD (neurofibrillary tangles) in PSD
1907/Fischer[110]	SP are associated with SD.
1910/Kraepelin[6]	Definition of AD
1936/Rothschild[121]	Introduction of personal factors in dementia*
1948/Newton[27]	The pathology of presenile and senile dementia are similar
1962/Kral[133]	Concept of benign and malignant memory dysfunction
1964/Kidd[134]	Description of paired helical filaments in NFD
1964/Terry[135]	Ultrastructure of NFD and SP (amyloid in core)
1967/Roth[136]	Diagnostic quantification of SP and tau in senile dementia
1972/Giurgea[137]	Therapy with nootropics (cognitive enhancers) in dementia
1974/Drachman[138]	Deficit in the cholinergic system and memory impairment
1978/Katzman[34]	AD and SD are the same entity
1984/Glenner[42]	Purification of amyloid protein
1984/Hollister[139]	Therapy with hydergine (vasodilator) in SD
1984/McKhann[36]	Probabilistic and clinical-pathological diagnosis of AD
1986/Summers[140]	AD therapy with physostigmine
1987/Kang[141]	APP cloning
1991/Goate[142]	Mutation in the APP gene causes gAD
1991/Wirak[47,143]	Transgenic mice (with mutated APP) generate amyloid
1992/Hardy[12]	Amyloid cascade hypothesis
1993/Corder[144]	The APOE4 gene leads to an increased risk of AD
1995/Braak[51]	AD stages according to neurofibrillary deposition
1995/Fritze[145]	Nimodipine (calcium channel blocker) ineffective against AD**
1996/Amaducci[30]	First case of AD consisted of metachromatic leukodystrophy
1996/Rogers[146]	Donepezil was the first drug (AChEI) against AD
1999/Petersen[56]	Introduction of the concept of MCI
1999/Rösler[147]	Rivastigmine (AChEI) for AD
1999/Winblad[48]	Memantine (NMDA inhibitor), anti-dementia and anti-AD drug
2019/Nicoll[17]	The first anti-AD vaccine trial was halted (Elan vaccine, 2002)
2004/Haan[72]	Review on the prevention of dementia
2006/Lesné[148]	Aβ oligomers/dementia in rats. Significant article withdrawn[87]
2006/Neumann[149]	Detection of TDP-43 protein in neurodegeneration
2007/Schneider[67]	The most frequent pathology in dementia is mixed
2008/Bertram[150]	Sporadic AD presents a highly complex genetic component
2008/Dubois[13]	New definition of AD based on biomarkers
2010/Chouliaras[151]	AD has an epigenetic component
2010/Olazarán[152]	Review of non-pharmacological treatments in AD/dementia
2010/Spector[153]	Biopsychosocial model in the genesis of dementia
2013/Boyle[154]	Most cognitive decline is not due to ATD***
2014/Doody[155]	Failure of AD trials with bapineuzumab and solanezumab
2015/Khachaturian[156]	Prevention of AD syndrome
2016/Satizabal[59]	Decrease in the risk of dementia (3 decades, Framingham cohort)
2017/Jack[14]	Biological definition of AD

Table 2 continue →

Table 2 continue →

Year/Main author	Description
2018/Rosenberg[80]	FINGER trial, decreased risk of cognitive decline
2019/Nicoll[17]	15-year post-mortem neuropathological follow-up of AD immunisation
2020/Livingston[75]	Preventable dementia risks (report of the Lancet standing Commission)
2021/Richard[84]	Inefficacy of anti-amyloid drugs (Bayesian statistics)
2021/Mullard[157]	Approval of aducanumab by the FDA
2022/Nelson[66]	LATE is present in 40% of dementias
2023/Mahase[158]	Approval of lecanemab for use in AD by the FDA

AChEI: acetylcholinesterase inhibitors; AD: Alzheimer disease; ATD: Alzheimer-type dementia; FDA: United States Food and Drug Administration; LATE: limbic-predominant age-related TDP-43 encephalopathy; MCI: mild cognitive impairment; NFD: neurofibrillary degeneration; NMDA: N-methyl-D-aspartate; PSD: presenile dementia; SD: senile dementia; SP: senile plaques.

*SP do not adequately match with dementia; **Administered in senile vascular impairment.

2.3.3. Development of Alzheimer disease treatments based on the amyloid hypothesis

The first step consisted in the confirmation of AD in transgenic mice expressing several genes causing gAD. In 1991, several teams from different laboratories published studies on MEDLINE showing that transgenic mice presented increased Aβ levels,[46,47] and later showed a cognitive decline (in mazes and other devices) similar to that observed in patients with AD. However, the typical AD pathology, including neuronal loss, could not be replicated in mice. This amazing development (more than 17 000 references on MEDLINE up to 2025) led to two main treatment pathways: vaccines against Aβ (active immunisation), with trials in transgenic mice showing their effectiveness in reducing Aβ levels in the brain; and another gigantic scientific effort: the creation of humanised anti-Aβ monoclonal antibodies[9,46] (passive immunotherapy). The introduction of vaccines (Elan AN-1792[17]) in humans was interrupted due to adverse effects, with participants developing post-vaccination encephalitis. The vaccines were effective in clearing cerebral Aβ but not in preventing progression of AD or reducing mortality in a 15-year post-mortem neuropathological follow-up study.[17] Table 2 includes the main milestones in the history of AD/dementia, to illustrate its historical progression and facilitate the discussion. Humanised monoclonal antibody therapy and its consequences will be analysed in the following sections.

2.3.4. New discoveries in Alzheimer disease

A) Cortical cholinergic deficit in Alzheimer disease and its treatment

This review briefly addresses the following relevant milestones in the history of AD: the importance of cholinergic innervation of the cerebral cortex by brainstem nuclei, demonstrated by Whitehouse[21] (Table 3), and the development of acetylcholinesterase inhibitors: donepezil, rivastigmine, and galantamine.[9] These drugs facilitate cholinergic function in the brain and cause a slight symptomatic improvement (increased alertness and memory lasting months in some patients), but do not cure AD nor clearly slow progression of the disease. They are still used in clinical practice. Memantine, based on a complex mechanism (glutamatergic NMDA inhibition),[47] has also failed to achieve a significant therapeutic repercussion. The analysis of these therapies, which have been relevant in the history of AD, is beyond the scope of this review (Table 2). From a historical perspective, this attempted treatment was important not only for the reasons mentioned above, but also because it demonstrated the feasibility of pharmacological treatment in AD, which represented a glimmer of hope in medicine and improved expectations among the

Table 3. Development of the nosology of Alzheimer disease†

Development	Year/Author
New disease	
Presenile AD is a new disease	1910/Kraepelin[6]
The nosological shift (1970s-1980s)	
A single clinical-pathological AD: presenile + senile dementia	1978/Katzman[34]
Diagnostic criteria	1984/McKhann[36]*
McKhann et al. criteria, pathological validation	-/Several authors[9]
Differentiation between genetic and sporadic AD	1991-1993/Several authors[9,36]
Definition of MCI	1999/Petersen[56]
Nosological shift (2007-2024)	
The biological construct of AD (biomarkers)**	
Predementia, "at-risk state for AD"§, and dementia	2008/Dubois[13]-2021/Dubois[159]
Biological construct of AD (in vivo)	2018/Jack[14]-2024/Jack[160]
Other nosologies	
AD is a syndrome	2010/Richards[20] 2019/Khachaturian[101]***
AD is a myth	2007/Whitehouse[21] 2018/Saint-Jean[161]

AD: Alzheimer disease; MCI: mild cognitive dementia.

† Main medical criteria. Criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) are not included.

*NINCDS–ADRDA criteria.

**With no pathological validation (or validation in population-based studies) but with clinical validation ("imprecise"): Oksengard AR, Cavallin L, Axelsson R, Andersson C, Nägga K, Winbald D, et al. Lack of accuracy for the proposed 'Dubois criteria' in Alzheimer's disease: a validation study from the Swedish Brain Power Initiative. Dement Geriatr Cogn Disord. 2010;30:374-80. This formulation has been called a "tower of Babel" due to its complexity.

***Malamud et al.[118] and Schenk[127] also clearly asserted this (Table 1).

§This is not a conventional medical "risk" (eg, arterial hypertension) as it does not improve with treatment (see Ackley SF, Zimmerman SC, Brenowitz WD, Tchetgen Tchetgen EJ, Gold AL, Manly JJ, et al. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. BMJ. 2021;372:n156).

population. Nevertheless, from the beginning, these drugs were known to be for symptomatic treatment and not curative. This stance is very different, as we will see, to the ACH and its staunch supporters,[48] scientists, the NIA, Big Pharma (in a descriptive, rather than a pejorative sense of the term), and a large section of the socioeconomic establishment that has supported this industry, as it has searched for a curative treatment targeting the causes of the disease, and has reformulated AD as a biological entity, which represents a significant conceptual switch.[49,50]

B) Alzheimer disease develops throughout life. Alzheimer disease as a biological construct

Many chronic diseases (arthrosis, cerebral arteriosclerosis) develop subclinically and manifest late; however, in the case of AD, this was confirmed with the findings by the research team of Braak et al.[51,52] at the University of Frankfurt, who with their German precision studied the brains of healthy subjects, and patients with cognitive decline and dementia (aged 1 to 100 years old), revealing that cerebral NFD and pre-NFD lesions appear

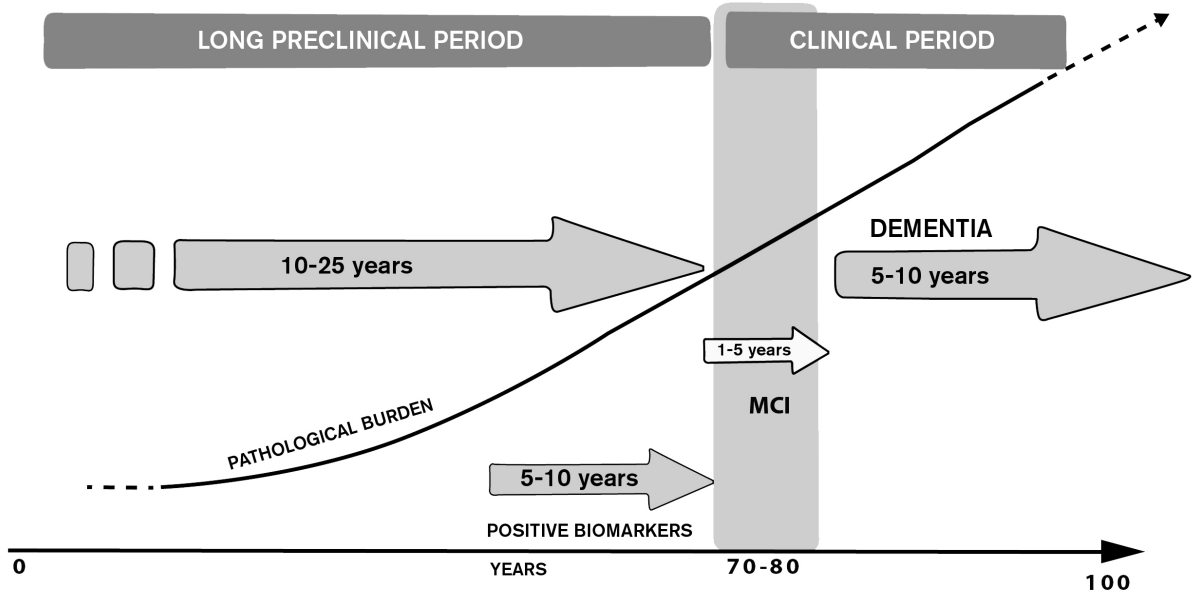


Figure 5. Probable progression of Alzheimer disease. Adapted from the Spanish edition of the book *Alzheimer: prevención desde la niñez* (Madrid: IACC; 2017) by Bermejo-Pareja, showing the progression of a possible case of Alzheimer disease. It should be remembered that in many patients, the pathological burden (neurofibrillary degeneration, senile plaques, or other) may not lead to cognitive decline or dementia, as it may not increase excessively during its possible progression, or because the cognitive reserve suppresses the harmful effect of pathological burden. The time periods indicated in the graph should be considered as mean ranges.

in youth (rarely in childhood) and increase throughout life, becoming practically universal among patients older than 85 years. Intense NFD is typically associated with cognitive decline, although this is not always the case, as pointed out by some authors including Gellerstedt[53] in 1933 (Table 1). This finding is contrary to the ACH, as the onset of Aβ deposition in AD occurs late. This led to a historical dispute around the relevance of this finding in AD between the "baptists" (strong supporters of the pathogenic relevance of Aβ)[49] and the "tauists" (more rational followers of the importance of tau protein). This debate began in the 1990s[54] and remains today (Arnsten et al.[55]). Besides this controversy, the study by Braak and his school,[51,52] as well as many others, has corroborated an indisputable fact: tau protein accumulation in the brain occurs early, preceding the onset of clinical symptoms of mild cognitive impairment (MCI, as defined by Petersen et al.[56]) and dementia. Typically, positivity for several biomarkers (CSF) occurs prior to the clinical manifestation of MCI or dementia; however, this does not necessarily mean that the presence of these biomarkers is a pathological indicator of future dementia, as is the case of cognitive alterations.[57] This progressive course of AD biomarkers is the pathogenic basis of the AD continuum.[58] Figure 5 shows a diagram illustrating AD progression, which is based on clinical, pathological, and biomarker data. The best clinical information comes from the initial Framingham cohort study (30-year progression), in which patients performed mental tests every two years, and which detected a subclinical cognitive decline in individuals who subsequently developed dementia.[59,60] Similar results were also obtained in a French cohort after 20 years of follow-up.[61]

Several studies with blood and CSF biomarkers and prospective studies with neuroimaging support this idea.[7,9] Figure 5 illustrates this progression, which has been named the AD continuum and has cemented the biological definition of AD, based on biomarkers (Aβ

and tau) and neuroimaging. Two different currents have emerged,[13,14] although both advocate a preclinical stage of AD (absence of MCI and dementia), and absence of pathology for its diagnosis. Over a decade, both have modified their complex assumptions on several occasions, always with a normative character and without a clear body of evidence.[7] One of these currents is led by the French neurologist Bruno Dubois,[13] who directed the International Working Group, all members of which are explicitly funded by Big Pharma. Dubois was the first to initiate a change in the nosology of AD, with a risky theoretical approach: focusing diagnostic criteria on the sophisticated tau and amyloid biomarkers in biological fluids (blood and CSF), and the costly neuroimaging biomarkers (MRI, PET) that detect presence of Aβ and tau in different parts of the brain, thus abandoning pathological studies.[50] Another group of scientists,[62,63] linked to the two main research funding sources (the NIA and the Alzheimer Association), led by Clifford Jack and sponsored by Big Pharma (some members of the group are shareholders in these companies), established similar nosological criteria. These were more aggressive from a medical perspective, as they assumed the possibility that the AD continuum may be detected in vivo (with experimental criteria) and diagnosed before patients begin to experience cognitive decline or dementia. In other words, AD may be established according to biological criteria only, with no pathological study nor clinical manifestations. Using these criteria, AD becomes a strictly biological construct. They incorporated not only detection of Aβ and (unphosphorylated or phosphorylated) tau in CSF, but also several sophisticated neuroimaging biomarkers in MRI, fMRI, and PET scans. Table 4 includes a summary of the A-T-N classification of AD proposed by Jack et al.[14] Their common objective is the early detection of AD, before its clinical manifestation, in order to attempt to prevent the clinical onset of the disease using drugs. There are several differences between the two groups' approaches (beyond the scope of this review). The International Working Group introduced the concept of "at-risk state for AD," for individuals with positive AD biomarkers but no clinical manifestations.[63,64] In this regard, see Table 3 (progression of AD nosologies) and 4, which illustrates the ATN classification of biological AD and which we may also liken to the tower of Babel, to echo the characterisation of Dubois' criteria by Giaconne et al.[65]

C) The pathology of dementia in the elderly is more complex than Alzheimer-type dementia

In the 21st century, with the advances in post-mortem antibody staining,[64] community-based autopsy studies (without the bias of clinics)[16] and autopsies of very elderly patients (including individuals aged 90 years and older) have changed our understanding of dementia in the elderly.[16] Probably, the most striking novelty is TDP-43 encephalopathy, also known as limbic-predominant age-related TDP-43 encephalopathy (LATE),[66] a new entity determined thanks to advances in molecular biology (specific antibodies) in autopsy studies (see Table 2), which is present in up to 40% of the autopsies of patients with dementia.[66] Furthermore, the majority of cases of dementia in elderly patients are not ATD but rather mixed dementia[16,67] (combinations of ATD, vascular dementia, LBD, LATE, hippocampal sclerosis, and others); indeed, common ND are not even the most frequent causes of dementia in very elderly patients.[68] In addition, it is very striking that the combination of multiple pathologies accounts for the majority of these dementias, whose cognitive correlation with each pathological process remains partially unknown.[69] In fact, many cases of dementia still lack a clear pathological correlate with current technology,[9,70] especially in very elderly patients (possible unidentified pathological alterations or high cognitive reserve).[70] These facts are decisively opposed to the ACH as the predominant pathophysiological cause of dementia in the elderly, or other restrictive hypotheses of the causes of this dementia. Figure 6 illustrates these combinations.[71]

D) The risk of dementia decreases in wealthy countries

A historically relevant review (see Table 2, Haan et al.[72]) suggested an idea that was later corroborated by evidence. This situation was first clearly demonstrated by a study including data from a period of 30 years from the Framingham cohort.[60] We should underscore that the authors of this study only identified education as a clear risk factor, with those completing secondary or higher education presenting lower rates of dementia decades later. After that study, a torrent of cohort population studies (and population registries, such as that published in Sweden) including follow-up periods of several decades, in practically all wealthy countries from North America and Europe, but not in Asia (neither Japan nor South Korea), have revealed a decrease in the

Tabla 4. Diagnostic classification of Alzheimer disease based on biomarkers [ATN]*.

Biomarkers (combinations)	Cognitive status		
	No cognitive alteration	**MCI**	**Dementia**
A–T–N–	Normal with no Alzheimer-type biomarkers	MCI with no Alzheimer-type biomarkers	Dementia with no Alzheimer-type biomarkers
A+T–N–	Preclinical AD (pathologic change)	MCI with pathologic change	Dementia with pathologic change
A+T+N–	Preclinical AD	AD-MCI (prodromal AD)	AD dementia
A+T+N+	Preclinical AD	AD-MCI (prodromal AD)	AD dementia
A+T–N+	Normal with AD and suspected non-AD pathologic change&	MCI-AD and suspected non-AD pathologic change&	Dementia, AD, and suspected non-AD pathologic change
A–T+N–	Normal, non-AD pathologic change	MCI, non-AD pathologic change	Dementia, non-AD pathologic change
A–T–N+	Normal, non-AD pathologic change	MCI, non-AD pathologic change	Dementia, non-AD pathologic change
A–T+N+	Normal, non-AD pathologic change	MCI, non-AD pathologic change	Dementia, non-AD pathologic change

+: positive; –: negative; &: concomitant or associated; A: beta-amyloid (Aβ) (positive amyloid PET scan or low level of Aβ42 in CSF); AD: Alzheimer disease; MCI: mild cognitive impairment; N: neurodegeneration (neurological lesion); T: pathological tau (increased phosphorylated tau in CSF and cortical tau PET).

AD with pathologic change (early stage) and AD represent only two different stages of the AD continuum.

Biomarker A: positive amyloid PET scan or low level of Aβ42 in CSF. Biomarker T: increased phosphorylated tau in CSF and cortical tau PET. Biomarker N: neurodegeneration or neuronal lesion biomarkers, including brain atrophy on MRI, hypometabolism on FDG-PET, and increased tau in CSF. The in vivo diagnosis of Alzheimer disease requires that a patient present positive A and T biomarkers.

*Based on Jack et al.[14] (2018), with abbreviated terms. These criteria were modified in 2014 by the original authors,160 who introduced a different classification (0: normal biomarkers; and 1 to 6 AD stages, according to severity); this classification is very complex and normative, and is not currently validated.

risk of dementia among elderly individuals.[9,73,74] This decrease has been quantified in some countries at 13% per decade;[19] however, it seems not to be continuous nor accompanied by precise understanding of risk factors, although the most clinically relevant had been identified to be no more than 12 to 15.[75] However, as some studies have suggested,[76,77] there may be more than 200, and may vary greatly between individuals.[78] In general, primary and higher education, lifestyle (physical exercise), smoking cessation, and avoidance of cardiovascular risk factors (hypertension, obesity) are considered essential.[59,60,74-78] There are difficulties when establishing the "realness" of several possible risk factors, as evidence is from observational cohort studies (which are very difficult to perform[79]) rather than clinical trials. However, the FINGER trial (a multidimensional study controlling for very diverse risk factors) has shown slight effectiveness in the prevention of cognitive decline in elderly individuals.[80] It is also unclear which pathological component of cognitive decline and dementia is responsible for this decreased risk, although several basic and clinical trials suggest the relevance of controlling cardiovascular or general vascular risk factors,[81,82] and of not forgetting general health status, which is better in developed countries.[83]

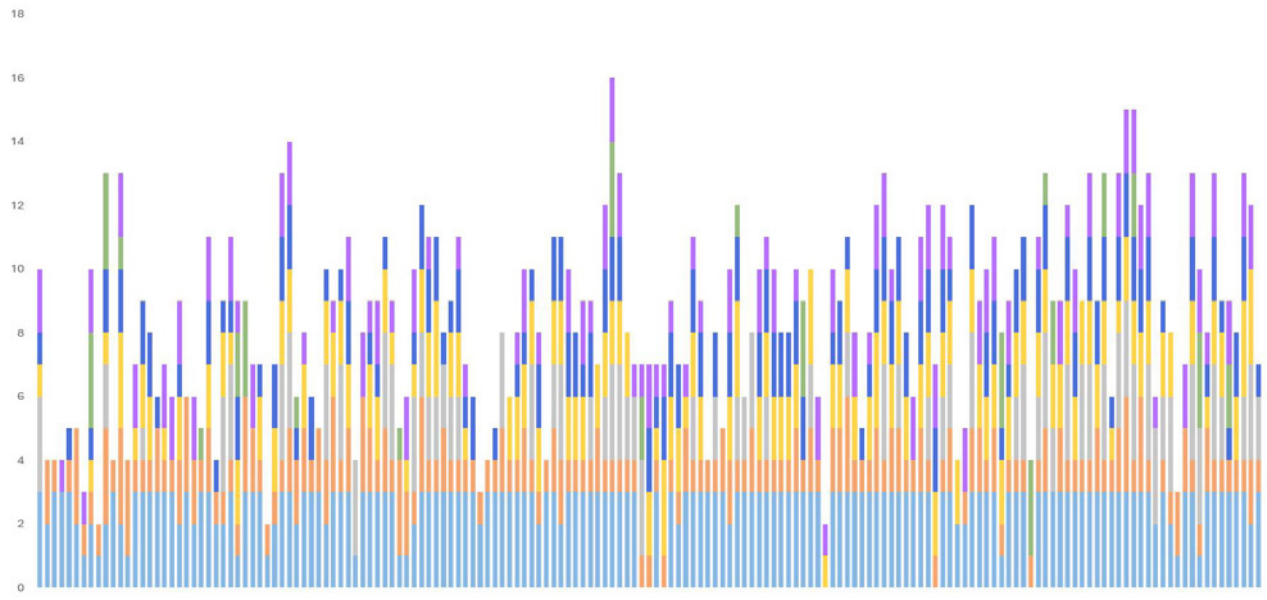


Figure 6. Pathological combinations in dementia. Spanish series of autopsy studies.

Each colour in the graph represents one of the most frequent types of pathology in a series of 167 cases of dementia from the Centro Reina Sofia de Alzheimer (Banco de Cerebros, Dr A. Rábano). Each line corresponds to one patient's autopsy study. Types of pathological finding by colour: light blue: Alzheimer disease; orange: vascular; grey: Lewy body dementia; yellow: limbic-predominant age-related TDP-43 encephalopathy; dark blue: hippocampal sclerosis; green: argyrophilic grain disease; purple: tau astrogliopathy. The height of each colour is proportional of the intensity of the condition. Taken from Burgueño-García et al.[71]

E) Failure of anti-amyloid drugs in "curing" Alzheimer disease

This is a long story that we must summarise. We may begin with a key study from 2021, conducted by Richard et al.,[84] who used Bayesian methods (enabling the factorisation of results from previous clinical trials and addition of the next) to show that, after six clinical trials of anti-Aβ humanised monoclonal antibodies (bapineuzumab, solanezumab, and gantenerumab), they determined a null therapeutic effect (Bayes factor of 1127, vs 0.09 in favour of a positive cognitive effect). This finding, together with those from previous studies, especially the one by Nicoll et al.[17] that showed that the elimination of Aβ (and its polymers) after vaccination (15-year follow-up) did not cure AD, have revealed the absence of therapeutic effect of these strategies in AD. Although it may be suggested that the new drugs approved by the FDA (aducanumab, lecanemab) condition a very slight (and debated) improvement, which has led to many publications,[7,9,32,46,85] if we stick to the facts, aducanumab was withdrawn from the market by Biogen, despite its approval by the FDA, given the low number of use requests.[7] It is relevant that Pfizer, the largest of the Big Pharma laboratories, abandoned anti-amyloid and AD therapy in 2018,[7,46] after the failure of bapineuzumab in a carefully performed trial with numerous patients and controls.[9] The situation of lecanemab is under debate,[86] as its adverse effects, including mortality,[87] seem excessive given its limited therapeutic effectiveness.[7] The controversy has even arrived in Spain.[88] Regardless of how the story of lecanemab and the most recent drug donanemab might end, it is clear that these drugs do not cure AD.[7,87]

With these therapeutic results obtained in trials targeting Aβ, it seems reasonable to critique the ACH.

Probably, the strongest and most concise argument is that of Herrup[46]: *1*) excess Aβ alone does not cause AD in humans or mice; *2*) its elimination does not cure AD in humans; *3*) stopping the production of Aβ by pharmacological manipulation of APP does not cure AD and "makes" mice and humans weaker. However, this story is complex, because the ACH has been reformulated by its authors on many occasions,[7] and its main authors, Hardy and Selkoe, still support it. The former has stated that he does not expect a magic bullet (drug) to cure AD, given the multiple pathology of sAD; the second author still believes in its plausibility.[7] However, the healthcare and pharmacological social and economic system that supports this nosology remains in place, and scientific paradigm shifts[35] require not only scientific confirmation, but also a decay of the medical-economic (ie, Big Pharma, diagnostic kits) and social infrastructure that supports it. Therefore, the main objective of this review is to shine a light on the nosologies of AD, not to critique them nor speculate about their future.

However, given the historical importance and persistence of the ACH (the theoretical basis of the biological construct of AD), it is appropriate to make some clarifications on the consequences of this continuation, with no proof of concept (of Aβ) of the cause of AD[7,9,32,46,89,90]: *1)* persistence of the ACH has been based on the fact that its followers have remained as a scientific pressure group; *2)* such pressure has excluded scientists and alternative hypotheses on AD and critics of their beliefs from biomedical fora, congresses, and journals; and *3)* its excessive pre-eminence has limited funding of other conceptions of AD and the diffusion of other ideas. It has been suggested that many supporters of the ACH believe in it almost religiously,[49] and this has been the main driving force of this situation,[89] with a refusal to accept the evidence of the failure of anti-Aβ therapies in trials performed according to its postulates.[7,9,46]

2.4. The current dilemma

Currently, critiques of the theoretical construct of AD as "amyloid and tau disease" (and the biological definition of AD) are increasingly evident, from a conceptual,[7,62,63,91,92] pathological,[93,94] clinical,[7,9,95,96] epidemiological,[97] therapeutic,[98] even ethical,[99] and definitively practical[100] perspective. This construct was created by a scientific elite that studies AD with sophisticated biomarkers that are only accessible in wealthy countries (and in selected environments). It seem unlikely that this conception, which is based on highly selective research, should manage to establish this new paradigm in the real world of dementia (research aside), unless an unexpected therapeutic success is achieved, which does not seem plausible considering the previous history (more than 30 years of unsuccessful therapies) and the character of this nosology, which has not resolved the actual physiology of APP and Aβ.[7]

The situation in the past few years, according to recent texts and many articles, is the consideration of sAD as a heterogeneous syndrome,[7,9,20,91-93,101] typical of a ND.[63,93,94] Genetic data support this: more than 70 associated alleles have been described, which are involved in pathways related to immunity, the microglia, inflammation, processing of lipids and APP, and vascular health. Furthermore, its clinical symptoms,[7,9] and especially its pathology, are heterogeneous, integrating multiple well-characterised entities; this largely explains the failure of drugs exclusively targeting Aβ pathology.[7] This conception of a syndrome (both for AD and SD) remained applicable during the first historical period of the description of AD by several authors (see Table 1); however, findings from the 21st century support a naturalistic interpretation. Numerous theories may explain this combination of multiple causal elements of the syndrome of dementia in elderly patients, as has been demonstrated with matrices (adaptive matrix model) or interconnected networks of different metabolic and cellular pathways,[7,46,102,103] typical of a complex ND.

The study of the second most frequently reported risk factor,[7,9] ageing,[7,9,31,62] and its biological basis, has largely been postponed by the NIA[104] and proponents of the ACH; it has again been considered an essential aspect to be studied[9,62] in the renovation of ideas around dementia in the elderly.[7,46] In this regard, one important milestone in the 21st century is the decrease in dementia in wealthy countries, which has mainly been analysed in population-based studies that detected cases of "dementia" (without distinguishing subtypes). This relevant fact is similar to what happened from the 1950s, when the incidence of myocardial infarction, cardiovascular disease, and cerebrovascular disease (stroke) was reduced through control of vascular risk factors. This control and lifestyle (greater education and increased physical exercise, improved diet) and the restriction of toxic habits (especially smoking) might plausibly be responsible for the decreased incidence of dementia.[9,57,60,73-75,105] The WHO and governments of countries presenting ageing

populations have already declared their support for this position.[9] Because, as described by Spanish researchers, "only prevention makes sense" in AD.[106] In this regard, FINGER trials of multidomain therapy including community interventions and healthy lifestyle in elderly patients have obtained promising results in individuals with poor cognitive performance.[80]

3. Conclusions

The historical progression of AD has followed the same path as many other diseases: the number of potential patients has progressively increased, generally expanding the criteria in mild or very mild cases.[107] For more than 50 years, AD, described by Emil Kraepelin in 1910, was conceived as a rare disease (a special PSD), separate from SD; this conception was based more on Kraepelin's personal criteria as the leader of psychiatry in Munich than on scientific data. This individualisation in the context of SD was questioned by many neurologists, psychiatrists, and pathologists, and even by Alois Alzheimer himself (Table 1).

Social conditioning and new pathological data (with ultrastructure) revealed that the pathological lesions associated with AD were identical to those present in SD. These events led to a conceptual change led by Robert Katzman and the NIA; the concept of AD as conceived by Kraepelin (the separation of AD and SD) was disputed and the PSD described by Alzheimer and SD were added together to conform a new entity, that is ATD, whose prevalence greatly increased with population ageing. A degenerative, non-vascular character was established, as well as its probabilistic clinical-pathological diagnosis (McKhann criteria). This change enjoyed social, national, and international success, and the new concept of AD was widely accepted.

Advances in genetics (casual genes in gAD) and molecular biology (biomarkers) in the 21st century started to undermine this nosology. The ACH was postulated as a pathophysiological (and almost causal) explanation to define AD, whose genesis was attributed to the presence of Aβ (the main protein involved in SP), which was believed to be toxic for the brain. This situation led to two main activities and one consequence. Activities:

1) A large number of studies, mainly performed in transgenic mice (with familial AD genes) in which several anti-Aβ mechanisms were able to minimise the presence of Aβ in the brain, which represented an experimental success. Likewise, they stimulated similar studies in humans. Vaccines (active immunisation) and anti-Aβ humanised monoclonal antibodies (passive immunisation) were trialled to achieve a decrease (or removal of the amyloid burden in the human brain), but this deprivation has not led to a cure for dementia nor halted AD progression. The "proof of concept" of the ACH has failed.

2) Introduction of a new nosology of AD as biological construct (with two main biomarkers: Aβ and phosphorylated tau) that allows for (experimental) in vivo diagnosis of AD and has made possible population-based study of biologically-defined AD.[108] This study revealed an increase in individuals with biologically-defined AD (as opposed to the usual clinical-pathological criterion), with rates up to three times higher among subjects aged 85 years old or older. Under the biological hypothesis, AD is considered to be much less frequent than in previous conceptions.

Consequence:

The main objective of this nosology (the discovery of pharmacological therapies) has not been achieved in initial or preclinical studies of AD. Despite its development in the past 10 years (Table 3), this new construct (described similarly, but not equally, by Clifford Jack and Bruno Dubois) has been widely criticised, from both historical (AD was always a dementia) and current perspectives (see "The current dilemma"), and especially as a new nosological entity,[7,91,92] which has led this proposal to a scientific cul de sac and the raising of some very critical voices, such as that of D.A. Smith,[109] emeritus professor at Oxford. Smith questioned whether it was ethical to include new patients in trials of anti-Aβ therapies and why Big Pharma did not share the outcomes of 20 of its latest trials with independent researchers for their analysis.

In this context, it is logical to suggest a reformulation of AD, and especially of dementia in the elderly, as previously explained. Fortunately, the decrease in the incidence of dementia in wealthy countries opens a new chapter of hope for improvement in dementia of the elderly, and encourages multiple lines of research and therapies that are still ongoing, which will probably enable us to revisit the concept of AD/dementia in the elderly, as well as the nosological definition of the multiple accompanying diseases. If a widely recognised redefinition of AD is not achieved, it seems likely that AD may become a historical myth, as has been suggested[21] (Table 3).

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Conflicts of interest

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