The amyloid cascade hypothesis: are we poised for success or failure?

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Abstract

The first description of Alzheimer’s disease (AD) was made in 1907 by Alois Alzheimer (Allgemeine Zeitschrift fur Psychiatrie und Psychisch-Gerichtliche Medizin 64, 3, 1907), although other contemporary physicians had made similar, and rather more complete, assessments of the neuropathological changes present in the AD brain (Fischer, Monatschr Psychiat Neurol 22, 17, 1907). Our knowledge of AD has increased dramatically and continues to accelerate. This year is 25 years after the publication of a series of papers that, in various ways, articulated the amyloid cascade hypothesis (ACH) for AD (Beyreuther and Masters, Brain Pathol 1, 241–251, 1991; Hardy and Allsop, Trends Pharmacol Sci 12, 383–388, 1991; Selkoe, Neuron 6, 487–498, 1991; Hardy and Higgins, Science 256, 184–185, 1992). This review will cover some familiar territory, but we shall also place the ACH into a wider context, compare it with other hypotheses for AD, explore the evolution of the hypothesis to encompass new findings, and determine, irrespective of the merits of the hypothesis itself, whether it has been useful for the research field, both in academia and in industry. Finally, we shall review how the ACH has led to a number of therapeutic approaches, all of which have, to date, failed to reach their primary efficacy end-points in clinical trials and reflect upon what the future may hold.

Keywords: Alzheimer’s disease, Amyloid cascade clinical development.


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Abbreviations used: AβOH, Aβ oligomer hypothesis; ACH, amyloid cascade hypothesis; AD, Alzheimer’s disease; ADAS-cog, Alzheimer’s Disease Assessment Scale – Cognitive; ADCS-ADL, Alzheimer’s Disease Cooperative Study-Activities of Daily Living; APOE, Apolipoprotein E; APP, amyloid precursor protein; BACE, β-amyloid cleaving enzyme; CCRH, cell cycle re-entry hypothesis; CDR-SB, Clinical Dementia Rating – Sum of Boxes; DPH, dual pathway hypothesis; FAD, familial AD; LRP, low-density lipoprotein receptor related protein; MCH, mitochondrial cascade hypothesis; MH, metabolism hypothesis; NFTs, neurofibrillary tangles; oAβ, Aβ oligomers; PET, positron emission tomography; PHFs, paired helical filaments; PS, presenilin; RAGE, receptor for advanced glycation endproducts; SAD, sporadic AD; SDS-PAGE, sodium dodecyl sulfate–poly acrylamide gel electrophoresis gels; VH, vascular hypothesis.

The hypothesis

The major support for the amyloid cascade hypothesis (ACH) comes from the combination, and interdigitation, of pathophysiology and human genetics. The origins of the ACH lie in the sequencing of the amino acid sequence of Aβ extracted from cerebral blood vessels (Glenner and Wong 1984b) and then brain parenchyma ( Masters et al. 1985) of postmortem brains from Alzheimer’s disease (AD) patients. This led to the identification and sequencing of amyloid precursor protein (APP) gene (Kang et al. 1987) that encodes the holoprotein from which the Aβ peptide is excised by the sequential action of β-amyloid cleaving enzyme to release the N-terminus of Aβ ( Hussain et al. 1999; Sinha et al. 1999; Vassar et al. 1999; Yan et al. 1999; Lin et al. 2000) and γ-secretase that cleaves at the C-terminus (De Strooper et al. 1998; Wolfe et al. 1999b). γ-secretase is a multiprotein complex comprised of presenilin (PS1) or PS2; aph1a or Higgins, Science 256, 184–185, 1992). This review will cover some familiar territory, but we shall also place the ACH into a wider context, compare it with other hypotheses for AD, explore the evolution of the hypothesis to encompass new findings, and determine, irrespective of the merits of the hypothesis itself, whether it has been useful for the research field, both in academia and in industry. Finally, we shall review how the ACH has led to a number of therapeutic approaches, all of which have, to date, failed to reach their primary efficacy end-points in clinical trials and reflect upon what the future may hold.

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aph1b; Pen2 and nicastrin (for review, see De Strooper et al. 2012) with the PS proteins incorporating the enzyme’s active site aspartyl residues (Wolfe et al. 1999a,b). Although other publications were articulating similar viewpoints (Beyreuther and Masters 1991; Hardy and Allsop 1991; Selkoe 1991), the ACH was expounded most trenchantly in 1992 (Hardy and Higgins 1992). In this admirably brief paper, the deposition of the Aβ peptide was portrayed as an upstream event in the evolution of AD, leading to cell death and/or the development of neurofibrillary tangles (hyperphosphorylated, insoluble tau aggregates) via elevation of intracellular calcium ion levels. A critical component of the ACH comes from human genetics, where a family history of early-onset AD led to a linkage analysis study that revealed a mutation resulting in a V717I amino acid change in the APP gene just C-terminal to the Aβ peptide sequence (Goate et al. 1991). This seminal work revealed that a single mutation resulted in early-onset AD that was pathologically identical to sporadic, late-onset AD. The potential for a genetic cause for AD had been made previously: in 1984, Glenner and Wong made the prescient observation that because the Aβ peptide deposited in the cerebrovasculature of elderly Down’s syndrome (Trisomy 21) subjects was identical (bar an experimental error at one position) to the 21 amino acids that were sequenced from sporadic AD (SAD) patients, a genetic defect on chromosome 21 was likely to be a cause of AD (Glenner and Wong 1984a).

Aβ/amyloid pathology is seen in all AD patients, by definition, although its relationship with cognitive decline is unresolved (Arriagada et al. 1992; Delacourte et al. 1999; Naslund et al. 2000). There are now hundreds of mutations to three genes, PSEN1, PSEN-2, and APP that can cause early-onset familial AD (FAD) (http://www.alzforum.org/mutations). These mutations all have the effect of increasing the amount of C-terminally extended Aβ peptides, or the ratio of aggregatory, longer forms of Aβ to shorter, more soluble forms, or to increase the aggregatory properties of the Aβ peptide directly (Citron et al. 1992; Suzuki et al. 1994; Borchelt et al. 1996; Duff et al. 1996; Scheuner et al. 1996; Bentahir et al. 2006; Hori et al. 2007; Inayathullah and Teplow 2011; Ni et al. 2011; Chavez-Gutierrez et al. 2012; Szaruga et al. 2015). The longer forms of Aβ are extended at the C-terminus with hydrophobic amino acids that greatly increase the propensity for aggregation (Jarrett et al. 1993). At this time, several groups made the critically important discovery that Aβ was a regular secretion product from cells that expressed the APP gene rather than being produced solely under unusual or physiologically stressful conditions (Haass et al. 1992; Seubert et al. 1992; Shoji et al. 1992); this breakthrough enabled the development of cell-based assays to screen for compounds to inhibit Aβ production. Ultimately, cell-based assays were used in the discovery of γ-secretase inhibitors: competitive (Esler et al. 2000; Li et al. 2000; Shearman et al. 2000); non-competitive (Dovey et al. 2001; Lanz et al. 2006) and modulator compounds (Weggen et al. 2001). The FAD mutations all localize to proteins involved in the production and properties of the Aβ peptide. With respect to SAD, the greatest genetic risk factor is Apolipoprotein (APOE) 4 (Corder et al. 1993). The human population has three major alleles of APOE – APOE2, APOE3, and APOE4 (Nickerson et al. 2000). One allele of APOE4 increases the risk of AD four-fold compared to an APOE3/APOE3 genotype; two copies of APOE4 increases the risk approximately 12-fold, and the APOE2 allele reduces risk compared to APOE3 (Verghese et al. 2011). While the biology of ApoE is undoubtedly complex (Holtzman et al. 2012; Liu et al. 2013), there is very strong evidence that show that ApoE is required for the deposition of amyloid from preclinical (Bales et al. 1999; Holtzman et al. 1999, 2000) and clinical (Schmechel et al. 1993; Jack et al. 2015) studies. Moreover, the increased probability of having brain amyloidosis matches the ApoE isoform dependent risk of succumbing to AD. Additional evidence for the primacy of the role of Aβ in AD comes from the A673T mutation (Jonsson et al. 2012) that significantly protects against AD. This mutation (Fig. 1) decreases both the production and aggregatory properties of Aβ (Benilova et al. 2014; Maloney et al. 2014).

In summary, the ACH accommodates a wide range of data that we have on AD into a coherent hypothesis. It is worth articulating three tenets that have to be true if ultimately we will refute the null hypothesis.

(i) The parenchymal deposition of the Aβ peptide is important pathophysiologically.
(ii) Aβ peptide deposition occurs prior to the frank neuronal and synaptic loss that is the hallmark of AD.
(iii) The evidence from mutations that cause FAD is informative and relevant to SAD.

*Fig. 1. Amyloid precursor protein familial Alzheimer’s disease mutations.* The diagram shows the β-site amyloid precursor protein cleaving enzyme 1 (BACE1) and γ-secretase cleavage points and the protective and pathogenic amino acid changes mediated by amyloid precursor protein (APP) mutations.
Taking each in turn, (i) is to a certain extent a matter of semantics. As a definite diagnosis of AD relies on neuropathologic evidence revealing Aβ plaques and neurofibrillary tangles, the presence of deposited Aβ peptide is a prerequisite. However, the role of deposited Aβ peptide as being the pre-eminent disease-causing Aβ species has been brought into question by the burgeoning literature on smaller molecular weight oligomeric Aβ (oAβ) (see later). Thus, it could be argued that the deposition of Aβ is irrelevant to the disease process as such, or at least of much lesser importance. (ii) is likely true although now open to a different interpretation. The ACH as originally conceived placed amyloid as upstream of tau pathology, and yet detailed neuropathological studies have shown that tau pathology is present from a very early age in some people and in all cases precedes amyloid pathology (Braak et al. 2011). However, correlative studies have shown that amyloid pathology likely drives tau pathology from restricted allocortical sites to proliferate throughout the cortex leading to widespread neuronal loss (Price and Morris 1999). (iii) is still a matter of significant debate, but it seems very likely that the familial and sporadic forms of the disease are identical in all major respects. For example, the neuropathology of SAD and FAD are indistinguishable from each other (Nochlin et al. 1993; Lippa et al. 1996). Thus, for the diseases to be fundamentally different, it would be necessary to explain why the pathological changes in a FAD brain lead to a different disease process than in a SAD brain. Furthermore, as stated previously, the greatest genetic risk factor for SAD is carrying an APOE4 allele which also brings forward the age of onset for the disease (Corder et al. 1993). In very large cohorts of FAD patients that all carry the same PSEN1 mutation, it has been demonstrated that the APOE4 allele also brings forward the age of onset (Pastor et al. 2003). If SAD and FAD were very different diseases, it would be unlikely that they would both be subject to the same genetic modifier.

Before exploring some of the deficiencies in the ACH, it is worth briefly considering alternative hypotheses that have been posited for the onset and progression of AD.

**Mitochondrial cascade hypothesis**

The mitochondrial cascade hypothesis (MCH) posits that age-related mitochondrial dysfunction ultimately leads to the pathology and symptomatology of AD (Swerdlow and Kahn 2004; Swerdlow et al. 2014). It also attempts to resolve the difficult question of whether SAD is a usual, but not necessarily universal, consequence of brain aging. Indeed, in very elderly cohorts, the prevalence of AD pathology may exceed 50% (Polvikoski et al. 2001). There is little doubt that there is evidence of mitochondrial damage in the brains of people suffering from AD (Lin and Beal 2006). Furthermore, fluorodeoxyglucose positron emission tomography (PET) imaging has revealed deficits in the AD brain quite early on in the disease process, which as a marker of oxygen uptake is likely affected because of alterations in mitochondrial function (Jack et al. 2012). Also, there is abundant evidence of increases in free radical damage in AD brains that again might result from dysregulated mitochondrial function (Sonnen et al. 2008). Some of the experimental support for the MCH comes from the use of cybrids. The process of making cybrids begins by treating a cell line with ethidium bromide to block mitochondrial DNA replication to from a ‘p0’ cell. These cells are then co-cultured with platelets from a human host (e.g. with AD) in the presence of polyethylene glycol that induces the transfer of platelet mitochondria into the p0 cells to form a cybrid (King and Attardi 1989) – a cell containing mitochondria from a different cell. Experiments with AD cybrid cells have shown an increase in Aβ production (Khan et al. 2000) and reactive oxygen species (Cardoso et al. 2004). The MCH uses such data to suggest that a mitochondrial deficiency in AD brains underpins an increase in Aβ production. In the MCH, Aβ is a biomarker for brain aging, but not a cause of AD as such.

In our opinion, the MCH fails to answer some key questions. Despite very large genome wide association studies (GWAS), no genes that encode mitochondrial proteins or proteins involved in bioenergetics have been found (Lambert et al. 2013). Some of the evidence in support of the MCH comes from cell biological systems that are significantly manipulated and might not reflect the human pathophysiological situation. For example, demonstrating that cybrid cell cultures show an increase in Aβ production does not reflect the situation in SAD, or, in most cases, in FAD, where the majority of mutations alter the ratio of Aβ metabolites or their propensity to aggregate, but do not increase the absolute amount – indeed, many reduce overall Aβ production (Chavez-Gutierrez et al. 2012; Szaruga et al. 2015). The MCH fails to account for the A673T mutation in APP (Jonsson et al. 2012) that has been demonstrated to protect against SAD by reducing Aβ production modestly and reducing its propensity to aggregate (Jonsson et al. 2012; Benilova et al. 2014; Maloney et al. 2014). One of the tenets of the MCH, that AD is largely a disease of aging, can also be questioned on several levels. For example, none of the genes that causes FAD is known to play a role in aging, and none of the mutations that causes progerias results in accelerated AD pathology (Nelson et al. 2011). Critically, the MCH does not articulate how mitochondrial dysfunction leads to the full panoply of AD pathology, a deficiency it shares in common with the ACH.

**Dual pathway hypothesis**

The dual pathway hypothesis (DPH) (Small and Duff 2008) seeks not to refute the ACH as such, but more to refine it especially insofar as SAD is concerned. Part of the
motivation for so doing is based on the failure of drugs targeting amyloid (amyloidocentric) to provide therapeutic benefit. In fact, from the time the DPH was published, the litany of failure for amyloidocentric drugs has significantly worsened (Cummings et al. 2014; Karran and Hardy 2014). Postmortem data from patients that participated in the Phase 1 AN1792 study (Nicoll et al. 2003; Holmes et al. 2008; Paquet et al. 2015), where amyloid was apparently cleared from the brains of patients but cognitive decline proceeded unabated, is used to support the view that amyloid deposition in SAD does not necessarily drive other pathologies, as is implicit in the ACH. The DPH posits that there might be upstream factors that are able to drive both the major pathologies, amyloid and tau, such that treatments downstream of these factors will not ultimately provide therapeutic benefit. The data supporting potential upstream mechanisms includes, for example, ApoE4, which might act to increase Aβ deposition via reduced clearance and increase tau phosphorylation via low-density lipoprotein receptor-related protein (LRP5) and LRP6 signaling to activate glycogen synthase kinase 3β activity.

However, and as pointed out by the authors, the data supporting ApoE4 mediating its effects via Aβ are very compelling and more substantive than are the links to tau pathobiology. Further, the phenotypic effect of ApoE4 to bring forward the age of onset for AD is present in both SAD and FAD (Pastor et al. 2003), strongly implying that SAD and FAD are similar disease processes. Finally, from neuropathological and clinical correlations, tau pathology is better correlated with both neuronal loss and symptomatology (Arriagada et al. 1992; Gomez-Isla et al. 1996). If ApoE4 was driving both pathologies, one might anticipate that ApoE4 would bring forward the age onset of disease and accelerate disease progression: while there is excellent evidence for the former, there are little data to support the latter. Nevertheless, the DPH seeks to resolve the disconnection between amyloid and tau pathology and to explore the upstream triggers for disease in SAD, which is totally unexplained by the ACH.

The metabolism hypothesis

The metabolism hypothesis has its origins from the work of Hoyer and colleagues (Hoyer et al. 1988; Hoyer 1991) who believed that the underlying cause of AD was cerebral glucose hypometabolism. To investigate this phenomenon, they developed a rat model that involved injecting streptozotocin intracerebroventricularly into rats (Lannert and Hoyer 1998). This resulted in decreased glucose/energy brain metabolism together with learning and memory deficits. Streptozotocin is an agent widely used in the diabetes field to destroy β pancreatic cells in rats to produce an insulin-dependent diabetic state. Since these early experimental approaches, a significant body of evidence has grown that indeed establishes that insulin signaling in the brain is significantly impaired. For example, many of the mRNA transcripts encoding key elements of the insulin signaling pathway are significantly depressed in multiple regions of the AD brain (Steen et al. 2005) leading to the description that AD is ‘Type 3 Diabetes’. Proponents of the metabolism hypothesis argue that insulin signaling is required for preserving synaptic connectivity and may play a role in neuronal stem cell activation and neuronal ‘resilience’. Some very interesting preclinical work has been performed with incretin mimetics such as liraglutide, which when administered via intraperitoneal injection to APP Swe/Ps1ΔE9 mice (25 nmol/kg od) was shown to reduce Aβ plaque load significantly (McCLean and Holscher 2014). There are also data that show that Aβ oligomers (oAβ) bind to and antagonize various components of the insulin signaling pathway and that this may lead to an increase in activity of GSK-3β, a known tau kinase (Morgen and Frolich 2015). Furthermore, as stated earlier, imaging studies using fluoro-deoxyglucose PET brain imaging, which is a measure of glucose uptake and neuronal activity, reveals deficits very early on in the clinical course of AD patients (Jack et al. 2011).

It is difficult to extrapolate the findings from the streptozotocin rat experiments to AD: there is very little face or construct validity given the relatively non-specific mechanism of action of the toxin. The role of oAβ to provoke insulin signaling abnormalities is rather weak, mainly because the role of oAβ is controversial (Benilova et al. 2012). It is difficult to assign a primary role of insulin signaling abnormalities in disease causation as currently there are no data from GWAS studies to support such a mechanism (Lambert et al. 2013), and the data that place insulin signaling abnormalities upstream of tau and amyloid pathology are not yet compelling. It may be the case, however, that insulin signaling pathways are adversely affected because of the AD disease process itself, and in general, this hypothesis has merit because it provides a number of testable hypotheses and avenues for therapeutic intervention. Indeed, there have been a number of small clinical experiments where insulin has been intranasally delivered directly into the brain with promising results (Craft et al. 2012; Bedse et al. 2015), leading to a much larger clinical trial that is underway (ClinicalTrials.gov Identifier: NCT01767909).

Cell cycle re-entry hypothesis

The cell cycle re-entry hypothesis might be considered a particular form of a more general hypothesis that posits that an age-related increase in DNA damage in neurons is responsible for neurodegenerative disease (Chow and Herrup 2015). Neurons are post-mitotic cells and therefore need to sustain their genomic integrity for life. Neurons might also be subject to significant stressors during life: being cells with a very high energy requirement, the potential for DNA damage
via reactive oxygen species is significantly coupled with the errors that can result from gene transcription (Poduri et al. 2013; Lodato et al. 2015). The first indication of a potential role for aberrant cell cycling in the brain came from the observations demonstrating that mitogen kinases had increased expression in the AD brain (Arendt et al. 1995) and that specific antibodies raised to paired helical filaments of tau purified from AD brain cross-reacted with epitopes in dividing cells (Vincent et al. 1996). Further work revealed that driving primary, differentiated neurons to divide by infecting with oncogenes c-myc and ras resulted in DNA duplication and increases in both anti-phospho-tau immunoreactivity and AD-like abnormally folded tau epitopes (recognized by ALZ50 antibody) (McShea et al. 2007). However, the cells did not enter mitosis, suggesting that the cells get blocked at the G2/M transition. The c-myc oncogene was also conditionally expressed in frontal cortex using CaMKII-Ta transgenic mice crossed to tet-o-Myc transgenic mice (Lee et al. 2009). c-Myc expression was initiated by removing doxycycline from the diet. The bigenic mice showed markers of cell cycle activation, DNA replication, hippocampal neuronal loss, and cognitive behavioral deficits. Surprisingly, given previous work, evidence for abnormal tau phosphorylation was not presented. In post-mitotic neurons, DNA repair is afforded by a variety of mechanisms which if disrupted can result in a number of serious neurological abnormalities including neurodegeneration (McKinnon 2013), but these are mostly early onset developmental conditions.

Linking frustrated mitotic cell division to the range of neuropathology evident in AD is currently challenging. While a plausible link to tau pathology can be made, the data suggesting a role for cell cycle re-entry in Aβ deposition is not substantial. Further, there is currently no human genetic evidence from GWAS studies that support a role for aberrant cell cycle re-entry (Lambert et al. 2013), and it is difficult to reconcile the effect of the A673T APP mutation to protect against AD into this schema (Jonsson et al. 2012).

**Vascular hypothesis**

The vascular hypothesis (VH) was originally based on the neuropathological observations that the AD brain has a disorganized and much reduced capillary and vascular network (Fischer et al. 1990; de la Torre and Mussivand 1993). There is now a significant body of evidence that supports an important role for the brain’s vascular system in AD (de la Torre 2004; Marchesi 2011). Some of the known risk factors for AD include hypertension in midlife and diabetes in late-life (and probably in midlife) both of which have significant vascular morbidities (Prince et al. 2014). A study of the localization of thioflavine T-staining amyloid plaques in a range of dementias (AD, Pick’s disease, Guam amyotrophic lateral sclerosis/parkinsonian dementia complex, Down syndrome, dementia pugilistica and prion disease) revealed significant reductions in the microvasculature and some co-localization of blood vessels and plaques (Buee et al. 1994). This latter aspect was investigated more thoroughly and the co-localization of haem-rich deposits, amyloid plaques, and blood vessels was demonstrated in AD and Down’s syndrome brains (Cullen et al. 2006). A very thorough investigation of this relationship was performed using the TG2576 and the PSAPP transgenic mouse models that both develop parenchymal amyloid deposition (Kumar-Singh et al. 2005). These studies revealed that 85–95% of dense core plaques were either centered on, or adjacent to, vasculature vessel walls. Interestingly, the same was not true for diffuse amyloid. However, in both these models, the Aβ composition of the plaques is dominated by the Aβ40 species, unlike AD plaques which are made predominantly of Aβ42 (Welander et al. 2009). Aβ40 is more soluble than the Aβ42 and more likely to be able to be trafficked to the vasculature via bulk interstitial fluid flow. However, these studies cannot confirm a temporal relationship – do amyloid plaques result in vascular damage, or does vascular damage result in plaques? To investigate this aspect, the generation of plaques was investigated using electron microscopy and the earliest signs of fibrillary Aβ appeared to form in the perivascular space. This work relates importantly to the clearance of Aβ from the brain: clearly, if extracellular concentrations of Aβ are kept low, the potential for aggregation will likely be diminished. A detailed analysis of the brain clearance mechanisms is beyond the scope of this review (see Weller et al. 2008; Tarasoff-Conway et al. 2015), but there have been some recent important developments. A clearance pathway – the glymphatic system – has been described for the first time (Iliff et al. 2012) that is part of the Aβ clearance mechanism. The glymphatic (glial-lymphatic) system consists of perivascular conduits formed by glial cell end-feet. Interestingly, in the context of AD, these glial processes are also a site of ApoE expression. Fluid is believed to be propelled through the glymphatic system at least in part by the pulsatile contraction of smooth muscle cells in the vasculature, providing a potential mechanistic link with the vascular system. There are several aspects of the VH that integrate multiple elements of features of AD: the known comorbidities, the important role in Aβ clearance, and providing potential sites for initial Aβ deposition. However, what is difficult to determine is primacy of effect. Does a vascular insufficiency leading to impaired Aβ clearance, or local vascular damage, provide the appropriate microenvironment for amyloid deposition, or does amyloid deposition result in vascular damage: or can it be both?

**Aβ oligomer hypothesis**

The Aβ oligomer hypothesis (AβOH) is a variant of the original ACH that currently has significant momentum
(Walsh and Selkoe 2007). The AβOH posits that small molecular weight oAβ represent neurotoxic agents that cause 

synaptic damage in AD. There are significant attractions to the AβOH, principal among which is a potential resolution of 
a major conundrum of AD research: amyloid plaques do not correlate in terms of their amount, nor brain regional 
location, with AD symptomatology or neuronal loss (Gomez-Isla et al. 1996; Delacourte et al. 1999). Indeed, it is 
difficult to visualize how very insoluble, relatively inert protein deposits are able to exert a damaging effect on 
the brain. Thus, oAβ might act at a distance from plaques and mediate toxic effects. There are wealth of data, beyond 
the scope of this review, that together provide a large body of 
supportive data for the AβOH. These include: the manufact-
ure of various aggregated forms of Aβ in vitro, using Aβ42, 
Aβ40, ratios, and modified forms thereof at supra-physi-
ological concentrations to make oAβ; the profiling of these 
using analytical techniques such as size exclusion chro-
matography, sodium dodecyl sulfate–poly acrylamide gel 
electrophoresis gels (SDS–PAGE), and EM imaging; the 
treatment of in vitro neuronal cell cultures with (usually) 
supra-physiological concentrations to induce neuronal cell 
distress; the investigation of oAβ to affect a number of 
important neuronal receptors (e.g. Insulin R, nicotinic 
receptors); the treatment of brain slice preparations to induce 
electrophysiological changes such as reduction or abolition of 
long term potentiation (LTP); the injection of oAβ into 
rodent brains to induce impaired cognitive functioning 
(Haass and Selkoe 2007; Ferreira and Klein 2011; Koffie 
et al. 2011; Mucke and Selkoe 2012; Hayden and Teplow 
2013; Hefti et al. 2013; Viola and Klein 2015). Also, there 
have been attempts to categorize oAβ in APP transgenic 
mice using anti-oAβ conformational antibodies (Liu et al. 
2015). The AβOH, if true, would also have a profound effect 
on clinical development, as it could mean that therapeutics 
that are targeting amyloid plaque would not be efficacious, 
and indeed might be positively deleterious if by disaggre-
gating plaques they released, or created favorable conditions 
for, increased levels of oAβ. Despite these data and 
significant support in the AD research field, generally, there 
are a number of fundamental questions that remain to be 
answered with respect to the AβOH (Benilova et al. 2012). 
Hepler and colleagues (Hepler et al. 2006) have shown 
convincingly that aggregated Aβ runs aberrantly in size 
exclusion chromatography, mainly because monomeric Aβ 
does not perform as a solvated sphere. Further, these workers 
have shown SDS-PAGE cannot be used to resolve different 
Aβ species unequivocally, and also that the appearance of 
oAβ in electron microscopy is heavily dependent on the 
properties of the surface upon which the Aβ aggregates are 
dispersed. Thus, many analytical procedures routinely used 
in the field are confounded. 

The interpretation of neuronal cell death induced by oAβ 
in vitro is also problematic. Often, such experiments use 
neuronal cell lines or primary rodent neurons to demonstrate 
Aβ-mediated cell distress and death, sometimes in a manner 
that discriminates between different oAβ forms (Ono et al. 
2009; Ahmed et al. 2010). However, in APP transgenic 
mouse models, which reveal plaque pathology that is very 
similar to that seen in AD, neuronal loss is usually completely 
absent (Firuzary et al. 1997a,b). Thus, human Aβ can be toxic 
to rodent neurons in vitro, but often not in vivo. 

The most challenging of these questions is to provide 
unequivocal evidence of the existence, and role, of oAβ in the 
AD brain. Attempts to measure oAβ in intercellular fluid in 
brain parenchyma of transgenic mice that develop Aβ plaque 
pathology have been very technically challenging (Hong et al. 
2014) as have measurements of oAβ in cerebrospinal fluid 
from AD patients. Indeed, recent work with sensitive assays 
has failed to reveal a difference between oAβ concentrations in 
AD versus controls (Yang et al. 2015). These studies have 
been confounded by a lack of a biophysical definition of an 
oligomer and no standard preparation of a single species with 
which to calibrate and control assays. It is important, in this 
context, to distinguish between measuring oAβ and extracting 
oAβ. There are multiple papers that use various techniques to 
extract a range of oAβ species from AD brains that can be 
subsequently revealed on denaturing SDS-PAGE, followed by 
western blotting using anti-Aβ antibodies (Ward et al. 2000; 
Upadhyaya et al. 2012). However, these techniques likely 
create oAβ species because of the physicochemical properties 
of the Aβ peptide as discussed earlier. Leaving aside these 
issues, perhaps the most compelling evidence for a role of oAβ 
could be inferred from human genetics – indeed, the V711T 
mutation that causes FAD provided the cornerstone for the 
amyloid cascade hypothesis (Goate et al. 1991). The APP 
gene has a wide range of different mutations (http://www.alz-
forum.org/mutations) that cause FAD and/or congophilic 
amyloid angiopathy (Fig. 1). These can be either N-terminal 
or C-terminal to, or within, the Aβ42 peptide. A consideration 
of the latter is particularly instructive because these are 
unlikely to affect the production of Aβ or the ratio of long to 
shorter forms that has been shown previously to be important 
in age of disease onset (Duering et al. 2005; Kumar-Singh 
et al. 2006). Mutations within the Aβ42 peptide are more 
likely to affect the folding of the peptide, although other 
aspects may also be affected, such as clearance from or 
degradation within the brain. However, a mutation that locked 
the Aβ peptide in an oAβ form, or greatly inhibited the 
formation of amyloid fibrils so as to increase the proportion of 
oAβ, would add significant weight to the AβOH. 

The amino acid position 2 of the Aβ sequence (with the 
N-terminal Aβ aspartic acid = 1) is particularly interesting as 
it has both protective (A2T) (Jonsson et al. 2012) and 
disease-causing (A2V) mutations (Di Fede et al. 2009) 
(Fig. 1). A2T results in a 50% reduction in Aβ production 
when over-expressed in primary mouse neuronal cells, which 
would equate to a 25% reduction in the heterozygotic state
The amyloid cascade hypothesis – current status

(Benilova et al. 2014). A2V, found as an autosomal recessive mutation in humans, approximately doubles production of Aβ by rendering APP a better substrate for β-secretase. However, both mutations also have effects on the aggregatory properties of the Aβ peptides that were revealed using synthetic Aβ40 preparations. Effects on Aβ42 were not informative for largely technical reasons: at the concentrations of Aβ used in these experiments, Aβ42 forms amyloid fibrils very rapidly compared to Aβ40 making dissection and measurement of aggregation very challenging. The protective A2T mutation increased the lag phase prior to aggregation and the change in Gibbs free energy compared by rendering APP a better substrate for β-secretase, thus demonstrating the reduction in aggregation. The protective A2T mutation almost abolished the lag phase, such that fibrillar amyloid was being formed almost immediately. Interestingly, antibodies that have been reported to be conformational, ‘oAβ specific’ (A11 and OC) (Kayed et al. 2007) failed to recognize either mutant Aβ in the soluble phase post-fibrillization despite a range of small Aβ species being visualized using electron microscopy. This finding rather casts doubt on the validity of these antibodies to measure oAβ specifically. Similar work was published using Aβ42 peptides (Maloney et al. 2014). Hori and colleagues (Hori et al. 2007) studied the effects of the H6R, D7N, and E22G mutations. All the mutations increased the rate of formation of fibrillary amyloid, but this was mediated differently. In the case of E22G, both seeding/nucleation and amyloid fibril elongation was increased significantly compared to wild-type Aβ. This led to increase in both protofibril and fibril formation. The effects of the H6R and D7N mutations were to increase significantly amyloid fibril elongation rate – that is, the rate at which monomers are added to the growing amyloid fibril. However, this led to a very significant reduction in the concentration and residence time of oAβ species: presumably, the addition of monomers to existing amyloid fibrils was energetically more favorable than the formation of oAβ and protofibrils.

The ΔE22 mutation initially caused significant excitement in the field because the first reports suggested that the phenotypic effect was to promote oAβ formation and prevent Aβ fibril formation (Tomiyama et al. 2008). However, subsequent work revealed that this was likely an assay artifact (Inayathullah and Teplow 2011). The effects of the ΔE22 mutation are two-fold: firstly, there was an increase in the formation of oAβ species. However, this effect was dwarfed by an extraordinary increase in the propensity of the mutant to form β-pleated sheet fibrillar amyloid that was ~400-fold faster than wild type.

A comparative study of the A21G, E22G, E22Q, E22K, and D23N mutations (Ni et al. 2011) showed that all of these species were able to form β-pleated sheet amyloid fibrils. With the exception of A21G, all of the mutants decreased the lag phase for the formation of Aβ fibrils, some of them dramatically (E22Q, D23N). A21G resulted overall in an increase in total fibrillization, as did E22Q. It is important to note that these mid-domain changes may have other effects as well; for example, these mutations can cause cerebral amyloid angiopathy as well as AD, implying changes in clearance mechanisms (Van Broeckhoven and Kumar-Singh 2006; Zhang-Nunes et al. 2006).

In conclusion, the effects of the mid-domain Aβ mutations on aggregation do not provide data in support of the AβOH, although caution is warranted in extrapolating from very artificial biochemical systems to the complexity of the human brain. Nonetheless, if anything the mid-domain mutations tend to increase the propensity of Aβ to form amyloid rather than oAβ. A compelling role for oAβ-type species is in the seeding of amyloid plaques. A wealth of careful and compelling science from Walker and Jucker, and others, have unequivocally demonstrated that a soluble Aβ species is able to seed Aβ plaque deposition (for review, see Walker and Jucker 2015). Furthermore, these species are very stable, long-lived, and prion-like (Ye et al. 2015). The seeding of Aβ plaque in humans has also recently been postulated as a consequence of the treatment of humans with extracts from pituitary glands (Jaunmuktane et al. 2015) or with dura mater grafts (Frontzek et al. 2016) although caution must be exercised in interpreting these data given the very heterogeneous nature of the implanted tissues.

For each of the hypotheses considered here, including the ACH, rejection of the null will require firstly, the development of a specific therapeutic approach that addresses a key mechanism that is predicted by the hypothesis to be pathological, and secondly, the demonstration that the therapy has efficacy in a placebo-controlled, randomized clinical trial in AD patients. Also, it is important to distinguish between the causes and the consequences of AD. It is likely that many of the processes that are featured in the various hypotheses previously considered do play a role in AD, but they do not initiate the disease.

A version of the ACH hypothesis is provided (Fig. 2) that we believe reflects, parsimoniously, the current state of knowledge. There is still a significant number of gaps in the ACH, many of which have been attacked by detractors of the hypothesis (Herrup 2015) and that we will address where possible.

Disease initiation

In SAD and FAD, we do not know what initiates Aβ deposition. The ACH has sometimes been interpreted to suggest an increase in Aβ production results in AD, and indeed there are data that support this view (Potter et al. 2013), but in fact, the majority of FAD mutations do not result in an increase in Aβ production, but an increase in the ratio of the longer to the shorter forms of the Aβ peptide (Citron et al. 1992; Suzuki et al. 1994; Borchelt et al. 1996; Duff et al. 1996; Scheuner et al. 1996; Bentahir et al. 2006;
Brain physiology that changes with age and offsets or compensates for age-related memory impairment.

**Fig. 2** Modified Amyloid Cascade Hypothesis. The scheme shows that the aggregation of Aβ is a key event but it runs in parallel with tau dysfunction. At some point, amyloid plaque provokes increased tau pathology that spreads throughout the brain. This process is accelerated by widespread deleterious effects to brain cells leading to system failure and dementia.

**Why is there no correlation between the levels of amyloid Aβ and cognitive impairment?**

This issue can be partly understood from the effects of FAD mutations and APOE4 genotype, the effects of which are to bring forward, in some cases dramatically, the age of onset of AD but not to accelerate the progression of the disease. This situation is concordant with amyloid Aβ either triggering a disease process, or surmounting some threshold before the disease is provoked (reviewed in Karran et al. 2011). In this case, one would not expect a correlation between Aβ amyloid and cognitive decline. Another way of thinking about this question is to consider that AD pathology – both amyloid and tau – can be accommodated by the brain by cell driven compensatory mechanisms until there is a deleterious cellular response that leads ultimately to system failure (De Strooper and Karran 2016).

**What is the connection between amyloid and tau pathologies?**

The ACH has no answer to this question currently, and in Fig. 2, this is represented by 'aggregate stress'. However, there are some very intriguing trends. The discovery that mutations to TREM2 are very significant risk factors for AD place the microglial cell centrally in the disease process (Guerreiro et al. 2013; Jonsson et al. 2013), an observation that others have made well before the genetic evidence was known (McGeer et al. 1988). TREM2 is a type I transmembrane protein that is expressed on microglia. A study of late-onset AD patients versus controls using whole-genome gene-expression profiling (Zhang et al. 2013) demonstrated that a module grouping innate immunity/microglia-related genes correlated best with clinical disease. TYROBP ranked highest as the module’s potential regulator. TYROBP, otherwise known as DAP12, encodes the signaling partner for TREM2. Thus, from two orthogonal data sources, the TREM2/Tyrobp signaling system has been implicated in AD. Homozygous, loss of function mutations in TREM2 and TYROBP cause Nasu Hakola disease that is characterized by cystic bone lesions, white matter loss, and dementia. TREM2 binds to a range of poorly defined ligands such as phospholipids, bacterial products and cell debris and receptor binding mediates microglial phagocytosis and promotes an anti-inflammatory cytokine profile (Daws et al. 2003; Cannon et al. 2012). The greatest risk for AD is associated with the R47H variant which causes loss of function by preventing normal folding of the protein (Kleinberger et al. 2014). An obvious hypothesis is that TREM2 signaling plays a role in the balance of pro-inflammatory responses versus phagocytosis of Aβ plaques (Kleinberger et al. 2014).

A series of GWASs studies has ultimately resulted in the identification of 22 susceptibility loci (Lambert et al. 2013),
of which a large group clearly are related to innate immune system regulation: complement receptor 1 (CR1), clusterin, CD33, the MS4A6-MS4A4 cluster, ABCA7, CD2AP, EPHA1, HLA-DRB5–DRB1, INPP5D, and MEF2C (Karch and Goate, 2015). It is feasible that as the effects of these genes on biological systems is unraveled, a pathway between amyloid and tau pathology will be found, and may reside in the brain’s inflammatory response to amyloid deposition.

The ACH can be rejected because amyloidocentric drugs have failed

It is of great concern, both to adherents of the ACH and its gainsayers, that none of the amyloidocentric drugs tested to date has met their predetermined primary endpoints. However, it is one thing to test a drug and quite another to test a hypothesis. In a thorough review of the recent

**Table 1** Outcome of Phase 3 clinical trials of amyloidocentric drugs

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Proposed mechanism of action</th>
<th>Phase 3 results</th>
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</thead>
<tbody>
<tr>
<td>Tramiprosate Aβ</td>
<td>Small molecule to prevent Aβ aggregation</td>
<td>1052 mild to moderate AD patients randomized to three groups: placebo, 100, 150 mg/kg bid for 78 weeks. No significant effects on primary outcome measures of ADAS-cog and CDR-Sum of Boxes (Aisen et al. 2011)</td>
</tr>
<tr>
<td>Tarenflurbil</td>
<td>Small molecule γ-secretase modulator to alter the ratio of Aβ peptides in favor of shorter, less aggregatory forms</td>
<td>1684 mild AD patients randomized to placebo, 800 mg bid tarenflurbil for 18 months. No significant effects on primary outcome measures of ADAS-cog and ADCS-Activities of Daily Living (Green et al. 2009)</td>
</tr>
<tr>
<td>Semagecestat</td>
<td>Small molecule non-competitive γ-secretase inhibitor to prevent production of all Aβ species</td>
<td>2600 mild-to-moderate AD patients randomized to placebo, 100, 140 mg semagecestat od for 76 weeks in two trials (ClinicalTrials.gov identifiers NCT00594568; NTC00762411) enrolled. Trials were halted after interim analysis showed increased incidence of skin cancer and worsening of cognition and activities of daily living (Doody et al. 2013)</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Humanized monoclonal antibody directed at amino acids 1–5 of Aβ peptide. Mediate amyloid plaque clearance via binding to plaque and promoting microglial activation</td>
<td>4500 mild-to-moderate AD patients randomized to placebo and 0.5 mg/kg IV every 13 weeks for 18 months in ApoE4 carriers, and randomized to placebo and 0.5 and 1.0 mg/kg IV every 13 weeks for 18 months in ApoE4 non-carriers in four trials (ClinicalTrials.gov identifiers NCT00575055; NCT00574132; NCT00676143; NCT00667810.) Trials were halted after completion of two trials demonstrated a failure to meet primary outcome measures of cognition and activities of daily living (Salloway et al. 2014)</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>Humanized monoclonal antibody directed at amino acids 16–24 of Aβ. Mediate amyloid plaque clearance via reduction of free concentration of Aβ peptide in the periphery and in CSF</td>
<td>2000 mild-to-moderate AD patients randomized to placebo and 400 mg solanezumab monthly IV for 18 months (Clinical Trials.gov identifiers NCT00905372; NCT00904683). Trials failed to meet their primary outcome measures of ADAS-cog an ADCS-Activities of Daily Living (Doody et al. 2014). A secondary analysis of mild AD patients pooled from both trials showed a significant effect on cognition (Siemers et al. 2016). An extension study revealed that the positive effects on cognition in the mild AD group were sustained over the next 2 years providing evidence for a disease-modifying effect (Liu-Seifert et al. 2015)</td>
</tr>
<tr>
<td>Gammagard®</td>
<td>Mixture of human immunoglobulins that were believed to reduce peripheral Aβ levels</td>
<td>Trial data currently unpublished. 390 mild-moderate AD patients randomized to 0.2 g/kg/2 weeks and 0.4 g/kg/2 weeks versus placebo for 18 months (ClinicalTrials.gov Identifier: NCT00818662). Gammagard failed to reach its co-primary outcomes of ADAS-Cog and ADCS-ADL</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; ADAS-cog, Alzheimer’s Disease Assessment Scale – Cognitive; CDR, Clinical Dementia Rating; ADCS, Alzheimer’s Disease Cooperative Study.

amyloidocentric drug discovery and development programs that have reached Phase 3 clinical testing (Table 1), it was shown that in several cases, there was a significant lack of translation from preclinical to clinical science, and in only two of the programs – semagecestat and solanezumab – was target engagement measured (Karran and Hardy 2014). However, there has been no doubt that this catalog of failure (Cummings et al. 2014) has been damaging: while several cogent arguments can and have been deployed to explain the lack of efficacy of these approaches (e.g. De Strooper 2014), nevertheless the field may lose patience and the will to continue with amyloidocentric approaches in the absence of tangible success. The field has not been without some encouragement, however. Solanezumab was shown to have a

Table 2  Amyloidocentric approaches in Phase 2/3 clinical efficacy testing for symptomatic AD

<table>
<thead>
<tr>
<th>Name</th>
<th>Proposed mechanism of action</th>
<th>Company</th>
<th>Trial characteristics</th>
</tr>
</thead>
</table>
| AZD3293 LY3314814     | Small molecule BACE inhibitor to prevent production of all Aβ species | AstraZeneca, Lilly                          | ClinicalTrials.gov Identifier: NCT02245737  
Primary outcome measure: change from baseline in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) Score in early AD (mild cognitive impairment to mild AD) in a 2-year study. Aβ/amyloid relevant inclusion criteria include positive amyloid PET scan or a lumbar puncture to assay for abnormally low Aβ CSF |
| Aducanumab BiIB037    | Human monoclonal antibody that binds specifically to amyloid plaque to facilitate clearance | Biogen                                       | ClinicalTrials.gov Identifier: NCT02477800/NCT02484547  
Primary outcome measure: change from baseline in the CDR-SB Score in early AD (mild cognitive impairment to mild AD) in a 1.5-year study. Aβ/amyloid relevant inclusion criteria include positive amyloid PET scan |
| Azeliragon PF-04494700, TTP488 | Small molecule antagonist of the receptor for advanced glycation endproducts (RAGE) with multiple Aβ-related mechanism of action | Pfizer, TransTech Pharma, Inc., vTv Therapeutics LLC | ClinicalTrials.gov Identifier: NCT02080364  
Co-primary outcome measures: change from baseline in Alzheimer’s Disease Assessment Scale – Cognitive (ADAS-cog); change from baseline in CDR-SB in mild AD in a 1.5-year study. |
| Gantenerumab          | Human monoclonal antibody that binds to conformational epitopes on fibrillar Aβ to facilitate clearance | Chugai Pharmaceutical Co., Ltd., Hoffmann-La Roche | ClinicalTrials.gov Identifier: NCT0205160  
Co-primary outcome measures: change from baseline in ADAS-cog; change from baseline in Alzheimer’s Disease Cooperative Study-activities of daily living (ADCS-ADL) scores in mild AD in a 2-year study. Aβ/amyloid relevant inclusion criteria include lumbar puncture to assay for abnormally low Aβ CSF |
| Solanezumab LY2062430 | Humanized monoclonal antibody directed at amino acids 16–24 of Aβ. Binds monomeric species to deplete free Aβ and reduce amyloid plaque | Eli Lilly & Co.                             | ClinicalTrials.gov Identifier: NCT01900665  
Primary outcome measure: change from baseline in ADAS-cog in a 1.5 year study. Aβ/amyloid relevant inclusion criteria include positive amyloid PET scan or a lumbar puncture for to assay for abnormally low Aβ CSF |
| Verubecestat MK-8931  | Small molecule BACE inhibitor to prevent production of all Aβ species | Merck                                       | ClinicalTrials.gov Identifier: NCT01739348  
Co-primary outcome measures: change from baseline in ADAS-cog; change from baseline in ADCS-ADL scores in mild to moderate AD in a 1.5-year study |

BACE, β-amyloid cleaving enzyme; AD, Alzheimer’s disease; PET, positron emission tomography.

246  E. Karran and B. De Strooper
significant effect on cognition in the Expedition and Expedition II trials in mild AD in a pre-specified secondary outcome (Siemers et al. 2016), and in a 3 year ‘staggered-start’ extension study following the initial blinded phase, there was evidence for a genuine disease-modifying effect (Liu-Seifert et al. 2015).

Has the ACH been useful?

Undoubtedly, it has. The ACH has provided a framework that has underpinned a huge amount of both academic and industry science. While Table 1 makes for sober reading, a huge amount of data and experience has been gathered regarding trial design, patient ascertainment, drop-out rates, placebo decline, biomarkers, and clinical assessment. Significant progress has been made in field of biomarkers in particular: it is difficult to imagine that the field would have initiated the AD Neuroimaging Initiative (Weiner et al. 2010, 2015) and developed a number of amyloid PET ligands in the absence of the ACH. The field has learned from failure, although more data sharing, especially between pharmaceutical companies, would facilitate information dissemination significantly.

The field has redefined AD in recognition that amyloid deposition occurs many years prior to the onset of symptoms, such that there is now a phase called preclinical asymptomatic amyloidosis (Sperling et al. 2011). This change in perspective has prompted a significant number of clinical investigations into presymptomatic patients – a move that would have been almost unimaginable not so many years ago, but one that is nevertheless supported by our growing understanding of the disease (Reiman et al. 2016).

The future: are we poised for success or failure?

Table 2 gives the current status of amyloidocentric therapeutic approaches in the clinic – an impressive list. The field awaits with great anticipation the results from verubecestat and solanezumab which are the most advanced in clinical development. If either therapeutic meet their primary outcome measures, a huge amount of work, in academia and industry, would seem to have been worthwhile, and at long last AD patients and those that care for them will have been given hope. But, what if they fail? The effects of FAD mutations are unequivocally to bring forward the age of disease onset: yet, there are little data to support the case that amyloid deposition triggers, but does not drive, the disease process. The long clinical silent phase between amyloid deposition and dementia suggest indeed a complicated process of cellular action and reaction, which we have called the cellular phase (De Strooper and Karran 2016) and might lead to secondary, irreversible, and damaging disturbances of normal brain homeostasis. Thus, it is conceivable that amyloidocentric approaches may only provide therapeutic benefit if they are administered prophylactically in a primary prevention-type clinical trial. In the most challenging clinical scenario, and depending somewhat on the mechanism of action of the therapeutic, this would mean treating at-risk individuals prior to amyloid deposition and many years before any cognitive symptoms are manifest. If an amyloidocentric therapy failed to act in such a trial, and presuming that it demonstrated adequate target engagement, despite all of the supporting evidence for the ACH, we would need to accept the null hypothesis. Clearly, we hope and anticipate that some of therapeutic approaches show efficacy well before this type of prevention study is completed. To answer the question posed by the title of this review: realistically, it is unlikely that the current agents under phase 3 clinical testing will provide outstanding therapeutic benefit. However, given the hints of efficacy in patients with mild AD from a secondary analysis of pooled data from Expedition and Expedition 2 trials with solanezumab (Siemers et al. 2016), and the promise of profound inhibition of Aβ production provided by verubecestat (AAIC Conference 2012), we believe, to quote Winston Churchill, that we are at the ‘end of the beginning’ in our fight against AD.

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