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Abstract

Background: Recent US proposals suggest defining Alzheimer's disease (AD) based on β-amyloidosis alone. This sparked debates that echoed historical ones about the significance of brain lesions and clinical phenotype.

Methods: This review covers debates on AD nosology through three key periods: AD's discovery in German-speaking countries in the early 20th century, its redefinition in Anglo-Saxon countries in the 1960s-1980s, and current debates on the biological or clinico-biological definitions of AD. Key players' opinions are focused on.

Results: At the beginning of the 20th century, AD was defined as a clinico-pathological entity. Debates arose around the pathological anchor, which included extended neurofibrillary tangles vs. neuritic plaques (Alzheimer vs. Fischer) and its association with senile dementia (Kraepelin). In the 1960s-80s, the debate shifted towards whether AD could be diagnosed using qualitative or quantitative neuropathological features and whether it was a unique process (Terry & Katzman) or had subtypes (Roth). The current definition proposed by the US Alzheimer's Association is based purely on biological β-amyloid abnormalities and represents a double break: from the historical clinico-pathological definition of AD and from the historical emphasis on tau or combined tau and β-amyloid high levels of pathology. Conversely, the clinico-biological proposal of the International Working Group remains aligned with historical concepts of AD.

Conclusion: This historical perspective illustrates the unresolved questions surrounding AD pathogenesis, role of lesions, and the clinical phenotype, especially for sporadic cases. The intense nosological debates throughout the history of AD also illustrate the diversity of theoretical frameworks for defining disease in medicine.

Introduction

Alzheimer's disease (AD) is a major public health issue. It causes around two-thirds of the estimated 57.4 million dementia cases in 2019, which are expected to reach around 152.8 million cases in 2050[1]. Initially, Emil Kraepelin defined it as a disease responsible for early-onset dementia in 1910. Throughout the 20th century, its definition has kept changing, and it became the leading cause of late-onset dementia. Recent developments now propose extending AD's definition to a sole biological abnormality, β-amyloidosis[2]. Interestingly, current debates reflect historical debates about defining AD based on the importance of brain lesions and clinical phenotype and the relative importance of tau and β-amyloid pathology. In this review, we cover the early AD definition debates between the Munich and the Prag Schools of Psychiatry (Alois Alzheimer & Emil Kraepelin vs. Oskar Fischer) on the importance of neuritic plaques and extended neurofibrillary tangles (NFTs) and their link to a specific phenotype (early-onset and/or late-onset dementia). Secondly, we review the 1960-80s period, which saw British and American groups diverging opinions on the uniqueness of AD at the key moment of extending the disease definition to late-onset cases. Finally, the article explores the current debate between the International Working Group (IWG) clinico-biological definition of AD[3] and the Alzheimer's Association (AA) sole β-amyloid-centered biological definition of AD[2]. While the first part follows a chronological plan, the second and third parts summarize the positions of key players without following a specific timeline. This review is not exhaustive and focuses on the opinions of important figures involved in nosography during the three key periods mentioned above. Translations from German are intentionally kept as literal as possible.

The early 20th century debate on the definition of AD: Is senile dementia a disease? Are the neuritic plaques worth the neurofibrillary tangles?

Facts and debate

In 1892, Paul Blocq and Georges Marinesco were the first to describe neuritic plaques in the brains of elderly epilepsy patients. They described them as "nevroglial sclerosis" nodules and speculated on their possible glial nature, but did not insist on making it a separate disease[4]. In 1898, Emil Redlich reported discovering neuritic plaques in a case of advanced senile dementia that he named "miliary sclerosis". Referring to similar observations, he proposed that it could be a distinguishing characteristic of this "severe" senile dementia[5]. In 1907, Oskar Fischer autopsied 81 cases and provided more detailed descriptions of the neuritic plaques[6]. He referred to these plaques as "drusy necrosis" or "druse," which are masses of small crystals. Fischer concluded that these plaques are unique because they

were only seen in cases of severe senile dementia, presbyophrenia, one of the five allopsychoses identified by Carl Wernicke in 1906 after Kahlbaum. It is characterized by confabulations, allopsychic disorientation, hyperactivity, affective disorder, and a fluctuating course[7]. Fischer believed that “druses” were “the most important pathological substrate of presbyophrenia.”

In parallel, Alois Alzheimer reported the case of Auguste Deter at a German congress on November 1906[8]. This case was unusual because of its early-onset (51 years old), the first-ever description of diffuse NFTs (that he named neurofibrillary changes), together with “miliary foci” corresponding to neuritic plaques. Alzheimer entitled his intervention “About a peculiar disease (*eigenartige Erkrankung*) of the cerebral cortex” and concluded that “we are obviously looking at a peculiar disease process (*eigenartiger Krankheitsprozeß*)”. In 1908, Francesco Bonfiglio, reported a second case similar to Alzheimer’s[9]. He also observed neuritic plaques in two patients with a history of syphilis, which contradicted Fischer's perspective. In 1910, Gaetano Perusini detailed Alzheimer's 1906 case report and added three new observations of early-onset dementia with similar neuropathological characteristics[10]. Perusini emphasized the pathological significance of neurofibrillary changes over neuritic plaques, as plaques are also present in other conditions. He also highlighted the differences between early-onset cases and senile dementia: the number of neurofibrillary changes and plaques is higher in early-onset cases than in senile dementia, and the early-onset of symptoms indicates a non-senile process. In 1910, Emil Kraepelin, who was the head of Alzheimer’s department in Munich, updated his Textbook of Psychiatry[11]. He coined the term “Alzheimer’s disease” (*Alzheimersche Krankheit*), and pursued a distinction between senile and presenile dementia. When referring to senile dementia he considered presbyophrenia as a severe form of it. Kraepelin insisted on the differences between senile dementia and AD despite similar neuropathological features: “While the pathological findings would suggest that we are dealing with a particularly severe form of senile dementia, the fact that the disease sometimes begins as early as the end of the 40s speaks against this to some extent. […] The clinical picture with the extremely severe stupor, the profound speech disorder, the spastic phenomena, the seizures differs in any case from presbyophrenia, as it usually accompanies the purely senile cortical changes, in a very decisive way.”

In 1910, Fischer further detailed neuritic plaques in a series of cases (n=275!)[12]. He suggested renaming "drusy necrosis" as "*Sphaerotrichia cerebri multiplex*, […] a filamentous formation that usually occurs in a spherical form." Fischer considered his *sphaerotrichia* as a neuritic plaques-centered condition associated with several phenotypes, most of which were observed in old age but were independent of the patient's age. He believed that

sphaerotrichia was not just a peculiar pathological feature of the brain, but a disease in the clinico-pathological sense, if associated symptoms were also present. In his series, only 2 individuals who did not show presbyophrenia exhibited "druses", but at a lower level. Fischer opposed statistical and frequency arguments to Oppenheim, who observed in 1909 a cognitively unimpaired individual with “druses”[13]. Regarding Perusini's work, he argued that neurofibrillary changes were only observed in 17% of his work, and that Perusini may have missed the earliest stages of his “druses”. Fischer insisted that pathology is more significant than phenotype and age for clinico-pathological nosographic classifications.

In 1911, Alzheimer differentiated his cases from Fischer’s *sphaerotrichia* based on early age of onset and unusual instrumental clinical features[14]. He noticed that the loss of cortical tissue and degenerative changes in the brain were not directly linked to "druses". This led him to conclude that "druses", although a common feature in senile dementia, were not the cause (*Ursache*) of it, but rather a concomitant feature (*Begleiterscheinung*). He observed that neurofibrillary changes were common, but in his cases, severity exceeded the average in senile dementia, and their topography differed. Alzheimer also observed new cases of elderly individuals similar to his original early-onset descriptions. He concluded, that age should not be a defining factor for disease classification: “there appear to be multiple bridges between these presenile diseases and the typical cases of senile dementia” and that there were “no valid reason to consider these [late-onset] cases as being caused by a particular disease process. They are senile psychoses, atypical forms of senile dementia.” He proposed a clinico-pathological entity without age boundaries, characterized by severe dementia with instrumental symptoms and extended neurofibrillary lesions. Alzheimer's cases represented only 17-21% of Fischer's *sphaerotrichia*.

In 1912, Fischer conducted further observations that supported his previous findings[15]. He noticed that 6% of individuals without cognitive impairment had “druses”. Fischer suggested that these cases might represent “a kind of latent brain change […], which would only have led to clinical signs if it had developed to a greater extent.” Fischer focused more on statistical arguments than mechanistic arguments, such as the higher prevalence of “druses” in presbyophrenia compared to cognitively unimpaired individuals, and the global load of “druses” being more important than the putative local toxic effect of individual “druses” and the observation of exceptions. He then discussed the early-onset cases similar to Alzheimer’s and confirmed their peculiarity regarding language impairment as well as the local temporal pathological load. However, he emphasized that these characteristics were also observed in some cases of presbyophrenia. Finally, Fischer acknowledged the uniqueness of neurofibrillary changes and considered these early-onset cases a special subgroup called “atypical following Alzheimer.”

The first World War and the death of Alois Alzheimer in 1915 marked the end of the initial German-speaking debate on the nature of AD. After the war, Fischer shifted his research towards extra-sensory perception[16].

Nosographic considerations

During the early 20th century, there were different views on how to classify diseases among key figures in the field. Alzheimer and Fischer were heavily influenced by the clinico-pathological method, which was introduced by Giovanni Battista Morgagni in the 18th century[17]. This method involves defining a disease based on both clinical and pathological changes and establishing a causal relationship between them. Fischer's 1910 article was particularly noteworthy as it thoroughly detailed both the clinical and pathological dimensions to define the new disease he proposed. Kraepelin also subscribed to this approach, but his 1910 Textbook of Psychiatry is more ambiguous. He coined AD as a new clinico-pathological disease. However, he believed that cognitive impairment in old age is caused by multiple factors and it is a continuum of symptoms (presbyophrenia is a severe form of senile dementia) and pathological changes that includes, but is not limited to, neuritic plaques and NFTs.

Alzheimer and Fischer ultimately agreed on the peculiarity of a new clinico-pathological entity, regardless of the age of onset. This condition included a portion of Kraepelin's senile dementia. However, they disagreed on both the clinical and pathological features, especially on the relative significance of NFTs vs. neuritic plaques.

Finally, it must be highlighted that Fischer-Alzheimer's nosological considerations had less impact than Kraepelin’s Textbook of Psychiatry, which distinguished between AD and presbyophrenia. This textbook had a strong influence on early 20th-century research on senile dementia played a significant role in the classification of dementia in the following decades[18,19].

The late 20th century debate on the definition of AD: Are the pathological changes so peculiar that they should suffice to define a disease?

In the 1970s, a significant milestone in the modern history of AD occurred with the "rediscovery" of AD[20]. Neurologist Robert Katzman, working at Einstein College in Bronx, NY, US, was the main proponent of this nosological reconfiguration. In his famous 1976 editorial, Katzman proclaimed: "Alzheimer disease and senile dementia are a single process and should, therefore be considered a single disease."[21] This proposal was mainly based on two research programs conducted in the 1960s in North America and Europe. The first

program involved the "ultrastructural" study of neuropathological changes using electron microscopy, led by neuropathologist Robert Terry at Einstein College[22]. This program showed a perfect similarity between AD and senile dementia. The second program showed strong and significant clinico-pathological correlations between the amount of neuritic plaques and NFTs and the severity of dementia symptoms in senile dementia[23,24]. This program was mainly led by psychiatrists in Newcastle, UK, including Garry Blessed, Bernard Tomlinson, and Robert Kay, under the direction of Martin Roth.

During this time, there were differences between key players in England and America that were highlighted during three workshops: CIBA Foundation[25], National Institute of Aging (NIA) Workshop 1[26], NIA Workshop 2[27].

Anatomic pathology as the cardinal point of nosological reconfiguration: The Proposals of Terry and Katzman.

At Einstein College, Katzman and Terry both worked in Saul R. Korey's department, which focused on a group of chronic neurological diseases such as Creutzfeldt-Jakob, Tay-Sachs diseases, and AD using animal models and techniques derived from clinical neurology, electron microscopy, enzymology, and neurochemistry[28]. As sociologist Ad Prins recalls in his dissertation, "the microscopic observations in the neuropathological laboratory were authoritative enough to inform clinical diagnosis" at Einstein College.[28] The Americans were thus convinced of the pathognomonic and pathogenic nature of some specific neuropathologic changes to operationalize the diagnosis of AD using pathological features alone. This is illustrated by the 1977 debate: "Dr. Grufferman: In the absence of dementia, wouldn't you hesitate to diagnose the living patient as having Alzheimer's or senile dementia just on the histologic diagnosis?", Terry replied: "No. If you gave us an opportunity to do the histology tests, I certainly wouldn't hesitate for a moment."[26] However, Terry also agreed that the observed pathological abnormalities were anchored to an abnormal clinical outcome. "Dr. Sokoloff: Then you would call a lot of normal people demented. Dr. Terry: No, because we are not counting plaques or tangles in the hippocampus. If you give me a good biopsy, we can be quite accurate on the basis of histology."[26]

Terry believed that only methodological limitations were responsible for the clinico-pathological inconsistencies. As early as 1968, he suggested: "Many lesions beneath the resolution limit of the light microscope might well be significant. We took serial 1mm sections before and after electron microscope sections. At neither end were plaques visible to the light microscope, but in between there were many lesions in the electron microscope."[25]

Terry and Roth differed on the multidimensional definition of the disease. For Terry, the neuropathological identity dominated for disease classification. For example, regarding the observation of the "bimodal" distribution of AD cases observed, with a group around 40-50 years of age and a group around 60-70 years of age. When Roth engaged in a debate, Terry replied that even if a bimodal distribution is found, it would only prove that there is another factor, and it does not necessarily mean that they are two separate diseases[26].

Integrating epidemiology, clinic, and neuropathology in the face of nosologic uncertainty: Martin Roth's project

According to Martin Roth, diseases are defined based on statistical associations of various dimensions such as clinical evaluation, institutional trajectory of patients, neurophysiology, neuropathological examination, etc[19,25]. Clinical judgment still plays an important role in the operationalization and concept of disease.

Roth's approach to nosological reconfiguration differs from that of Americans. Instead of centering unitary lesions, Roth's team quantitative approach led him to propose a threshold concept as the gold standard for defining AD[29]. In the 1980s, he believed that a diagnosis of AD should not be confirmed by postmortem Alzheimer pathology assessed by qualitative and subjective criteria, but on a pathological threshold anchored to an abnormal clinical outcome[29]. Eventually, both Roth and Terry agreed that neuropathological examination alone could be used to operationalize the diagnosis of AD, but with qualitative (Terry) or quantitative (Roth) concepts of AD.

Roth emphasized the need to identify the factors that cause certain individuals to reach a certain threshold of pathology and develop symptoms. Unlike Terry and Katzman, he was cautious about merging early and late-onset cases: "I hope we are not falling into the pit of assuming that the question of distinction between Alzheimer’s disease and senile dementia is settled, because it is not. We need still to ask if there is a bimodal distribution in age. I believe there is a crop of cases with presenile dementia up to age 55 or 60. Then there is a long gap, and you don’t see cases again until age 70 or 75”[26]. Roth proposed to name the late and early-onset cases Type I and II, respectively, to highlight the differences between them[29].

Operationalization, caution and nosographic considerations

Martin Roth and his group did not collaborate with Robert Terry or Katzman in operationalizing the diagnostic criteria of AD. The initiatives for defining the 1984 clinical[30] and the 1985 neuropathological diagnosis criteria of AD[31] were led by some branches of the US National Institute of Health, and only Terry and Katzman participated.

Roth's concept of the disease was multidimensional, but he eventually agreed in the 1980s that in the case of AD it could be reduced to the clinico-pathological dimensions as illustrated in his threshold concept of AD that can then be used alone as a gold standard[29]. Regarding operationalization, he proposed criteria for AD based on positive phenotypical and exclusion biological criteria in book chapters[32], and was involved in the World Health Organization's International Classification of Diseases.

Although lesions were central to their vision of AD, Terry and Katzman were careful when proposing AD diagnostic criteria, demonstrating that their concept of AD was clinico-pathological, even if for operationalization pathological information alone could suffice. In 1983, they defined "Senile Dementia of Alzheimer Type" as a clinical approach to operationalize the diagnosis of AD[33]. They stated that AD is a clinic-pathological diagnosis which can only be approximated by the clinician. In 1985, they introduced the first neuropathological criteria for AD diagnosis and proposed high and increasing with age pathological thresholds of NFTs and neuritic plaques to diagnose AD, even in the absence of a helpful clinical history[31]. They also suggested revising the thresholds downwards in the presence of a positive clinical history of AD. The consensus regarding these various thresholds demonstrated the desire to base the neuropathological diagnosis of AD on an abnormal clinical presentation rather than just an abnormal biological process. Consequently, the concept of disease remains aligned with a clinico-pathological entity despite the use of pure pathological criteria. Ultimately, the 1985 criteria aligned with Roth's threshold concept[29].

In 1997, the NIA updated the 1985 neuropathological thresholds to require a history of dementia to confirm AD[34]. Eventually, the 2012 NIA-AA guidelines agreed to disentangle between the clinical phenotype of patients with substantial AD neuropathological change (Alzheimer's disease) and the presence and extent of neuropathological changes of AD observed at autopsy, regardless of the clinical setting (AD neuropathological changes)[35]. Consequently, there is no longer a neuropathological threshold anchored on cognitive impairment to diagnose AD. Instead, a new pure pathological entity describing abnormal histopathological changes. This illustrates the inadequacy of Terry's and Roth's beliefs that a neuropathological abnormality (feature and/or threshold) alone could be used to operationalize the diagnosis of a clinico-pathological disease.

The early 21st century debate on the definition of AD: Should the biological changes define a disease?

Early attempts in defining AD in the absence of symptoms

In the 1990s-2000s, new evidence came to light in the study of autosomal dominant AD. This led to the development of the β-amyloid cascade hypothesis, which proposed a deterministic biological model of AD centered around β-amyloid in 1992[36]. This hypothesis received numerous supporting pieces of evidence[37], but also many limitations[38]. During this time, it also became possible to identify cognitively unimpaired individuals with AD neuropathologic changes using imaging and biochemical biomarkers. The International Working Group (IWG) led by Bruno Dubois, a French Neurologist, was the first to conceptualize separate nosographical entities for these biomarker-positive cognitively unimpaired individuals in 2010, restricted to a context of research[39].

The IWG distinguished between "Asymptomatic at-risk state for AD" and "Presymptomatic AD." The former can be identified through evidence of β-amyloidosis or tauopathy in the brain using positron emission tomography (PET) or cerebrospinal fluid (CSF), while the latter applies to carriers of rare autosomal dominant monogenic AD mutations[39]. This distinction illustrates the clinical anchor of this biological diagnosis: “In the absence of knowledge about the value of [β-amyloid] biological changes to predict the further development of the disease, the asymptomatic phase of AD should still be referred to as an “at-risk state for AD””, whereas “presymptomatic AD […] applies to individuals who will develop AD.” Therefore, despite the possibility of an operationalization of diagnosis using biological tools alone, the IWG concept of AD remains aligned with a clinico-pathological entity.

In 2011, the revision of the 1984 National Institute of Aging (NIA)-AA clinical criteria of AD also provided research criteria for preclinical AD[40]. This revision came not only to clarify the use of biomarkers alone for the diagnosis of AD, but also with a biological redefinition of the concept of AD: “encompassing the underlying pathophysiological disease process, as opposed to having “AD” [that] connote[s] only the clinical stages of the disease.” This redefinition did not use clinical prognosis as an anchor for AD definition: “We postulate that AD begins with a long asymptomatic period during which the pathophysiological process is progressing, and that individuals with biomarker evidence of early AD-[pathophysiological changes] are at increased risk for developing cognitive and behavioral impairment and progression to AD dementia. […] we acknowledge that some of [cognitively normal individuals with AD-pathophysiological changes] will never manifest clinical symptoms in their lifetime.”

In 2015, a joint meeting took place between the IWG and the AA in Washington, DC, US[41]. During the meeting, it was clarified, aligned with the 2010 IWG proposal, that biomarkers abnormality could be considered a disease in asymptomatic individuals, as long as it eventually progresses to clinical symptoms. The meeting also discussed the

operationalization and use of biomarkers that fulfill these conditions, such as the combination of β-amyloid and tau biomarkers. This combination extended the IWG definition of presymptomatic AD beyond autosomal-dominant AD and towards the 2011 NIA-AA definition of preclinical AD: “Based on the high-risk or low-risk dichotomy for a further progression to clinical AD, we propose to consider the terms of “preclinical AD” when the risk is particularly high (e.g., both Aβ and Tau markers beyond pathologic thresholds) and that of [at-risk for AD] when the evolution to a clinical AD is less likely or still needs to be determined (only one pathophysiological marker considered abnormal).” From this 2015 joint meeting, the IWG and the AA took two opposite directions.

The NIA and AA proposal: AD as an abnormal biological process, unanchored to the clinical picture

In 2018, the NIA-AA update of the research criteria returned to the 2011 biology-anchored AD definition[42]: “AD should be defined as a biologic construct”, aligned with the “AD neuropathologic change” label proposed by the 2012 NIA-AA neuropathological criteria[35]. Eventually, operationalization of the proposed AD definition aligned with the joint IWG-NIA meeting (combination of β-amyloid and tau biomarkers defines AD) but for pathological and not clinical reasons: “both Aβ and paired helical filament tau deposits are required to fulfill neuropathologic criteria for AD, which suggests that evidence of abnormalities in both Aβ and pathologic tau biomarkers should be present to apply the label “Alzheimer’s disease””. Finally, they propose to differentiate the groups “Alzheimer’s pathologic change” and “Alzheimer’s disease” in individual with biomarker evidence of β-amyloidosis alone or biomarker evidence of both β-amyloid and tau pathology, respectively.

In 2023, the AA presented provisional versions of the revision of the 2018 research framework, with a will to “to inform both research and clinical care.”[2] The AA confirmed the epistemological shift toward a biology-anchored AD definition and extended it further: “Our position is that the onset of β-amyloidosis defines the initially detectable stage of AD.” Regarding operationalization, the diagnostic biomarkers were anchored on β-amyloid PET, as a validated biomarker of β-amyloid pathology.

The IWG proposal: AD as a clinico-biological entity anchored to the clinical picture

In 2021, the IWG reviewed the evidence regarding the relationship between β-amyloid and tau biomarkers and the future clinical prognosis in asymptomatic individuals. However, it concluded that the evidence was insufficient to put into practice the biological diagnosis of presymptomatic AD that was proposed in 2015[3]. As a result, the IWG reconsidered its earlier position and determined that the combination of β-amyloid and tau biomarkers was not enough to define preclinical AD, as “the best current estimates of lifetime dementia risk

range from 5% to 42%." Therefore, the IWG recommended that "asymptomatic individuals who are biomarker positive should be classified as at-risk for progression."

Nosographic considerations

This early 21st century nosological debate highlights a debate on the concept of AD, while new biomarkers allow for an operationalization of AD diagnosis using biological tools alone. The IWG keeps the historical clinico-pathological definition of AD, but allows for an operationalization using only biological tools as long as they are validated against a clinical anchor, i.e., the prognosis of developing clinical symptoms. It thus aligns with the 1980s Terry's & Roth's attempts to propose a pure pathological definition of AD, using pathological thresholds anchored to a clinical outcome. The NIA & AA initiatives, on the other hand, propose that specific biological abnormalities are the new anchor to define AD, independently of the current or future clinical prognosis. This redefinition can be considered as an epistemological historical break, as it no longer requires the presence of clinical symptoms to diagnose AD, but only to determine the stage of the disease. This breaks away from the previous clinico-pathological definitions of AD that have been used since the early 20th century. The 2023 AA β-amyloid-centered AD definition, without reference to tau or a pathological threshold, also breaks with historical views, that emphasized the importance of tau pathology or the combination of β-amyloid and tau pathology at high levels as characteristic neuropathological features of AD. It first anchors AD definition to a biological model: the β-amyloid cascade hypothesis.

Beyond the theoretical consequences, this break has also practical consequences as it strongly impacts the individual's outcome, epidemiology and public health. Indeed, preclinical AD, defined according to the NIA & AA initiatives, represents around three times the number of symptomatic cases[43], amongst whom, less than 50% will develop symptoms in their lifetime[44].

Discussion

AD has been a topic of important debates for nosographic definitions for over a century. At the beginning of the 20th century, AD was defined as a clinico-pathological entity, and debates arose around the pathological anchor and their associated clinical phenotypes. Alzheimer believed that extended NFTs with a severe and instrumental phenotype were the hallmarks, whereas Fischer supported the neuritic plaques with a broader phenotype (presbyophrenia). Eventually, Kraepelin's multidimensional vision of senile dementia, which included, but was not limited to NFTs and senile plaques, prevailed. In the 1960-80s, an

updated clinico-pathological definition of AD was extended to include cases of late-onset, and the debate shifted towards whether AD could be diagnosed using qualitative or quantitative neuropathological features, and whether it was a unique process (Terry & Katzman) or had subtypes (Roth). Operationalization of the similar clinico-pathological AD concept led to both clinical and pathological criteria. For pathological criteria, the initial operationalization of AD clinico-pathological concept using neuropathological thresholds alone proved to be unsuccessful and unsatisfactory. Presently, debates are centered around an epistemological shift from the unified clinico-pathological concept of AD (IWG), towards a separation between the clinical and pathological dimensions of AD (NIA & AA). According to the NIA & AA, AD should be defined solely based on the pathological dimension, including its biological correlates. The most recent AA developments anchor AD definition on the β-amyloid cascade hypothesis. The clinical dimension is only used for staging purposes, which can have significant implications for public health and clinical practice.

To facilitate understanding of the nosographic similarities and differences between authors across time, we propose in this review a nosographic reading framework along two dimensions: 1) the concept of disease, 2) the operationalization of diagnosis. This is summarized in Table 1. In particular, this reading framework helps to better understand how a similar clinico-pathological disease concept in the 1980s could lead to a set of operationalization criteria using either pure clinical, clinico-pathological or pure pathological criteria[30,31,33]. It also explains the current fault lines between between the IWG and the AA about the definition of disease, even though they have agreed to diagnose AD in asymptomatic individuals based on biological markers of β-amyloid and tau pathologies, following a joint meeting between the IWG and NIA in 2015. This historical perspective and this reading framework highlight that the AD concept proposed by the AA, based purely on biological changes, represents a historical epistemological break. The reason being that despite important nosographic debates, the clinico-pathological nature of AD was accepted without question before 2011 and the NIA-AA proposal.

The historical debates between Alzheimer and Fischer, regarding the significance of extended tau pathology and the unitary neuritic plaque, are still relevant in discussions of AD neuropathological features today. In the 1960s-1980s, it was discovered that high levels of NFTs and neuritic plaques, along with neuronal loss, are correlated characteristics of early and late-onset AD using more sensitive staining, quantitative, and correlative approaches[23,31,33,45]. A consensus emerged that high levels of these neuropathological features were paralleling characteristic neuropathologic lesions of AD[31]. However, there is still ongoing debate about the relative importance of β-amyloid and tau pathologies, as well as low and intermediate levels of pathology for disease classification. On the one hand, the

β-amyloid cascade hypothesis, proposed since 1992, centers on a deterministic biological model of AD, which received numerous supporting evidence[37]. This model impacted the NIA-AA 2012 neuropathological criteria, where the presence of neuritic plaques without NFTs represents the first levels of AD neuropathological changes[35]. Some authors still prefer to refer to a different nosological category (Pathological Aging) for these cases[46]. It is important to note that some dimensions of parenchymal β-amyloid pathology (diffuse plaques) are not considered defining AD neuropathological characteristic[35]. On the other hand, the lack of specificity of NFTs limits its usefulness as the sole defining feature of AD, and numerous limitations of the β-amyloid cascade hypothesis have emerged[38]. This led to alternative probabilistic models, including but not limited to β-amyloid, especially for sporadic AD[47]. Current neuropathological and PET findings also highlight that tau pathology, more than β-amyloid pathology, is a better correlate of neurodegeneration and symptoms[48,49], and a better stratifier of clinical prognosis in cognitively unimpaired individuals[50]. Neuropathologists have been debating the nosological classification of isolated NFTs: some argue that it is part of AD[51], while others suggest it may be a distinct condition called Primary Age-Related Tauopathy[52]. The 2023 β-amyloid-centered definition of AD aligns with the β-amyloid cascade hypothesis and departs from previous views from Alzheimer, Roth, and Terry, who emphasized the importance of tau pathology or the combination of β-amyloid and tau pathology at high levels as characteristic neuropathological features of AD. A distant parallel can be drawn with Fischer's *sphaerotrichia*, which focused on neuritic plaques[16]. However, Fischer emphasized the clinical features of *sphaerotrichia* and the low frequency of neuritic plaques in asymptomatic individuals (6%) to classify it as a disease.

The long-lasting nosological debates demonstrate the uncertainty surrounding the pathogenesis of AD, especially for the late-onset sporadic cases which represent the vast majority of cases based on the current definitions[47,51–53]. This uncertainty allowed for the use of various theoretical frameworks in defining AD, as recently outlined by Maartje Schermer[54]. She demonstrated that the NIA & AA definitions of AD were aligned with Boorse's Statistical Theory[55], which proposes that the starting point for defining a disease is the biological anomaly (relative to a biological norm), regardless of its clinical consequences, and is commonly used in anatomic pathology (e.g., atheroma). Conversely, the IWG clinico-pathological definition is in line with Nordenfelt's Holistic Theory of health[56] which proposes that the starting point for defining a disease is the biological cause of an individual's abnormal functioning (relative to a norm), and is frequently used in psychiatry (e.g., the Diagnostic and Statistical Manual of Mental Disorders). It is important to understand the various implications of disease theoretical frameworks since there is no one-size-fits-all definition. Nordenfelt's theory implies that disease impacts an individual's functioning, while

Boorse's definition does not necessarily have such implications. As AD has been considered a clinico-pathological entity following Nordenfelt's theory since 1906, any changes in disease definition theories that are not clearly and properly disclosed may lead to misunderstandings among stakeholders.

Recent advancements suggest that AD should be redefined based not only on the presence of β-amyloid and tau pathologies along with clinical symptoms but also on the genetic background of the individual[47,53]. This resonates with Roth's proposition to differentiate type I and type II AD[29]. The peculiarities of these clinical forms, particularly the tau load and the prevalence of atypical forms, also coincide with certain fault lines in the Alzheimer/Fischer debate. It raises the question of whether the new AD subcategories proposed by Korczyn[53] & Frisoni[47] should be renamed after Alzheimer (limited to the early-onset subtype with extended Tau pathology and atypical symptoms) and Fischer (the rest).

The historical perspective we propose highlights the difficulties of operationalizing a clinico-pathological concept of AD based on pathological thresholds alone. Throughout history, low levels of AD neuropathologic changes have not been considered responsible for clinical symptoms, while only the highest levels were deemed responsible. However, some individuals pass through a natural biological progression from no to high levels of pathological changes, which current frameworks fail to capture. A biologically-anchored definition, as proposed by NIA & AA, avoids these threshold difficulties and debates around the level of evidence required to demonstrate the anchor on a clinical outcome.

Conclusion

Since the first descriptions what is now known as AD, there have been major debates about the normal or pathological nature of this entity. This historical review demonstrates that the AA β-amyloid-centered definition of AD represents a double break: both from the historical clinico-pathological concept of disease, and from the historical emphasis on tau or combined tau and β-amyloid high levels of pathology as characteristics features of AD. These historical debates also shed light on other highly topical clinical and scientific issues in the Alzheimer field, such as the role of tau or β-amyloid lesions and lesion thresholds.

In conclusion, as there is still lack of certainty about the cause(s) of sporadic AD and the respective roles of the neuropathologic lesions, it appears appropriate to refer to Jean Nicolas Corvisart. In 1818, while commending the clinico-pathological approach introduced by Giovanni Batista Morgagni, Corvisart emphasized that clinical medicine should be the essential, guiding element, rather than autopsy.[57]

Table 1. Evolution of AD concept, definition and diagnostic among the key players involved in nosography in the three key periods of AD history (1900s-1910s, 1960s-1980s, and 2010s-2020s).

		Emil Kraepelin		Alois Alzheimer	Oskar Fischer	Robert Terry & Robert Katzman	Martin Roth	International Working Group	National Institute of Again & Alzheimer Association
Disease concept		Clinico-pathological & Multifactorial		Clinico-pathological	Clinico-pathological	Clinico-pathological	Multidimensional (clinico-pathological for AD)	Clinico-biological	Biological
Disease definition (criteria)	Disease name	Alzheimer's disease	Senile dementia	Alzheimer's disease	*Sphaerotrichia* multiplex *cerebris*	Alzheimer's disease	Alzheimer's disease	Alzheimer's disease	Alzheimer's disease
	Clinical features	Early-onset severe dementia with instrumental symptoms	Continuum from normal aging	Severe dementia with instrumental symptoms	Presbyophrenia (amnestic dementia)	Dementia	Dementia	Specific phenotypes of mild cognitive impairment and/or dementia	
	Characteristic pathological and/or biological features	Extended neurofibrillary tangles	Multifactorial (including but not limited to neurofibrillary tangles and neuritic plaques)	Extended neurofibrillary tangles	Neuritic plaques	Extended neuritic plaques + neurofibrillary tangles	Extended neuritic plaques + neurofibrillary tangles (+ other factors?)	β-amyloid ± tau abnormal biomarkers	β-amyloid (+ tau until 2023) abnormal biomarkers

Diagnosis operationalization (tools)	Clinico-pathological (clinical history + autopsy)	Clinico-pathological (clinical history + autopsy)	Clinico-pathological (clinical history + autopsy)	Clinico-pathological (clinical history + autopsy)	Clinico-pathological (clinical history + autopsy)	Clinical & clinico-pathological (clinical history + autopsy) & qualitative and quantitative pathological (autopsy)	Clinical & clinico-pathological (clinical history + autopsy) & quantitative pathological (autopsy)	Biological & Clinico-biological	Biological & Clinico-biological

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