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Review

Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging?

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Abstract

For 70 years after Alois Alzheimer described a disorder of tangle-and-plaque dementia, Alzheimer's disease was a condition of the relatively young. Definitions of Alzheimer's disease (AD) have, however, changed over the past 30 years and under the revised view AD has truly become an age-related disease. Most now diagnosed with AD are elderly and would not have been diagnosed with AD as originally conceived. Accordingly, younger patients that qualify for a diagnosis of AD under both original and current Alzheimer's disease constructs now represent an exceptionally small percentage of the diagnosed population. The question of whether pathogenesis of the "early" and "late" onset cases is similar enough to qualify as a single disease was previously raised although not conclusively settled. Interestingly, debate on this issue has not kept pace with advancing knowledge about the molecular, biochemical and clinical underpinnings of tangle-and-plaque dementias. Since the question of whether both forms of AD share a common pathogenesis could profoundly impact diagnostic and treatment development efforts, it seems worthwhile to revisit this debate.

Keywords: Aging; Alzheimer's disease; Amyloid; Dementia; Transgenic mice

At the opening of the twentieth century, Alois Alzheimer reported non-elderly demented individuals whose brains contained characteristic histopathologic features called plaques and tangles [3]. Shortly thereafter, Oscar Fischer recognized brains of elderly demented individuals also contained plaques [53]. In subsequent years, the medical community assimilated these observations so that the former situation was considered a disease and assigned a diagnostic eponym, Alzheimer's disease (AD) [105]. The latter situation was considered a normal part of aging, and for many decades hence syndromically referred to as senile dementia [4,18].

In the decades that followed, AD was a rather uncommon entity. Senile dementia, on the other hand, became increasingly prevalent as life expectancy increased. Whether or not a normal part of aging, the fact that senile dementia so adversely affected people's lives could no longer be ignored. In the second half of the twentieth century, expectations of what medical art and science could deliver were also growing. A case could be made that treating senile dementia was warranted. Up to this point, those dementing before the age of 65 had a disease, AD, and those after the age of 65 did not. The time to dispose of this arbitrary divide had come.

In a powerful and influential 1976 editorial, Katzman argued "Alzheimer disease and senile dementia are a single process and should therefore be considered a single disease" [93]. This justified making dementia syndrome research a national health priority and invigorated research into the phenomenon. Expanding the definition of AD to include those with senile dementia swelled the ranks of those diagnosed to such an extent it caused some to claim an "Alzheimerization" of dementia [1,178]. Today, AD is far and away the most commonly diagnosed dementia. When dementia overlap syndromes, such as mixed vascular-degenerative dementia are considered, the processes underlying AD (which can also drive changes of the cerebrovasculature) could be held to account for an even greater percentage of the overall dementia burden than it already is.

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Thirty years later, it is time to pay homage to the prescience of the Katzman editorial, as well as key observations leading up to it [16]. It is also time to reflect on the tremendous strides clinical and molecular neuroscience have made towards understanding both the original AD (as described by Alzheimer) and senile dementia. It seems reasonable to consider Katzman's 1976 editorial within the context of the clinical and scientific advances it helped spur. Finally, this review will attempt to discuss AD from a perspective of aging, operationally defined here as the aggregate of clinical and molecular changes that develop over the course of one's life, but which are not felt to represent an actual disease process.

1. Beta amyloid and the "Amyloidization" of Alzheimer's disease

If the field of dementia research has indeed experienced "Alzheimerization" in recent decades, then AD research can be further said to have undergone "amyloidization". Many investigators feel the key to understanding AD lies in deciphering the nature of the extracellular plaques seen in those with the disease. These plaques consist largely of an amyloid protein derivative called beta amyloid.

Amyloid proteins are beta-sheet proteins that can aggregate. When viewed by polarized light microscopy, following Congo red staining aggregations manifest a typical green birefringence pattern. Extracellular cortical plaques observed in persons with AD, elderly non-demented persons without clinical AD, dementia with Lewy bodies, non-demented persons following head trauma, temporal lobe epilepsy, the MELAS syndrome (mitochondrial encephalopathy, lactic acidosis and stroke), cerebrovascular disease and Down's syndrome largely consist of an amyloid protein called beta amyloid (Aβ) [5,83,92,107,126,136,153]. Beta amyloid, in turn, is a proteolytic degradation product of a larger protein called amyloid precursor protein (APP). Homozygous APP knock-out mice show early clinical and histologic sequellae (in the form of gliosis), which suggests APP is necessary for proper neuronal function and perhaps cerebral development [227]. Studies also demonstrate APP can influence a variety of cell processes [9,218]. Nevertheless, normal APP physiology remains poorly understood.

Considerably more is known about APP processing (see Fig. 1) [192]. Proteolysis by an enzyme or enzymes called alpha secretase(s) can occur 83 amino acids from APP's intracellular carboxyl terminal. Alternatively, proteolysis by enzymes called the beta secretases (BACE) cut 99 amino acids upstream of the APP carboxyl end. An enzyme complex, the gamma secretase, further processes the remaining carboxyl end of alpha secretase (C-terminal fragment α; CTFα) or beta secretase (C-terminal fragment β; CTFβ) digested APP. This complex consists of the following proteins: presenilin 1 or presenilin 2, nicastrin, APH-1 and PEN2 [47]. Gamma secretase proteolysis does not uniformly occur at a single amino acid, although proteolysis either 57, 59 or 61 amino acids up from the APP carboxyl terminus is most common. A second gamma secretase cut also occurs 50 amino acids from the APP carboxyl end, which generates a 50 amino acid (from the APP carboxyl end) degradation product called the amyloid intracellular domain (AICD) [156].

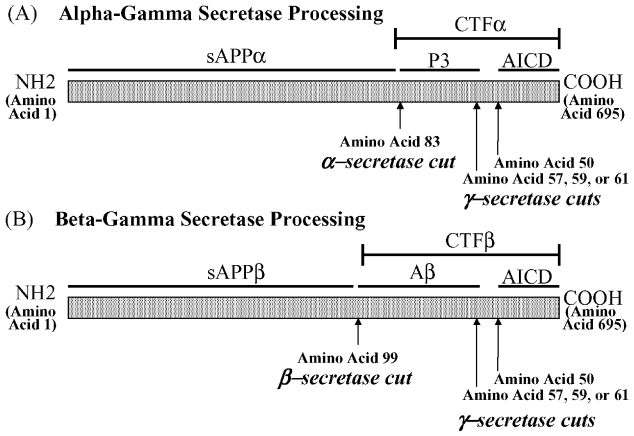

Fig. 1. APP processing by the alpha, beta and gamma secretases. Note the amino acid positions of the APP protein itself are numbered starting from the amino end, while the sites where secretases cut APP indicate the number of amino acids upstream from the APP carboxyl end. Only the key neuronal 695 amino acid isoform of APP is shown. CTF, C terminal fragment; sAPP, soluble APP; AICD, amyloid intracellular domain.

Initial data suggested AICD protein translocates to cell nuclei and regulates gene transcription via a process functionally reminiscent of Notch-mediated transcription regulation [27,42,100,189,215]. As first reported, the phenomenon involved binding of the AICD to specific cytoplasmic "adaptor proteins" (Fe65, Jip1b) followed by subsequent binding of the resulting complex to a histone acetytransferase (Tip60) inside the nucleus [27,100,215]. It was further proposed that via this mechanism AICD protein facilitated creation of a feedback loop through which APP protein status could modulate transcriptional activation of the *APP* gene itself [215]. It is important to note, though, the story of how APP protein status regulates gene expression is still unfolding. Recent data indicate AICD control of Tip60 may not involve nuclear translocation or even membrane release of the AICD fragment [28], or that APP itself may activate Tip60 through a gamma-secretase independent pathway [75].

Following sequential alpha and gamma secretase proteolysis, in addition to the AICD two other main APP degradation products are produced. The peptide flanked by the alpha and gamma secretase cuts is a 3 kDa fragment called p3. The much longer amino terminal portion persisting upstream of the alpha secretase cut is titled soluble APPα (sAPPα). sAPPα appears to act as a trophic factor [144]. Beta-gamma secretase processing precludes sAPPα production, creating instead a long amino-end fragment called sAPPβ. The 40–42 (although it can be 38–43) amino acid segment directly created by beta and gamma secretase proteolysis is the beta amyloid peptide.

Beta amyloid plaques vary morphologically [46]. Plaques containing neither reactive glia nor degrading neurite projections are called diffuse plaques. The presence of degenerating neuronal processes and reactive glia within and around the plaque is often associated with the presence of a homogeneous appearing, darkly staining core and plaques containing such are called dense core plaques. Dense core plaques are also called senile or neuritic plaques. The fact that diffuse plaques can exist suggests amyloid plaque deposition is not necessarily associated with immediate neuronal demise. While diffuse plaques occur in a variety of degenerative and non-degenerative conditions, neuritic plaques are particularly likely to exist in persons with AD. Therefore, criteria for the histopathologic diagnosis of AD assume the presence of numerous cortical neuritic plaques indicates AD, while the absence of numerous neuritic plaques eliminates AD as a diagnostic consideration [19,34,97,138,139].

To complicate matters, neuritic plaques also occur in the non-demented elderly [5,65,103]. Indeed, among the very old plaque histopathology cannot accurately distinguish those with dementia from those without dementia [36,40,72,94,150,165,188,200,224]. Observations such as this have fueled a long-standing controversy as to which is more important in diagnosing AD, clinical symptoms/signs or brain histopathology. If brain histopathology trumps clinical presentation, then those with neuritic plaques but not dementia technically have AD. Similarly, demented AD-diagnosed individuals without sufficient neuritic plaques cannot technically have AD. If clinical presentation trumps histopathology, then what clinicians are truly diagnosing is an Alzheimer's syndrome. In the Alzheimer's syndrome, typical AD brain histopathology may or may not be present.

From a practical standpoint, among the demented elderly plaque pathology is so common that approximately 90% of those with the Alzheimer's syndrome also meet AD histopathologic criteria [58,106]. When dealing with elderly patients, though, considerable diagnostic angst exists for four reasons. First, there are patients with the Alzheimer's syndrome, no other obvious clinical explanation for their dementia, and plaque pathology insufficient to render a diagnosis of AD. For example, one large clinicopathologic series from federally designated AD centers found of 1833 individuals clinically diagnosed with AD, 190 did not receive a concomitant pathologic diagnosis of AD and therefore their AD clinical syndrome did not correlate with their histologic assignment. This study suggests the number of persons with discordant clinical (AD) and histologic (not AD) diagnoses is small but not inconsequential [131]. Further, for some of these individuals histologic assessment will fail to identify an alternative diagnosis [58]. Second, there are patients with cognitive complaints not severe enough to meet criteria for the Alzheimer's syndrome that will have sufficient plaque pathology to render an AD diagnosis. Some of these patients will die without ever dementing. Third, there are those with dementia judged secondary to non-AD causes who will meet AD histologic criteria [152]. Fourth, some demented individuals diagnosed with AD will have not only AD histologic changes, but also histologic changes that suggest an alternative explanation for their dementia syndrome [38]. How to resolve issues such as these depends on whether elderly individuals cognitively decline because they have AD, or whether elderly individuals have AD because they cognitively decline.

The lion's share of currently conducted AD molecular and biochemical research relates to beta amyloid. Providing conceptual guidance to these efforts is the amyloid cascade hypothesis. The amyloid cascade hypothesis postulates an overproduction of beta amyloid causes AD and all its associated clinical, histopathological, molecular and biochemical manifestations [39,70,71,190,191]. Data supporting the amyloid cascade hypothesis stem from studies of early onset, autosomal dominant AD. All the autosomal dominant deterministic mutations (in the APP, presenilin 1 and presenilin 2 genes) favor processing of APP by the beta-gamma secretase cleavage system, and in such a way that beta amyloid 1–42 is preferentially generated [186].

The amyloid cascade hypothesis presumes AD is a primary disease of amyloidosis, and that amyloidosis in AD is not a secondary consequence of other more basic cell level pathophysiology. Initially, the amyloid cascade hypothesis proposed amyloidosis in the form of amyloid plaques was causal. As the hypothesis has evolved, ascendancy of the plaque as the principal upstream pathology in AD has been challenged by the possibility that soluble beta amyloid oligomers are the key toxic moiety [113,114,216]. Several hypotheses addressing mechanisms of oligomer toxicity are currently undergoing critical assessment. In this regard, two particular postulates are worth noting. In one scenario, amyloid oligomers access intracellular organelles such as mitochondria and compromise their function [125]. The other scenario is supported by data showing soluble amyloid oligomers specifically bind certain synaptic membrane proteins [63]. Such oligomer-specific binding appears limited to hippocampal and cortical synapses, where it may interfere with long-term potentiation and modify intracellular signal transduction events [108]. Because of this ligand-like effect, some refer to soluble beta amyloid oligomers as "Aβ-derived diffusible ligands" (ADDLs) [101]. Therefore, beta amyloid oligomer toxicity could potentially explain the noted poor relationship in AD subjects between plaque counts and dementia severity [209], as well as the observation that synaptic dysfunction may precede neuronal loss in AD subjects [95,212].

Brain amyloid deposition is also associated with local inflammatory and immunologic alterations. Such observations lead some to propose inflammation is relevant to AD neurodegeneration [132]. In this regard, inflammatory or immunologic paradigms are often viewed as a corollary of the amyloid cascade hypothesis. The inflammatory/immunologic hypotheses argue that although beta amyloid may have direct neurotoxicity, at least some of its toxicity might actually be an indirect consequence of a beta amyloid protofibril-induced microglia activation and astrocyte recruitment. This inflammatory response may repre-

sent an attempt to clear amyloid deposition. However, it is also associated with release of cytokines, nitric oxide and other radical species, and complement factors that can both injure neurons and promote ongoing inflammation [182]. Indeed, levels of multiple cytokines and chemokines are elevated in AD brains, and certain pro-inflammatory gene polymorphisms are reported to associate with AD [143,182]. The relevance of such phenomena to AD is further supported by epidemiologic data suggesting exposure to non-steroidal anti-inflammatory drugs (NSAIDS) may reduce AD risk [133,172]. However, multiple prospective short duration trials of NSAIDS in AD prevention and of NSAIDS, steroids and hydroxychloroquine in actual AD have been therapeutically unimpressive [2,21]. A prospective long-duration prevention trial designed to assess the ability of two anti-inflammatory agents, celecoxib and naproxen, was initiated but is currently on hold due to toxicity concerns [128].

The amyloid cascade hypothesis mostly developed from and is supported by studies of early onset, autosomal dominant AD. Its status in this "familial AD" (FAD) etiologic hierarchy seems reasonable. A wealth of biochemical data defining both beta amyloid overproduction and underclearance phenomena can also be used in support of the amyloid cascade hypothesis [63,112,203,228], and help justify its extrapolation to late onset, non-familial AD. Given the high age-related prevalence of late onset AD [50], if this extrapolation proves correct then investigators studying aging will need to consider protein amyloidosis as a primary cause of aging. This extrapolation, though, may ultimately hinder diagnostic and treatment advances if in fact aging is not a consequence of amyloidosis, and if late onset AD proves to be a primary neurodegenerative disease of aging rather than a primary amyloidosis. In essence, before concluding late onset AD is a primary amyloidosis, it would be worth resolving whether amyloidosis causes aging or aging causes amyloidosis.

2. Tau and tangle pathology in the most common "Tauopathy"

Intracellular neurofibrillary tangles consist of tau protein. Tau normally exists in phosphorylated and unphosphorylated states [73,124]. The phosphorylated state is characteristically seen in undifferentiated dividing cells, and is called fetal tau. Differentiated cells contain unphosphorylated tau. In differentiated cells, tau associates with the microtubule cytoskeleton. Phosphorylated tau appears not to associate with cytoskeletal microtubules. Tau phosphorylation status is regulated by a series of serine-threonine kinases, as well as phosphatase enzymes [13].

In tangle-containing neurons, tau exists in a hyperphosphorylated state. Tangle tau is reminiscent of fetal tau, although several additional serine and threonine residues are uniquely phosphorylated in AD tangle tau [61]. It is not definitively known whether abnormal tau phosphorylation is mediated mostly by increased kinase activity, decreased phosphatase activity or a combination of both possibilities [62]. The tau kinases are not specific to tau, and these enzymes also play integral roles in cell metabolism and replication events.

Neurofibrillary tangles are characteristic of AD, and tangle counts correlate more closely with the degree of clinical dementia than plaque counts [10,11,59,148]. In addition to considering plaques, AD histopathology criteria provide tangle count diagnostic guidelines [19,34,138]. In AD, tau-tangle events are not widely considered to drive the disease process. While tau gene mutations can induce neurodegeneration, such mutations are associated with familial frontotemporal dementia (FTD) rather than familial AD [149]. Also, tangle formation does not necessarily represent a terminal cell event. In AD brain histopathologic studies, it is common to find tangle-bearing neurons that contain both intact nuclei and ongoing transcriptional activity [23,76]. Indeed, it is estimated by some that tangle-bearing neurons may survive for decades [33,142].

Further, while tangle counts reflect dementia status better than plaque counts, tangles do not provide the best available histologic reflection of cognitive decline [33,209]. As far as histologic markers go, synaptic density correlates best with clinical status [32,33,43,44,185,209]. While an early mechanistic-oriented study suggested tau aggregation might itself represent the cause of synaptic pathology in AD [145], data inconsistent with this possibility subsequently emerged. Although these later data did show tangle-containing neurons demonstrate striking reductions in synaptophysin message expression (a marker of synaptic health and integrity) compared to non-tangle containing neurons, in AD neurons synaptophysin reductions exist independent of tangle presence or even tau serine 396/404 phosphorylation [24,25]. This argues that although a relationship between tangle and synapse pathology perhaps exists, neither tangle formation nor tau phosphorylation can entirely account for declining synaptic density in AD.

In addition to AD and some FTD, abnormal tau phosphorylation with tangle formation is seen in progressive supranuclear palsy (PSP), corticobasal degeneration and the parkinsonism-dementia complex of Guam [213]. The association of tangles with a variety of disease states supports the "tauopathy" concept of neurodegenerative disease [111], although tauopathy as a primary cause of neurodegenerative disease is currently only demonstrable in a handful of familial FTD cases. In all other situations the genetic basis for tangle formation is unknown.

Aside from AD and FTD, the most studied tauopathy is PSP. In PSP, most of those affected (90%) possess a particular tau genotype, the H1/H1 genotype. H1/H1 status clearly does not cause PSP, since PSP is a rare disease and most (over 60%) of the general population also carry the H1/H1 genotype [120]. The H1/H1 genotype, therefore, is either permissive for PSP or else facilitates tangle deposition in ways

that render persons with clinical PSP more likely to receive a post mortem PSP diagnosis.

Tangles are also found in non-demented adults [81]. Tangle deposition begins in the third decade and increases with age [20]. Therefore, if the elderly dement because they have AD, then AD is a disease that essentially spans all of adulthood. Further, because AD (both clinically and histopathologically) has the potential to affect most people, then AD is a disease that afflicts most people for most of their lives. Alternatively, if the elderly develop AD because they dement, then tangles can be seen as a general marker of brain aging. Under this scenario, those with more tangles at a given age would be judged to have less successful brain aging than their age-matched counterparts with fewer tangles.

3. Epidemiology and genetics of early and late onset AD

Epidemiologic data identify two distinct AD populations, those with clearly recognizable autosomal dominant inheritance and those without. Patients with autosomal dominant AD typically present at far younger ages than those without obvious autosomal dominant inheritance. The late onset group tends to manifest either sporadic or pseudosporadic epidemiology. In this regard, the term pseudosporadic is technically more accurate, because it acknowledges that while classic Mendelian inheritance is not unequivocally demonstrable, those with late onset AD are more likely to have AD-affected relatives than those without AD [77].

The transition between the early and late onset subtypes is usually identified as 55, 60 or 65 years of age. Attempts to mark a chronologic border, though, are complicated by the fact that persons with sporadic AD can present before the age of 55, and those with autosomal dominant AD can dement after the age of 65. Despite this overlap, though, the epidemiology of early and late onset AD may provide pathogenic insights. Persons with autosomal dominant AD usually present in their fourth or fifth decade, less commonly in their third or sixth decade, and even more rarely beyond those limits [26,88,176]. The age distribution of these cases is generally consistent with that of a bell curve. This pattern is reminiscent of other known Mendelian diseases, in which affected individuals present within the confines of a particular minimum and maximum age range. Pseudosporadic cases, on the other hand, can rarely present in the fifth or sixth decade, but beyond the sixth decade the proportion of those with pseudosporadic AD begins to rise in an exponential fashion (Fig. 2) [55,77,173]. This implies that although autosomal dominant AD does tend to manifest within a particular age range, it is not a disease of aging in the same sense that the pseudosporadic form is. The possibility that early and late onset AD, despite various shared pathologic features, are fundamentally different diseases therefore requires consideration.

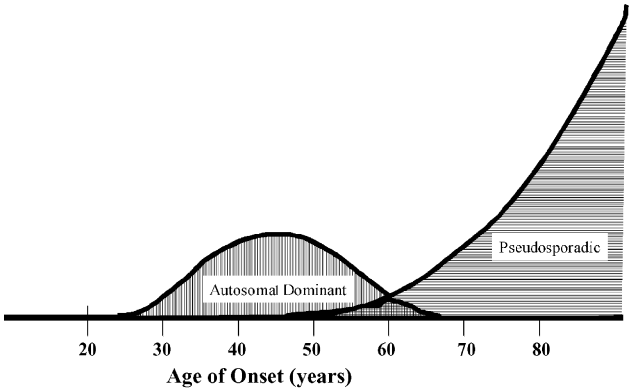

Fig. 2. Distributions of persons with autosomal dominant and pseudosporadic AD. Autosomal dominant AD is not a true disease of aging, while pseudosporadic AD is. Proportions of those with autosomal dominant AD and pseudosporadic AD are not shown to scale.

Three "deterministic" autosomal dominant genes are known. Mutations in these genes cause AD. These genes include the APP gene on chromosome 21, the presenilin 1 gene on chromosome 14 and the presenilin 2 gene on chromosome 1 [60,115,193]. Mutation of each gene increases production of the beta amyloid derivative of APP [186]. Recently, APP gene duplication was shown to cause autosomal dominant, very early onset AD (manifesting in the third decade) [177]. Since some degree of APP processing to beta amyloid normally occurs [56], overexpression of APP itself should increase beta amyloid production. Down's syndrome individuals also carry APP duplications, develop beta amyloid brain amyloidosis and manifest adult onset cognitive destabilization. Cognitive destabilization in Down's syndrome, though, typically occurs in the fifth decade [22]. This observation is relevant because attempts to extrapolate findings from Down's syndrome to AD are frequently made. It is only valid to do this if one assumes the genetic and clinical similarities between AD and Down's syndrome outweigh the genetic and clinical differences. The finding that the age-of-onset of cognitive decline differs substantially between those with isolated APP duplication and those with chromosome 21 trisomy suggests Down's syndrome is not a faithful model of early onset, autosomal dominant AD, let alone late onset, pseudosporadic AD.

When age of onset is used to define early versus late onset AD, most autosomal dominant cases fall within the early onset category. It is important to note that not all early onset cases, though, are autosomal dominant. A very small percentage of total AD meets early onset criteria, and only a limited number of early onset cases show autosomal dominant inheritance. Despite this, literature citations sometimes state early onset, autosomal dominant cases constitute 5–15% of all AD [74,175]. It is worth considering the accuracy of this estimate. A conservative assumption is that most early onset, autosomal dominant patients will present before the age of 60 and also have an affected parent that developed AD before the age

of 60. Clinical experience suggests far less than 1% of those diagnosed with AD meet these two criteria (R.H. Swerdlow, personal observation). Therefore, APP, presenilin 1 and presenilin 2 mutational screening is reasonably indicated for an exceptionally small percentage of AD subjects. Indeed, presenilin 1 (the most commonly mutated of the deterministic AD genes) is the only one of the three genes for which mutational screening is commercially available.

Late onset, pseudosporadic AD is not associated with deterministic gene mutations. It is, however, genetically influenced. By far the most established genetic risk factor is the apolipoprotein E (*APOE*) gene on chromosome 19 [37]. Three allelic variants of the *APOE* gene exist within populations, the *APOE2*, *APOE3* and *APOE4* variants. In most populations, possessing one *APOE4* allele increases the likelihood the carrier will develop AD, and carrying two copies increases this likelihood even more. The molecular basis for this association is not definitively known. Not everyone with an *APOE4* allele will develop AD, and approximately half of those with AD do not carry an *APOE4* allele [146]. Epidemiologic data suggest that although having an *APOE4* allele is not deterministic for AD, having an *APOE4* allele tends to move up the age of onset in those perhaps destined to develop AD anyway [15,121]. Since most people probably have the potential to develop AD, what possessing an *APOE4* allele does from an epidemiologic perspective is increase the chance individuals will develop AD before they die.

APOE genotyping of cognitively impaired individuals is commercially available. Carrying an *APOE4* allele does increase the likelihood a patient with cognitive complaints will also manifest sufficient cortical plaques to warrant a histopathologic diagnosis of AD [169,187]. *APOE* genotyping can increase or decrease the specificity of an AD diagnosis, as well as address the likelihood that those with AD-like prodromes will progress to frank AD over the next several years [131,160]. Otherwise, it cannot be used as a surrogate or substitute for the clinical diagnosis. If a patient is clinically diagnosed with AD and does not have an *APOE4* allele, the diagnosis is still AD.

It is worth noting the *APOE4* allele also associates with a poor recovery from severe traumatic brain injury [29,147]. This raises the possibility that *APOE*'s association with AD might result from effects on brain plasticity rather than direct effects on AD-specific pathophysiology. Consistent with this possibility, in addition to its effects on AD the *APOE* gene in general appears to influence aging. Relative to its frequency in the overall population, the *APOE4* allele is underrepresented in the oldest old [96,123,155,184]. It will be interesting to see whether future identified AD risk factor genes also influence aging. If so, gene variants that promote overall longevity more than they do successful brain aging could actually increase AD risk. Conversely, gene variants that reduce longevity more than they do AD risk, while not beneficial in general, could appear to decrease AD risk.

4. Clinical knowledge advances: Alzheimer's, mild cognitive impairment, and beyond

Establishing AD as a common condition justified creation of centralized AD research centers [98]. Over the past two decades, these centers have to a large degree defined current AD clinical perspectives. Most of the subjects studied at these centers are elderly, and therefore this approach has mostly advanced our knowledge of the late onset form of the disease. Thanks largely to these centers, we now have both cognitive exam and clinical history-based diagnostic approaches that are fairly standardized and reliable [52,140]. Perhaps the most important lesson learned from these efforts is that AD is so insidious that elderly persons with AD may in fact have AD for decades before they are diagnosed.

The term mild cognitive impairment (MCI) was developed to categorize patients with cognitive complaints not sufficient to warrant a syndromic diagnosis of dementia [161]. Yet, most persons meeting MCI criteria will over subsequent years deteriorate to a point that they meet dementia criteria, and for most of these the diagnosis will be AD [162]. A logical extension of this is that what clinicians are actually seeing in most with MCI is the initial manifestation of a progressive degenerative dementia that will eventually meet AD diagnostic criteria [141].

It now appears cognitive decline begins even before the MCI syndrome can be diagnosed. Neuropsychological testing seems able to identify individuals likely to develop cognitive decline either before those individuals voice complaints of cognitive decline or meet MCI criteria [8,48,85,119,129,163,179,180,183,197,211]. It also appears possible to estimate which individuals will receive an AD diagnosis at the earlier end of the late-onset AD age spectrum decades before that diagnosis will be made [198,199]. Because it is necessary to consider such studies might simply be revealing early baseline differences in cognitive reserve, specific efforts were made in relevant studies to address this possibility by controlling for academic achievement and intellect, two recognized surrogates of cognitive reserve [198,199]. The authors of these studies concluded cognitive reserve phenomena, therefore, could not account for their findings. These data as well as the neuropsychological testing literature, therefore, suggest AD cognitive decline is a trajectory that runs throughout adulthood (Fig. 3).

This realization reflects the diagnostic dilemma clinicians evaluating patients with cognitive complaints actually face. With elderly patients, the pertinent issue confronting the clinician is not whether the patient has truly experienced cognitive decline, but rather whether sufficient cognitive decline has occurred to warrant a diagnosis of AD. Creating the MCI diagnostic entity has provided clinicians the ability to acknowledge someone is developing cognitive changes before those changes meet AD criteria. However, MCI has its own criteria [223], and it is not uncommon for patients with memory complaints to appear too intact on neuropsychological testing or historical inventory to qualify for either an AD or

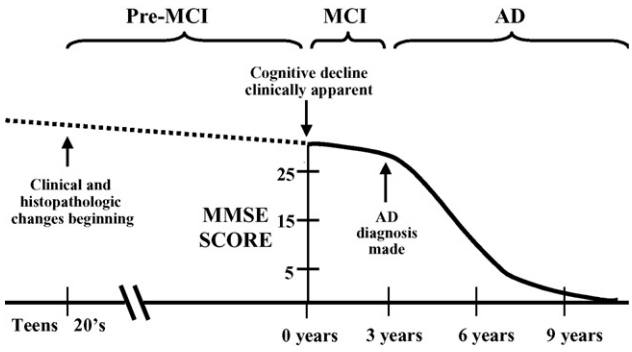

Fig. 3. Cognitive decline in Alzheimer's disease follows a trajectory that appears to include most of adulthood. AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, mini mental state exam.

an MCI diagnosis. Perhaps a diagnostic entity of "pre-MCI" is also needed to provide clinicians a way to syndromically classify these individuals, since there is currently no way to clinically designate them beyond the ICD-9 general symptom code for "memory loss not otherwise specified" [84].

Of course, individuals with early-onset, autosomal dominant AD also cognitively deteriorate over time. Partly because of the limited number of these patients, the a priori presumption that subjective cognitive decline in these patients is due to AD, and the ability of deterministic gene mutational analysis to alleviate uncertainty about the diagnosis, there are fewer data evaluating whether such individuals pass through pre-MCI and MCI states during the course of their decline [54,151]. In any case, most neurologists evaluating a cognitively declining young adult with a family history of autosomal dominant AD and a known APP, PS1 or PS2 mutation would diagnose that patient with AD, even if the degree of cognitive decline technically warranted only a syndromic diagnosis of MCI. Similarly, for the patient profile now presented the key clinical dilemma distinctly differs from that of the potential late onset AD patient. Unlike the late onset patient, where the crucial clinical question relates to whether a particular degree of cognitive decline has occurred, for the early onset patient the key question is simply whether or not there is cognitive decline.

When approaching AD from an aging perspective, it is important to know just how much risk increases with age. This has been a longstanding contentious issue. The frailties of very advanced age confound both neuropsychological testing parameters and activity of daily living independence [210]. This renders the clinical diagnosis somewhat arbitrary. The inability to sort controls from subjects at advanced ages because we simply do not know what is cognitively expected of the very elderly further complicates such analyses. Thus, while it is clear persons can reach their ninth and tenth decade and probably beyond without dementia, it is not possible to render a consensus "percentage" of those that do. This perhaps explains why some epidemiologic surveys find conversion rates seem to reach a maximum, perhaps in the 10th decade of life [137], while others find given enough time possibly everyone has the potential to develop clinical AD [57,68,91,166,168]. If histopathology defines the AD diagnostic gold standard, it is pertinent to note a recent autopsy study of centenarian brains reported 95% met at least minimal CERAD and Khachaturian histopathologic criteria for AD [90]. In another study, with histopathological assessments of 159 brains from persons (either demented or non-demented at the time of death) aged 85 years or older, all 159 brains "showed at least mild AD pathology" [166], although it is important to note this designation did not reflect a strict histopathologic diagnosis of AD but rather referred to the fact that all brains assessed contained at least some tangle or plaque pathology. The qualitative nature of this observation should also not detract from the fact that quantitative total plaque counts (the sum of both diffuse and neuritic plaques) were in one study able to segregate rigorously certified non-demented subjects (who did not have memory complaints) from those with a clear-cut dementia syndrome [134].

It is worth considering whether any histologic marker permits rigorous segregation of AD from non-AD elderly subjects. Although quantitative plaque and tangle pathology (at least as defined by current AD histologic diagnostic criteria) fails on this account, one study of 7 AD and 14 age-matched controls found CA1 neuron counts were consistently lower in those with AD [220]. There was no inter-group overlap; CA1 neuron counts were in each case reduced in the AD group. Additionally, for non-AD subjects of various ages, observed variations in CA1 neuron counts did not correlate with age. The authors concluded CA1 neuron loss is therefore not an age-related phenomenon, and AD must involve events that do not occur as part of normal or even "accelerated" aging [220]. A related study evaluated whether entorhinal neuron counts from "preclinical AD" brains (defined as meeting AD histopathologic criteria despite an absence of clinical dementia) resembled those of non-demented individuals without AD histopathology or demented individuals with AD histopathology [167]. As was the case with the non-demented, no-AD histopathology brains, the preclinical AD brains did not show significant neuronal loss. A third relevant clinicopathologic study of elderly persons with and without AD dementia found tangle counts inversely correlated with neuron counts in the CA1, entorhinal cortex and Brodman's area 9 regions [59]. In this study, the extent of these histopathologic changes (tangle counts and neuronal loss) also correlated reasonably well with MMSE scores.

These neuronal count studies suggest onset of clinical AD and degree of dementia correspond better with neuroanatomic-specific neuronal loss than plaque and even tangle histopathology. However, neuron counting does not address issues of neuron function. None of these studies address potential mechanisms underlying CA1, entorhinal or frontal cortex neuronal loss, and so cannot exclude the possibility such mechanisms are themselves age-related. Age-related biochemical or molecular change could account for these findings if CA1 or other regional neuronal death requires a degree of change to exceed a particular thresh-

old. It seems premature, based on these data, to conclude late onset AD requires an "independent pathological process" that is not associated with aging [220]. This line of reasoning is supported by a fourth neuronal count study, which concluded CA1 neuronal death in AD is a relatively late stage histopathologic feature [221], indicating it represents a downstream consequence of more primary events. Moreover, other studies of elderly AD and control subjects report CA1 neuron counts do not distinguish those with dementia from those without, and that there is in fact an inverse correlation between CA1 neuron counts and increasing age [195,214].

Regardless, even if there exists a small cadre of those who simply will not develop neurodegenerative-related cognitive decline no matter how long they live, we can probably say with confidence that beyond the age of 100 such individuals represent a minority. Since what is held to be normal largely depends on the majority status of a population, at advanced ages it seems more reasonable to assume the oldest old come to meet AD criteria because they dement, as opposed to assuming they dement because they have AD. To some degree the NINCDS-ADRDA criteria have circumvented this issue by identifying a 90 year old cut-off for diagnosing AD [135]. Nevertheless, it seems logical to conclude the 89 year old and the 91 year old presenting to their physician with cognitive decline significant enough to cause social and/or occupational dysfunction have more in common pathogenically than do the 89 year old pseudosporadic case and the 35 year old with an autosomal dominant history of cognitive decline.

5. Implications for diagnostics development

AD is still primarily a clinical diagnosis [135]. For the clinician, convincing oneself a patient truly has AD can consume considerable time. It is often necessary to obtain the history from, in addition to the patient, one or more informants and informants may not present consistent stories. In addition to general medical and neurologic examinations, a cognitive examination is indicated. Further complicating matters is the fact that for the elderly, the main challenge of the physician is not to determine whether the patient has experienced cognitive decline, but rather whether a particular threshold of cognitive decline has been reached. Early in the course of a degenerative dementing disorder this threshold can seem somewhat subjective. Further, the implications of an AD diagnosis to a patient and their family are substantial. For these reasons, most clinicians can probably identify a case in which they diagnosed a patient with AD even though they were uncomfortable doing so. Development of paraclinical tests to corroborate (or refute) clinical suspicions could potentially address this issue.

Considerable effort has gone into AD biomarker development [99]. The most consistently reported advances come from studies evaluating cerebrospinal fluid (CSF) concentrations of beta amyloid 1–42 in conjunction with either total tau or hyperphoshorylated tau levels [41]. On average, beta amyloid 1–42 levels are reduced in AD subject CSF, perhaps due to diminished transport through brain parenchyma. Mean CSF total and phosphorylated tau levels, on the other hand, are increased and this is felt to reflect neuronal damage. Measuring CSF tau and beta amyloid levels (many investigations focus on tau:beta amyloid ratios) can help distinguish subjects with AD from control subjects [82,127,205]. It is important to note, though, relevant studies compared persons with AD to "healthy controls", not controls with functionally borderline memory complaints and no signs of an alternative cause of cognitive change (the common situation for which a useful biomarker test is most needed). Even under these ideal circumstances group segregation was incomplete, and predictive values were not superior to clinical impression. In addition to these studies of AD, a study of CSF tau and beta amyloid levels in MCI found a combination of elevated tau and reduced beta amyloid helped identify which MCI-diagnosed individuals were most likely to progress to a diagnosis of AD over the next 4–6 years [69].

Despite these impressive findings, while clinically available biomarker tests can certainly increase the clinical suspicion or raise the level of certainty of the clinical diagnosis, no particular test can actually serve as a surrogate of or substitute for the clinical diagnosis. This applies to CSF, serum or urine biochemical analyses (of tau, beta amyloid and neurofilament thread protein levels); risk factor genotyping (of *APOE* alleles); magnetic resonance biochemical survey (magnetic resonance spectroscopy); structural neuroimaging approaches (hippocampal volume determination, diffusion tensor imaging); and functional neuroimaging (positron emission tomography) [35,164].

The ability to use positron emission tomography to image plaque or plaque/tangle burdens has recently created much excitement in the field [102,194]. The results of these efforts, though, demonstrate this approach may not constitute a diagnostic panacea. The reason for this is that in published analyses, histopathology overlap was seen between demented and non-demented elderly individuals [51,102,194]. In retrospect this outcome is not surprising, as histologic surveys clearly demonstrate among the elderly plaque counts do not reliably distinguish those who were demented at the end of life from those who were not [36,40,72,90,94,150,165,188,200,224]. Plaque imaging in persons diagnosed with MCI also shows substantial heterogeneity, with subjects falling into either AD, control or "intermediate" groups based on in vivo plaque burden [45,122]. Moving beyond MCI, Pittsburgh Compound B (PIB) was also used to evaluate five "high IQ" elderly individuals with "memory impairment" (IQ-MI) not severe enough to qualify for either dementia or MCI syndromic diagnoses. It was found 40% of the IQ-MI group had PIB binding levels that overlapped with those of five concomitantly studied AD subjects [171].

In the course of AD biomarker development studies, initial data often suggest considerable diagnostic potential. Following this early success, it is commonly shown that in typical

clinical settings, the biomarker in question is not particularly useful or is only useful under rare circumstances. This perhaps reflects the fact that what is needed in the clinical arena are not biomarkers that can distinguish those with no dementia from those with obvious dementia, but rather biomarkers that can distinguish elderly individuals whose cognitive decline does not interfere excessively with social or occupational functioning from those whose cognitive decline does.

Developing such diagnostics will prove logistically difficult if not impossible [67]. After all, for elderly individuals entering AD studies whether or not someone qualifies as a control or patient requires some degree of subjective judgement. This substantially complicates biomarker trial design and interpretation. Moreover, given the commonality of AD among the elderly, investigators cannot know whether today's control is tomorrow's AD subject. Because in old age developing AD is not an all-or-none situation, biomarker tests approaching AD as an all-or-none condition probably will not work.

6. Implications for treatment development

AD treatment preclinical development relies heavily on the use of AD transgenic mice. These mice are engineered to express mutated human APP genes, mutated human presenilin 1 genes or combinations of both. Mice utilized by different investigators also vary in the type of promoter used to express the transgene, the nature of the transgene mutation, and for mutant APP mice the isoform (length) of the APP protein product [17,64,89]. Mice that express a mutated human tau transgene in addition to mutated human APP and PS1 transgenes also exist [154].

These animal models have permitted investigators to begin addressing fundamental issues of beta amyloid amyloidosis and neurofibrillary tangle physiology. They have shed considerable light on how particular mutations in the APP, PS1 and tau genes affect processing and handling of these proteins. Plaque and/or tangle deposition in the mice increases with time, and quantification of plaque and/or tangle histopathology is technically possible. As compared to wild-type mice, the transgenic mice prematurely develop behavioral deficits. Onset and progression of behavioral deficits is quantifiable using standardized assessment strategies widely held to sensitively reflect cognitive status [7,104].

These transgenic mouse models show no-to-little acceleration of neurodegeneration [79], so admittedly they are poor models of a neurodegenerative disease. The degree to which this impacts on the reliability of these mice for therapeutic development depends, therefore, on whether AD is a primary disease of amyloidosis that secondarily manifests neurodegeneration, or whether it is a primary neurodegenerative disease that secondarily manifests amyloidosis. For individuals with early-onset AD due to APP and PS mutations, the former situation clearly applies.

The situation in late-onset AD is more complex. An argument can certainly be made that late-onset AD more likely constitutes a primary neurodegenerative disease. After all, both demented and non-demented elderly individuals can manifest similar degrees of amyloidosis [36,40,72,90,94,150,165,188,200,224]. Cellular changes associated with aging, such as oxidative stress and mitochondrial dysfunction, cause secondary amyloidosis [207]. Autosomal dominant forms usually present with a relatively young age of onset, and unlike the late onset forms cannot truly be considered diseases of aging. For reasons such as these, it may turn out that early onset, autosomal dominant AD is a primary amyloidosis and late onset, pseudosporadic AD is a primary neurodegenerative disorder.

The treatment-related implication of this debate is interventions that effectively treat early onset, autosomal dominant patients may only marginally benefit late onset cases. Indeed, if it turns out persons develop late onset AD because they age (a true disease of aging), optimal treatment approaches may need to focus more on "fixing" aging than on reversing or retarding amyloidosis. If correct, then ameliorating age-related cell level molecular changes would in any case secondarily reduce amyloidosis.

Human clinical trials of treatments already known to benefit AD transgenic mice may practically resolve this issue. Various interventions successfully ameliorate AD transgenic mouse behavioral decline and/or plaque accumulation. A table summarizing just some of these interventions is provided in Table 1. Only those interventions that also have at least some human track record are provided, since such examples are best suited to help put the question posed above in perspective or to shed light on this question in the foreseeable future [6,12,14,30,31,49,66,78,80,86,87,109,110,116,117,118,130,138,157–159, 170, 174, 181, 196, 201, 202,204,206,208,217,219,222,225,226]. For the sake of brevity, treatments reported to reduce transgenic mouse brain amyloidosis are not included in the table if there is no human track record and also no reports to show the treatment clinically benefits the mice.

If interventions such as those in Table 1 do not substantially benefit late onset human AD subjects, it would suggest the transgenic mice have a fundamentally different disorder. To summarize the clinical outcomes column of Table 1, available human trial data suggest any potential benefit (if indeed there is any benefit at all) will be on the level of slowed progression, rather than arrested progression.

If interventions that benefit the transgenic mice are shown to benefit early onset, autosomal dominant AD subjects but not those with the common late onset form, it will additionally imply early and late onset forms of AD are fundamentally different disorders. Data addressing this point are currently lacking, as the vast majority of human clinical trial experience comes from studies of late-onset, non-autosomal dominant AD; no phase II or III trials specifically designed to treat autosomal dominant AD are reported in the literature. In any case, it seems worthwhile to consider the possibility that treatments

Table 1
Will treatment protocols that benefit AD transgenic mice benefit humans with AD?

Treatment	Reduces amyloid in mice	Behavioral, cognitive or other clinical benefits in mice	Used or tested in humans	Human experience
Vitamin E	Yes and no	Not reported	Yes	Does not prevent cognitive decline, but cannot rule out minimal slowing of decline
Gingko Biloba	No	Yes	Yes	Does not prevent cognitive decline, but cannot rule out minimal slowing of decline
Melatonin	Yes	Yes	Yes	Does not benefit sleep difficulties in AD
Curcumin	Yes	Yes	Yes	Under study in AD
Docosahexaenoic acid	Yes	Not reported	Yes	Widely available; under study in AD
Almonds	Yes	Yes	Yes	Widely available
Ibuprofen	Yes	Yes	Yes	No specific AD trials, but widespread human use
Flurbiprofen analogs	Yes	Not reported	Yes	Under study in AD
Atorvastatin	Yes	Not reported	Yes	Widespread human use; under study in AD
Lithium	Yes	Not reported	Yes	No specific AD trials, but substantial human experience
Valproic Acid	Yes	Not reported	Yes	Substantial human experience; under study in AD
Pioglitazone	Yes	Not reported	Yes	Used in diabetes; under study in AD
Aβ vaccination	Yes	Yes	Yes	Phase IIa trial inconclusive, although primary clinical endpoints were negative
Aβ antibodies	Yes	Yes	Indirectly	Inconclusive case series of AD subjects receiving immunoglobulin reported
Butyrylcholinesterase inhibition	Yes	Not reported	Yes	Widely used in AD subjects since 2001; possible symptomatic benefit but impact on cognitive decline rates unclear
Enoxaparin	Yes	Not reported	Yes	Used in humans, but not specifically tested in AD
"Cerebrolysin" peptides from porcine brain	Yes	Yes	Yes	Reported to improve cognition in AD subjects
Caloric restriction	Yes	Not reported	Yes	No AD trials yet
Environmental enrichment	Yes and no	Yes	Yes	Unclear

that work in one type of AD may not work as well in the other.

7. Conclusions

Whether or not late-life dementia represents a disease state or is part of aging, it is imperative to recognize it destroys lives. Efforts to intervene medically are justified at both humanistic and economic levels. Katzman's 1976 editorial pointed out it was irrational to assume those dementing before the age of 65 had a medical problem, while those dementing after 65 did not. The case was persuasively made based on data available at the time. As Katzman wrote, when considering persons with plaques, tangles and dementia, "neither the clinician, the neuropathologist, nor the electron microscopist can distinguish between the two disorders, except by the age of the patient" [93].

Advances spurred by this statement, though, suggest it may no longer be advantageous to consider tangle and plaque dementias as one entity. At the gene level, molecular neuroscience now distinguishes a number of different Alzheimer's diseases. At the clinical level, emerging data suggest cognitive decline that accompanies aging probably never represents a benign process. Whereas at the time of Katzman's editorial it was believed that with cognition, age-associated "minor changes do not result in the functional disability or increased mortality that can be directly attributed to Alzheimer disease" [93], it increasingly appears late onset AD constitutes a continuum that manifests years and probably decades before AD diagnostic criteria are met.

Whether appropriate or not, lumping the original AD and senile dementia cases has resulted not only in the "Alzheimerization" of dementia research, but also in its "amyloidization". Underlying most current AD research efforts is the assumption that beta amyloid amyloidosis is the etiologic cause. This assumption is extrapolated from a very limited number of early onset, autosomal dominant AD cases. While this form of AD can rightly be considered a primary amyloidosis, studies attempting to address whether late onset AD is also a primary amyloidosis are inconclusive. Despite this, by default early and late onset AD are generally considered one entity.

Interestingly, while Katzman's editorial helped make AD a malady intimately associated with aging, research into AD has largely ceased to consider the molecular, biochemical and physiologic roles aging might play in this disorder [207]. Since the vast majority of those with an AD diagnosis are elderly, and the risk of developing AD rises with advancing age, it seems reasonable to consider the following question: do the elderly dement because they have AD or do they have AD because they dement? Resolving this conundrum could influence the ongoing search for better diagnostic tools and more effective treatments.

Finally, it is worth considering whether the amyloid cascade hypothesis in its current forms provides adequate

insight into the etiology of late onset, sporadic AD. No matter how strong the arguments made against the amyloid cascade hypothesis, though, in the absence of rival hypotheses it will likely by default remain the dominant AD paradigm. In terms of generating rival hypotheses, because AD and aging are so entwined, considering AD from an aging theory perspective seems appropriate. One such attempt was recently published [207].

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