# Chapter 21
# Why Are Humans Vulnerable to Alzheimer's Disease?

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**Lay Summary** Since Alzheimer's disease (AD) is harmful, it is somewhat of a mystery as to why it hasn't been eliminated by natural selection. Typically, AD has been thought to be "invisible" to natural selection because people have already passed on their genes by the time that AD manifests (usually after age 65). But, this hypothesis may not tell the whole story. One possible explanation is that since the E4 form of the *APOE* gene, a strong risk gene for AD, is very similar to that of our ape-like ancestors but is not currently the most common form in humans, it may have been selected against by natural selection. In addition, as humans take care of their extended family (who shares their genes) even when they are no longer able to have children themselves, the ability to remain cognitively functional in old age may have been selected for. A second possibility is that AD exists in humans because it is the inevitable cost of other features that are beneficial to us—our highly neuroplastic brains, for example. If the benefits outweigh the costs, AD may be maintained despite the severe disadvantages experienced by the elderly. Finally, a third consideration about AD is that it is common due to the mismatch between the environment and lifestyle humans typically sustained during their evolutionary history and the contemporary post-industrialized environment, characterized by high-calorie diets, sedentary lifestyle, and a shortage of pathogens (resulting in autoimmune dysfunction)

An evolutionary approach has implications for rethinking the biological hallmarks of AD. The brains of AD patients have two characteristic signs—abnormal accumulations of a protein called amyloid-β into "plaques" between

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A. Alvergne et al. (eds.), *Evolutionary Thinking in Medicine*,
Advances in the Evolutionary Analysis of Human Behaviour,
DOI 10.1007/978-3-319-29716-3_21

brain cells and accumulation of abnormal tau protein into "tangles" inside neurons. These lesions are commonly thought to be the cause of neuron death in AD, but there is no direct evidence for this in humans. To date, experimental drugs that have targeted plaques have been ineffective and some have hastened the disease. There is a possibility that plaques and tangles may be harmless by-products of the actual destructive processes, or might even serve an adaptive function, such as trapping free-floating amyloid-β in the brain or protecting against a natural but harmful bodily process called oxidative stress. If this is the case, care should be taken when developing clinical therapies, because interrupting one of the body's beneficial responses may make symptoms worse rather than better.

## 21.1 Introduction

Alzheimer's disease (AD) is a mysterious disorder for which etiology and treatment remain elusive despite over a century of research. The stakes involved are tremendous. In the USA, AD is currently the sixth leading cause of death. Over five million Americans are estimated to have AD, and this number is expected to rise to 13.8 million by the year 2050 [1]. The global prevalence of AD was 26.6 million in 2006 and is estimated to rise to 106.8 million by 2050 [2]. Although industrialized nations with long-life expectancies are most vulnerable, due to AD usually (but not always) being a disease of advanced age, much of the developing world is struggling with the burden of AD as well [3]. The cost of care per year is over $200 billion in the USA alone and this cost more than doubles if the contributions of unpaid caregivers, including family members, are included [1]. The rise of AD incidence and mortality is a looming public health crisis, and despite many completed and ongoing clinical trials, we await an effective treatment.

An evolutionary perspective may help illuminate a way forward. One of the aims of evolutionary approaches to medicine is to identify the ultimate reasons, that is, the original causes, for illness and disease. Perhaps by understanding the evolutionary origins of AD, future researchers and clinicians will be in a better position to treat or prevent this devastating disease. Toward that end, the current chapter discusses some recent evolutionary perspectives on AD and how they may inform public health policy, research, and medical practice.

The most fundamental question that an evolutionary approach can address with regard to AD is "why are humans vulnerable to the disorder?" Disorders that are "harmful, common, and heritable" [4] should normally be eliminated by natural selection; the fact that AD is such a widespread phenomenon invites the question of how it arose and why it has been maintained in human populations over the millennia. Related to this question is the matter of the major risk gene for AD—*apolipoprotein-E*

(*APOE*) and its isoforms. A number of explanations for the maintenance of AD vulnerability in the human lineage relate to the hypothesis that there are reproductive benefits to the genes responsible for AD, which may outweigh the evolutionary costs of the disorder. Another set of hypotheses is related to the mismatch between the contemporary post-industrial environment and the environmental features humans (and thus AD vulnerability genes) encountered across most of their evolutionary history.

Most of these perspectives have implications for the conceptualization of AD, but of most direct relevance to contemporary research into AD pathology and therapeutic interventions are the hypotheses about the nature of AD pathophysiology, specifically amyloid-β (Aβ) plaques and paired helical filament tau (PHFtau) neurofibrillary tangles. These pathological lesions have generally been seen as causal processes in neurodegeneration, but adopting an evolutionary perspective suggests a rethinking of these biological hallmarks of AD as neutral by-products or even ameliorative adaptations rather than harmful lesions. Additionally, perspectives on mechanisms of pathological transmissibility and phylogenetic analyses of AD-like signs can further illuminate how the medical and research community can move toward therapeutic interventions for the disorder.

## 21.2 Research Findings

The most straightforward answer to the question of why humans are vulnerable to AD (but one which turns out to be, at best, incomplete) is that AD arose as the result of a genetic mutation but, like other diseases of old age, is invisible to natural selection, since it generally imposes its cost long after people have already reproduced [5, 6]. Genetic disorders that are fatal before puberty are rare because their carriers die without passing on their genes, but AD usually manifests later in life, long after most people would have already had children.

This is a parsimonious explanation that would be satisfactory but for several complicating factors. Firstly, there is evidence that AD-related genes and biological processes may confer some fitness disadvantages early in life, long before the typical manifestation of AD, when the force of natural selection is the strongest. The gene shown to be most reliably associated with the risk of developing AD is *APOE*, which is involved in the production of apolipoprotein E, the major lipid carrier in the brain. *APOE* has three common alleles known as E2, E3, and E4; E4 carriers are at the highest risk of developing AD [7, 8]. However, E4 also confers a higher risk of atherosclerotic cardiovascular disease [9, 10], which does manifest earlier in life and sometimes during the reproductive lifespan. Additionally, there is evidence to suggest that the E3 and especially the E2 alleles may protect against the formation of plaques and tangles that may otherwise occur early in life or following a head trauma [11, 12]. During our evolutionary history, these factors may not have been invisible to natural selection at all, if they meant a differential chance of surviving, reproducing, and successfully raising young. The E4 allele may also be

associated with a younger age at menopause [13] (although the evidence is equivocal [14]), which would have presented a salient selection pressure in favor of alternate alleles that allowed for longer reproductive periods.

There is a second potential problem with the notion that AD is invisible to natural selection; phylogenetic analysis reveals that the E4 allele is the ancestral form of the *APOE* gene. In other words, the gene corresponding to *APOE* in all nonhuman primates has the same amino acid structure as the human E4 allele, strongly suggesting that the E2 and E3 forms only arose after the human lineage split from that of chimpanzees and bonobos [15, 16]. The fact that less than 30 % of people presently carry one or two copies of the E4 allele [17] indicates that there has either been selection against this allele (perhaps due to the mechanisms discussed above) or genetic drift or selection favoring the E3 allele, which about 95 % of humans carry [17].

If the E4 allele has been selected against, this indicates by definition that it has a net fitness cost relative to E2 and E3 alleles, and thus is, in fact, visible to natural selection. It is also possible, however, that the prevalence of the newer E3 allele relative to E4 is purely due to random genetic drift and not natural selection. If this is the case, it may have been due to a population bottleneck at some point in our species' history, wherein a sharp reduction in the population randomly happened to leave mostly E3 carriers alive and able to reproduce, and left only a relatively small number of E4 alleles in the population. At any rate, the fact that E4 is the ancestral allele means that this risk allele for AD did not abruptly appear and evade natural selection for millions of years, but rather that it has always been present in humanity and has begun to be replaced by the E3 allele (and, to a lesser extent, E2).

A further challenge to the possibility that natural selection is powerless to remove AD susceptibility genes is the grandmother hypothesis; this is the idea that humans, unique among primates, contribute to their genetic fitness not only by providing parental care to children, but also by helping care for their grandchildren as well [18, 19]. In the harsh environment of pre-industrialized societies, any additional measure of childcare, such as feeding or protection, can mean the difference between life and death. For most of our evolutionary history, we lived in such environments. If post-reproductive individuals can reap fitness benefits by assisting in the care of their grandchildren (which in turn helps those children survive and pass on genes), unimpaired functioning in later life is no longer invisible to natural selection. Thus, AD and other diseases of old age may have been selected against if they prevented elderly individuals from caring for their extended families [18]. On the other hand, there is some controversy surrounding the grandmother hypothesis, in particular over whether the fitness benefit of grandmaternal care outweighs the cost of ceased reproduction. It is possible that menopause (i.e., a period of reproductive senescence) was selected for due not to the benefits of grandmothering, but because offspring borne by older females result in less resources available for offspring borne by younger relatives [20]; this is known as the resource competition hypothesis. Nevertheless, Cant and Johnstone [20] suggest that regardless of why reproductive senescence evolved, older females can definitely contribute to the fitness of their grandchildren, meaning that post-reproductive functioning may be selected for

regardless of why it evolved. In other words, it is possible that natural selection could theoretically act on post-reproductive females. It is currently unclear exactly how male longevity and reproductive life history tie into this hypothesis, if at all, since there is little evidence that male care leads to increased fitness of grandchildren [21], although continued ability of longer-lived males to provide for families could possibly play a role.

In sum, there are a number of reasons to think that the continued existence of AD vulnerability in humans is due to more than just the declining power of natural selection as we age. The early-life disadvantages conferred by AD vulnerability genes, particularly *APOE*, is one such reason. Another is the fact that the *APOE*-E4 vulnerability allele was present in our prehuman ancestors and had to be either strongly selected against or encounter significant genetic drift to have such a relatively low frequency now. Finally, there is the possibility that the post-reproductive ability to take care of one's grandchildren has been selected for, meaning that cognitive impairment in old age can be selected against even once a person is beyond his or her childbearing years.

### *21.2.1 AD and Antagonistic Pleiotropy*

If AD is heritable and has been selected against at all, natural selection should have eliminated it, but this has not happened yet. A common explanation for the maintenance of AD vulnerability in humans relates to a concept known as *antagonistic pleiotropy*. In antagonistic pleiotropy, a gene has multiple effects on a phenotype, some of which are beneficial for fitness while others are detrimental. If the net fitness effect of the gene is beneficial, it will be maintained despite its negative effects. Naturally, benefits that occur during peak reproductive years heavily outweigh disadvantages that occur after reproductive years. The concept of antagonistic pleiotropy was originally formulated to explain the general bodily deterioration associated with aging [22] (see also [23]) and has been invoked to explain brain aging in particular [24].

In the last several decades, some evidence has accumulated that AD may be the result of—or *APOE* the subject of—antagonistic pleiotropic processes. There is some evidence that the E4 allele may guard against spontaneous abortion [25], cardiovascular reactions to psychological stress [26], and liver damage in the cases of hepatitis C [27]. It is conceivable that the fitness benefit accrued from these and other potential advantages may outweigh the cardiovascular and AD risks conferred by the E4 allele and lead to its maintenance in the gene pool, although there is currently no direct empirical support for this. Finally, there is a body of evidence showing that the E4 allele may confer cognitive advantages when carriers are young, and the cognitive impairments come only later in life [28].

AD might also be the long-term, accumulated cost of the neuroplasticity responsible for humans' characteristically long period of brain development and profound ability to learn. Human synaptic plasticity undoubtedly contributes to our

ability to survive, reproduce, and care for the young. According to Bufill et al. [29], the same characteristics of human neurons that allow them to form new associations well into adulthood (such as high levels of aerobic metabolism and partial myelination) also put them at increased vulnerability to oxidative stress. This oxidative stress is hypothesized by Bufill et al. [29] to precede, and perhaps initiate, the cascade of events leading to Alzheimer's pathophysiology and cell death.

Another perspective, elaborated by Reser [30], is that the neurodegeneration seen in AD may have been selected for because it is an adaptive downregulation of brain metabolism. According to Reser [30], as organisms age, *crystallized intelligence*—i.e., existing knowledge and abilities—becomes more important than *fluid intelligence*—the ability to reason abstractly and problem-solve (see [31]). Since the brain is an energetically costly organ, it may be adaptive for the body to divert crucial metabolic resources away from the less crucial processes as the individual ages; in this way, the neurodegeneration process can be selected for the calories that would otherwise be mobilized for less important brain areas are available for survival and reproduction. Note that this hypothesis refers to the preclinical neurometabolic changes that precede AD, not the debilitating condition of AD itself. In Reser's [30] view, it was very rare that early humans would have lived long enough to see this process culminate in AD as we recognize it. Thus, the hypothesis states that while the metabolic precursors of AD [32] may have been selected for, clinical AD is an unintended result of the extended lifespan made possible by modern public health and medicine (see also Mismatch, below). This hypothesis naturally depends on whether the metabolic downregulation seen in the brains of pre-AD individuals is associated with any significant savings of energy—if these changes are not associated with lowered energy expenditure, they could not have evolved as metabolic reduction mechanisms. Longitudinal fluorodeoxyglucose PET (positron emission tomography) neuroimaging studies that measure resting glucose metabolic rates may be able to provide further evidence for Reser's [30] hypothesis.

Antagonistic pleiotropy is one form of balancing selection, in which multiple alleles are maintained in a gene pool because the level of fitness they confer differs under different circumstances. If the *APOE* E4 allele is not subject to some form of balancing selection (thus far, antagonistic pleiotropy is the only form of balancing selection that has been proposed for AD), then the allele's relatively low prevalence may mean it is, in fact, on its way to extinction. This is true whether it was natural selection or genetic drift that caused the takeover of the E3 allele relative to E4. If E4 confers a net disadvantage, natural selection will continue to select against it until it is eliminated. Even if it does not, Keller and Miller [4] believe that genetic drift will eventually eliminate the E4 allele because over time, drift tends to drive the predominant neutral allele, in this case E3, to fixation (i.e., the rarer alleles get crowded out and the more common allele eventually becomes the only one).

### 21.2.2 Mismatch Hypotheses

Another set of hypotheses regarding AD views the disorder as an unfortunate by-product of mismatch between the environmental features humans have encountered across evolutionary time and the contemporary post-industrialized environment. AD and the *APOE* E4 allele have been linked to cardiovascular disease, hypertension, obesity, and insulin resistance [33, 34]. Not only do these conditions share risk factors such as lack of exercise, smoking, and poor diet, but insulin resistance in the brain is being investigated as an important mediator of the neurodegeneration found in AD [35, 36] Based on these associations, the explanation behind high rates of AD may be similar to evolutionary perspectives on obesity, cardiovascular disease, and diabetes; the sedentary lifestyle and high fat, high sugar diets of the developed world are not what our bodies were evolved to deal with. Very few hunter-gatherers would have regularly expended as few calories daily as a person who drives to work, sits in front of a computer for ten hours, drives home, and goes to bed. Even in light of the evidence that differences in levels of physical activity may not fully account for differences in obesity between industrialized societies and hunter-gatherers [37], sedentary lifestyles may still contribute to related disorders, including AD. Similarly, our appetitive and metabolic systems were designed to seek out the most energy-rich foods available (those naturally high in fats and sugars) and expend the calories in a thrifty manner, since sustenance was not always plentiful. Today, those same systems drive us toward calorie-rich and nutrient-poor foods designed to take advantage of our fat and sugar preferences, and our metabolisms may be too energy efficient for our low levels of physical activity, leading to obesity and the accompanying maladies.

The result of this environmental mismatch for many humans is the metabolic syndrome. This condition is characterized by abdominal obesity, insulin resistance, dyslipidemia, oxidative stress, inflammation, hypertension, atherosclerosis, and risk of cardiovascular disease. The metabolic syndrome is increasingly recognized as an important risk factor for Alzheimer's disease as well. A central feature of the metabolic syndrome is the resistance to the glucose-lowering effects of insulin and chronically elevated levels of insulin. This often, but not always, leads to diabetes. For the brain, this may result in the cascades of pathophysiological processes seen in AD. Vicious cycles of inflammation; oxidative damage to proteins, lipids, and nucleic acid; resistance to insulin and other trophic factors; calcium dysregulation; caspase activation, mitochondrial, lysosomal, and proteasomal dysfunction; Aβ generation; and tau phosphorylation and fibrillization are set-ups that lead to synaptic loss and neuron death [29].

Fox et al. [38] present intriguing preliminary data that AD may share elements of immune disorders, in that the disorder is more common in regions where environmental pathogens are at low levels. The logic behind this *hygiene hypothesis* is that our immune system is evolved to fight a moderate level of pathogens from our environment; in modern environments where pathogen levels are low, the immune system attacks harmless substances (as in allergies) or other bodily tissues (as in

autoimmune disorders)—another case of environmental mismatch (See also Chap. 15 in this volume). Not only does AD present inflammatory features reminiscent of autoimmune disorders, but also it shows a similar pattern as well; rates of AD are strongly negatively correlated with regional parasite stress and other related measures [38]. Future studies controlling for variables such as genetic population markers would provide a powerful test of this hypothesis.

### *21.2.3 Alzheimer's Pathophysiology*

Another focus of evolutionary approaches to medicine involves identifying the nature of disease pathology. The hallmark brain lesions of AD are Aβ plaques and PHFtau neurofibrillary tangles. The traditional view has been that plaques and tangles lead to neuronal death [39], but the nature of this relationship is unclear. The amyloid cascade hypothesis posits that oligomers or plaques of Aβ are toxic to cells and directly cause the sequence of events leading to neurodegeneration. The amyloid cascade hypothesis is supported by early-onset familial AD, which is a Mendelian disorder involving mutations in the *presenilin 1*, *presenilin 2*, and *amyloid precursor protein* (*APP*) genes. These abnormalities result in biochemical processes that create high levels of Aβ, leading to the formation of plaques (as well as tangles) and onset of AD before the age of 65, sometimes much earlier. The causative role of Aβ in the non-familial type of AD, known as sporadic AD, is more circumstantial, based mainly on the correlation, quite modest, between dementia symptoms and plaque load, but the amyloid cascade hypothesis has been at the center of AD research for decades nevertheless.

The amyloid cascade hypothesis has led to a line of therapeutic research aimed at either removing Aβ plaques or preventing their formation. Clinical trials with drugs targeting Aβ have been disappointing so far. For instance, one active immunization trial was ineffective at slowing dementia or reducing PHFtau tangles, vascular injury, or total and soluble concentrations of Aβ, even though it dispersed the plaques themselves [40]. Two other recent large trials of passive immunization directed at Aβ failed to show benefit for their primary outcomes [41, 42]. Another trial using an agent that prevented the formation of Aβ had to be terminated early due to the experimental group's declining at a faster rate than the placebo group [43].

While the failure of any particular drug does not disprove the amyloid hypothesis, cumulatively these results do begin to raise the question as to whether Aβ plaques are a "red herring" in the search for an effective AD treatment. Aβ plaques may be downstream to the primary pathological process(es) of AD rather than the instigator, and may or may not be part of the causal chain of events at all. Accumulating evidence suggests that it may be soluble oligomeric Aβ, rather than Aβ plaques per se, that are neurotoxic [44, 45], and Aβ plaques have even been hypothesized to be protective phenomena that may guard against harmful, free-floating amyloid [46–49]. Perhaps, the molecular structure of Aβ is a design

feature to facilitate amyloid aggregation into "sinks" that immobilize oligomeric Aβ to limit neuronal damage [50].

Some evidence suggests that Aβ is functional in small amounts (involved in functions such as synaptic transmission, memory, cholesterol transport, motor activity, and neuroplasticity) and only toxic in higher amounts [51–55]. Soscia and colleagues [48] have shown that Aβ has antimicrobial properties in vitro. Castellani et al. [56] point out that Aβ toxicity has only been demonstrated in vitro but has not been shown to be toxic in vivo. These researchers posit that Aβ is an antioxidant released as a compensatory response to oxidative stress. This is an important perspective in light of the evidence that oxidative stress, rather than Aβ, may be the initiating event in the biochemical cascade that eventually leads to Aβ plaques, PHFtau tangles, and cell death [29, 56]. The hypothesis that Aβ is neutral or even beneficial rather than harmful is consonant with the data that cognitively normal individuals may have heavy plaque load but no brain atrophy [57–60], a finding that is troublesome for the hypothesis that excess Aβ causes neurodegeneration.

Neurofibrillary tangles of PHFtau are the other hallmark sign of AD, but their relationship to Aβ is still a matter of debate. Depending on the nature of the study, tangles appear to either precede [61] or follow [62] plaques in the pathological process. The two pathologies might also interact in a destructive cycle to cause neuronal death [63]. Another possibility, however, is that, similar to Aβ plaques, neurofibrillary tangles act as protective aggregations to mitigate neuron damage from PHFtau oligomers. Lee et al. [64] suggest a mechanism by which phosphorylated tau might work along with Aβ as an antioxidant to protect neurons against oxidative damage.

### *21.2.4 Transmissibility of AD Pathology*

Research into the way that Aβ oligomers and especially PHFtau spread through the brain has revealed that "seeds" of misfolded Aβ and tau proteins can spread by acting as templates that spur further misfolding and thus propagation of abnormal proteins from neuron to neuron across synapses [65, 66]. Whether this transmission is a positive or a negative phenomenon depends on the nature and function of tau (see above), but it should be noted that this transmission method is at least superficially analogous to that of prions, the infectious proteins that cause bovine spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD), and a number of other rapid neurodegenerative disorders in humans and nonhumans. Unlike prion diseases, however, it is important to note that there is no evidence for inter-individual transmission of AD via air, physical contact of any sort, blood or ingestion. Prions are structurally abnormal proteins that spread by inducing normal proteins to misfold as well, resulting in severe and fatal neurodegeneration. While prions are not alive and do not possess DNA, they still spread via a Darwinian process involving mutation and selection [67]. Li and colleagues [67] suggest that this tendency to mutate makes CJD and other prion diseases difficult to treat, as

drug-resistant proteins are quick to evolve; to date, no effective treatment has been found for prion diseases. It is conceivable that the comparable transmission mechanism of AD pathology may make the development of protein-targeting drugs difficult for the same reason.

### *21.2.5 Comparative Perspectives*

The incidence of AD-like pathology in nonhuman animals is highly pertinent to this discussion (see also Chap. 19), both because phylogenetic relationships are of interest to evolutionary researchers and because animal models are so popular in the study of AD pathology and treatment. Various combinations of the three hallmark signs of AD—Aβ plaques, PHFtau tangles, and age-related cognitive impairment—have been found in a variety of nonhuman species, including apes, monkeys, dogs, bears, whales, birds, some rodents, and fish [68–75], with amyloid plaques being the most common finding. Crucially, however, all three hallmarks have not been observed in the same nonhuman individual [29], so the term "Alzheimer's disease" has not been readily applied to nonhuman cases. When AD-like patterns of pathology (i.e., age-related cognitive decline accompanied by plaques and/or tangles) are found in nonhumans however, the same characteristic almost always applies: The individual in question is generally an older specimen whose lifespan has been prolonged, via domestication or captivity, beyond what it might achieve in the wild [18, 49].

## 21.3 Implications for Policy and Practice

While it may be too early for evolutionary approaches to provide specific treatment options for AD, the current research does offer some suggestions on how to conceptualize the disorder clinically and some considerations that may point toward potentially effective interventions. For example, as Ashford [16] points out, the evolutionarily salient discovery that E4 is the ancestral *APOE* allele actually has implications for the development of treatments. Conceptualizing E4 as a harmful allele implies a solution based solely on identifying and blocking those effects of E4 that increase AD risk. On the other hand, conceptualizing E4 as a neutral allele and E2 and E3 as protective would more naturally lead to treatments based on inducing ApoE E2 or E3 protein synthesis, developing ApoE E2 or E3 agonists, or—as recent lines of research have begun to examine—changing the configuration of ApoE E4 to make it behave like ApoE E2 or E3 or using peptides that mimic endogenous ApoE E2 or E3 [16, 76]. Furthermore, the reconceptualization of E4, E3, and E2 as "neutral," "somewhat protective," and "most protective," respectively (rather than the current "bad," "neutral," and "protective," respectively) may also inform how clinicians choose to communicate the results of genetic testing to patients.

The implications for how we should conceptualize Aβ are far from conclusive; yet, perspectives from evolutionary approaches to medicine suggest that we at least proceed with caution where amyloid plaques are concerned. Answering ultimate questions about the origination of traits has not been an emphasis of standard modern medical approaches, at least until the recent emphasis on evolutionary approaches to health [77, 78]. Yet, certain implicit assumptions can be identified in the literature and viewed through an evolutionary lens; in the case of AD, plaques and tangles have traditionally been treated as if they are harmful by-products of the brain's biochemistry—that is, toxic proteins that the human brain happens to be exposed and vulnerable to via an accident of its evolution. The amyloid cascade hypothesis views AD lesions in this way, and thus points inexorably toward a solution based upon removing plaques and tangles. By contrast, a perspective that seeks but does not assume ultimate answers about AD lesions encourages caution and further inquiry into the nature of plaques and tangles, to determine whether they are, in fact, harmful by-products, neutral epiphenomena, or beneficial adaptations.

The disappointing results from recent clinical trials that targeted Aβ plaques do not necessarily suggest that such treatments are ineffective or harmful. Yet, the assumption that plaques are themselves the proper target of clinical intervention may be premature, in light of evolutionary perspectives on their pathophysiology. Researchers developing new AD drugs would be advised to consider the theoretical implications of targeting plaques without knowing whether they are a cause of neurodegeneration, an inert byproduct, or a compensatory response to some other "upstream" process such as metabolic dysfunction, inflammation, or oxidative stress. Clinicians who are discussing opportunities for clinical trials with patients should also be aware of the uncertainty regarding the role of Aβ plaques as they present the risks and benefits of enrolling in particular studies.

If the pathogenic protein propagation process [65] is substantiated as an important mode of AD pathology transmission, as it is in prion diseases, the recommendation of Li et al. [67] that upstream processes are better targets for therapeutic interventions than the abnormal proteins themselves may also hold true for AD. In prion disease, stabilizing or reducing the expression of the normal prion protein is more likely to be effective, according to Li et al. [67], than targeting the abnormal and ever-changing misfolded proteins, and the same may hold true for AD; even if Aβ plaques and PHFtau tangles are determined to be injurious lesions, which has not been confirmed in humans, directly attacking them may not be fruitful if their conformation is variable, thwarting specifically targeted drugs. In such a case, modifying upstream processes such as apoliporotein-E or β- and γ-secretases, enzymes that cleave amyloid precursor protein into Aβ, may be more effective at clearing Aβ. Caution is advised, however, as these enzymes play roles in other functions as well. Indeed, while the γ-secretase inhibitor semagacestat was effective at preventing Aβ formation, it resulted in worsening of dementia and other symptoms [43]. This has been widely presumed to be due to off-target activity of the drug, as γ-secretase plays a role in Notch signaling and other pathways. Still, another consideration is that the prevention of Aβ formation itself may have been deleterious.

Observations of AD-like pathology in nonhuman animals have revealed that such pathology is most likely to be found in elderly specimens who lived beyond the typical natural lifespan for their species. It should be noted that a similar condition applies to humans—in the environment in which we evolved, before modern hygiene and healthcare, life expectancy at birth was around 40 years, and 60 years would have been old age [79]. Our ability to use cultural innovations to extend our lives has resulted in an "unnaturally" long lifespan for humans in developed nations. This perspective is, of course, another mismatch hypothesis; AD can be viewed as a disorder revealed by extended lifespans due to modern advances in health. Individuals who live up to age 85 may have as much as a 50 % risk of developing AD; Terry and Katzman have argued that the difference between people who die with dementia and those who die without it is only a matter of timing, and if we all lived to age 130, everybody would have dementia [80]. This "inevitability" model of AD essentially posits that any human brain, and perhaps those of our close nonhuman cousins as well, will succumb to the disease given enough time.

The argument that AD is an inevitable consequence of aging may or may not be borne out by the evidence; if true, however, it is a practical consideration for physicians, researchers, medical ethicists, and policymakers to take into account. As we continue to develop new ways to prolong the health and longevity of our bodies, we may eventually outstrip the ability of our brains and minds to keep up. This fact should not be viewed as bleak, but rather as a call for increased effort and funding for AD research. Between 2010 and 2013, the National Institutes of Health allocated on average around $476 million of funding per year to AD research. Compare this to the $2 billion, $3 billion, and $5.5 billion that went toward research on cardiovascular disease, HIV/AIDS, and cancer, respectively [81]. We join our colleagues in hoping for successful clinical research and cures to these diseases, but those successes will only underscore the need for greater momentum toward the search for an AD cure.

As investigations into the nature of AD and potential therapeutic interventions continue, it is our belief that evolutionary perspectives will only add to the power of this research, theoretically grounding previous findings as well as revealing new ones. While the applications of evolutionary approaches to medicine, and especially to AD, are still in their infancy, they hold promise toward the goal of a better understanding and treatment for the disease.

## Glossary

*APOE* A gene involved in the expression of a protein called apolipoprotein-E. This protein is implicated in transporting cholesterol through the bloodstream. There are three variants of the protein caused by different forms of the gene, known as E2, E3, and E4 or sometimes ε2, ε3, and ε4. The E3 allele is the most common. The E4 allele is associated with a higher risk of

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| | cardiovascular disease and AD than E3, whereas the E2 allele is associated with a reduced risk of AD relative to E3 [8, 82]. |
| Amyloid-β | (pronounced "amyloid-beta"; a.k.a. beta-amyloid, Aβ) One of the proteins involved in the pathology of AD. It can take one of several forms including oligomers, which are small chainlike molecules, and plaques, which are large insoluble aggregates of Aβ that accumulate in the brains of Alzheimer's patients. Its normal function is not well-understood, although it may be involved in immune response, cellular metabolism, or a number of other processes. Aβ is formed when a protein called amyloid precursor protein (APP) is cut by two other proteins, known as β-secretase (beta-secretase) and γ-secretase (gamma-secretase). Aβ in plaque or oligomeric form has traditionally been thought to be one of the causes of the neurodegeneration seen in Alzheimer's disease. |
| Tau protein | The other protein whose abnormal processing forms the signature neurofibrillary tangle of Alzheimer's disease. Normally, tau functions to stabilize microtubules, which support the cytoskeleton of neurons in the central nervous system. As part of its normal function, tau changes its shape via phosphorylation, a process wherein phosphate groups bind to tau and allow it to change configurations. In Alzheimer's disease, tau becomes saturated with phosphates, a process called hyperphosphorylation, which promotes its misfolding into filamentous structures called paired helical filaments. These paired helical filaments, in turn, aggregate into neurofibrillary (i.e., "nerve fiber") tangles, which, along with plaques, are a marker of Alzheimer's disease. Tau tangles have been thought to play a role in neuron death. |
| Oxidative stress | A process caused by by-products of metabolism in which so-called reactive oxygen species or free radicals overwhelm the body's ability to neutralize them, potentially causing damage to DNA and proteins. Reactive oxygen species are molecules or ions of oxygen that are missing one electron, making them highly reactive. Oxidative stress may play key roles in a number of neurodegenerative diseases, including Alzheimer's disease. |

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