Chapter 19
Dementias of the Alzheimer Type: Views Through the Lens of Evolutionary Biology Suggest Amyloid-Driven Brain Aging Is Balanced Against Host Defense

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Lay Summary The major risk factor for Alzheimer's disease (AD), like so many other chronic diseases, is advancing age. Here, we ask whether certain key pathological features of the disorder also appear in other species of primates and how they are related to their marked variations in life spans. Concentrating on two such alterations, one dealing with a "sticky" type of protein called amyloid beta and a protein of importance in the transport of cargo along nerves called tau, we find that there is indeed such evidence and that the times of their appearance support the notion that they are responding to some basic processes of aging, or even some yet unknown process. These changes, however, do not reach the advanced pathology seen in our species and which define AD. Why is that? First, environmental factors are important influences upon disorders of aging: Captive, caged monkeys and apes show significant amounts of amyloid beta in their brains. Second, genetic differences are of major significance as to why only some old people develop AD. For the common sporadic, late-onset forms of the disease, by far the most important risk factor involves genetic variations in apolipoprotein E (apoE), which delivers lipids to our neurons. The gene comes in three "flavors" (alleles) known as *E2*, *E3*, and *E4*. While neither necessary nor sufficient to cause the disease, people with the *E4* allele are far more likely to develop AD as they age. Surprisingly, our primate cousins and our ancient human precursors appear to have an allele that is closer to this "bad" *E4* allele. Why has such allele not been eliminated by natural selection? We suggest that its lower efficiency in delivering lipids to certain infectious agents may be the reason

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APOE4 evolved and persisted in certain populations of humans subjected to great hazards of infectious diseases, including malaria. A great deal more research is needed to clarify the relationships between infectious agents and AD. In any case, it is important to consider an infectious etiology for AD.

19.1 Introduction: Species Variations in Neurodegenerative Disorders of Aging

Aging is a lifelong process that plays out differently in each tissue. The ovary and the brain both have irreplaceable cell populations: The ovarian oocytes are fully formed before birth and are lost irreversibly at exponential rates with exhaustion at menopause by midlife [1]. In contrast, brain neurons are rarely replaced in adults and are largely stable into midlife, when they show increasing risk for damage during pathological processes of brain aging [2]. Although humans may be unique among mammals in developing the extremes of neurodegeneration found in later clinical stages of AD [1], many primates also develop varying degrees of AD-like changes. We focus here on the senile plaques containing amyloid β-peptide (Aβ) and neurofibrillary tangles (NFT) with hyperphosphorylated tau, which are diagnostic of AD when they reach certain levels in particular brain structures.

Some levels of Aβ deposits and NFTs also arise at later ages in primate clades (Fig. 19.1). This similarity in outcomes of aging implies that mild AD-like processes are evolutionarily ancient and may have arisen in early mammals before 60 million years ago. The adult ages of mild AD-like changes range several-fold and approximate the life span of each species. Primates show extreme variations in brain aging over a fourfold range of life spans from pro-simians to great apes. Chimpanzees and other great apes at advanced ages have modest accumulations of brain Aβ aggregates that would not qualify as the senile plaques of AD [3, 4]. Moreover, among the great apes, NFT are rare [5]. While baboons show more extensive neurofibrillary changes [6], aging macaque monkeys have modest synapse loss [7], and little evidence of neuron loss [8]. However, definitive proof awaits higher resolution analysis of neuron and synapse density by optical fractionator techniques. Of great note, human neuronal loss is modest in individuals who have no significant cognitive impairment at advanced ages, but among AD individuals, neuronal loss becomes severe early, during preclinical stages. The present evidence supports Rapoport's hypothesis [9] that AD is unique to humans. We can exclude one possibility that the Aβ peptide has undergone evolutionary change in primates. Remarkably, the Aβ sequence is identical across most vertebrates from zebra fish to human. However, the β-amyloid precursor protein (APP) gene has species differences relevant to Aβ production [10, 11].

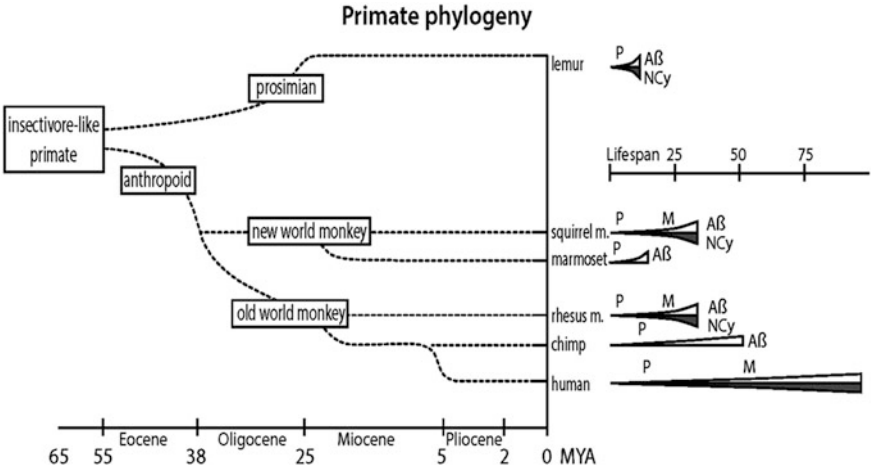

Fig. 19.1 Brain aging of primates organized by phylogeny. Aβ, deposits of the fibrillar Aβ aggregates in brain parenchyma; M, menopause; P, puberty; NCy, neurocytoskeletal disorganization, identified as tau hyperphosphorylation only in species marked as t+. Mouse lemur, *Microcebus marinus*, *t+* [95–98]; squirrel monkey, *Saimiri sciureus* [99–102]. Common marmoset, *Callithrix jacchus* [103–107]. Rhesus monkey, *Maccaca mulata*, *t+* [108]. Chimpanzee, *Pan troglodytes* [3, 5, 109]

Conclusions about possible AD-like changes in other species must be tempered by two caveats. First, all studies are from captive animals under conditions of housing and diet that differ widely from their natural habitat [12: 1]. Most captive apes and monkeys, for example, are obese (see also Chap. 21), and small cage spaces increased brain amyloid several-fold in monkeys [13]. While some field observations suggest that older chimpanzees retain competence in foraging and in complex social behaviors [14, 15], their numbers are too few for generalizations. None from natural habitats have been killed for examination of their brains (unthinkable in this era of endangered species). Second, the advanced ages reached by captives would represent an extreme minority in nature, where background mortality is high from predators, injuries, and infections.

That said, the evidence shows that brain aging in primates and other mammals varies widely in some proportion with differing species life spans and emerges later in life span when most reproduction has been achieved by young adults, which are always the majority age group. Thus, brain aging, as observed in captivity, arises at later ages that are less subject to natural selection. The wide range of species differences in primate brain aging, as well as life span differences, must represent genetic differences between species that were at some level shaped by natural selection. Many other phylogenetic comparisons such as those shown in Fig. 19.1 underscore the plasticity of aging in ovaries and other tissues [16, 17].

19.2 Research Findings: Evolutionary Hypotheses for the Origins of AD-like Dementias

19.2.1 Antagonistic Pleiotropy

We consider an evolutionary hypothesis to explain how *APOE4*, as the major genetic risk factor for AD, could persist globally despite its adverse associations. The possibility that this "bad gene" has benefits at an early stage of life but also confers disease risk later in life is described in the antagonistic pleiotropy hypothesis of aging.

The antagonistic pleiotropy hypothesis for the evolution of life spans was proposed by George Williams five decades ago to involve hypothetical gene variants showing advantage early in life but harm at older ages [18]. Extending the classical concept of genetic pleiotropy as a multisystem effect of a gene variant, Williams hypothesized that some alleles selected for benefits to early survival may have later adverse consequences that were not selected against because most of the reproduction is accomplished by young adults [18, 19]. Although not discussed by Williams, we emphasize that in natural populations the major causes of mortality are infections, as observed in wild chimpanzees and in human foragers living with limited access to modern medicine [20]. With the great reduction of infections in the twentieth century that allowed the doubling of life spans, humans are experiencing greatly reduced selective pressure for resistance to infections. Moreover, with greatly improved infant survival allowing reduction of family size, fecundability is also under diminishing natural selection. *APOE* alleles can be considered as having potential roles in both host resistance and reproduction.

The three *APOE* alleles may be the largest "public" allele system involved in both AD and longevity: Depending on the population, a single copy of *APOE4* increases the risk of AD by about twofold [21, 22] and shortens life expectancy by about 5 years [23]. Women *APOE4* carriers have twofold–fourfold greater vulnerability to AD than men [24, 25]. The minor allele *APOE2*, however, is AD-protective [26, 27] and is also associated with exceptional longevity [23].

More than 10 genes are now associated with late-onset AD [28]. Among them, the *APOE* allele system is the best understood in terms of its evolutionary history and trade-offs, which show evidence of antagonistic pleiotropy. Another example may be the Aβ peptide, which, as noted above, occurs in most vertebrates from fish to great apes to humans. An adaptive role in host defense is suggested by its antimicrobial activity against common human pathogenic infections [29].

19.2.2 Selective Advantage in Host Defense

The evolutionary history of the *APOE* alleles points to *APOE4* as the human ancestral allele. Here, we argue that the major genetic risk factor for the late-onset

sporadic forms of AD, the *APOE4* allele, was selected across evolutionary history because of its selective advantage in host defense. The APOE protein is secreted by the liver. By its binding to the LDL receptor, APOE plays a major role in the blood transport and clearance of cholesterol and triglycerides. While APOE3 binds preferentially to the phospholipid-rich HDL, APOE4 binds the triglyceride-rich VLDL [30]. It is also important in the brain, where it is secreted by astrocytes to supply lipids to neurons. While a role for resistance to *Trypanosoma brucei* was initially suggested as a cogent example [31], a more significant selective advantage may involve resistance of *E4* carriers to the malaria plasmodia, which require host lipids for replication. Several lines of evidence support this hypothesis.

First, we consider the evolutionary history of *APOE*. Chimpanzees, our closest great ape relatives, share with human APOE4 the two arginine (R) residues 112 and 158 (Table 19.1). However, unlike humans, chimpanzees and other primates have not shown APOE isoforms. By microsatellite dating, the human *APOE3* allele with 112-cysteine emerged about 225,000 years ago (range 180,000–580,000 years ago) [32]. This range spans the emergence of anatomically modern *H. sapiens* and precedes our immigration from Africa [20]. Fossil DNA sequences of two Denisovans further show that *APOE4* existed even earlier in our genus, consistent with the earlier limit above [33]. *APOE2* appears to have arisen after *APOE3* [32]. In modern populations, *APOE3* is predominant (60–90 %), while APO4 prevalence ranks second (5–40 %) and *APOE2* is generally third (1–10 %) [34].

Second, while chimpanzees and other great apes share R112 and R158 with humans, they differ at residue 61, which is R in human (R61R) but threonine (R61T) in great apes (Table 19.1). The Mahley research group showed the critical role of R61 in lipid binding with transgenic mice, which also resemble great apes at these residues: By targeted APOE replacement of R61T, the mouse APOE protein acquired human APOE4-like lipid binding [35]. To test these ideas further, the Finch Lab made a mouse with targeted replacement of the chimpanzee *APOE* gene. Preliminary data show that chimpanzee *APOE* resembles human *APOE4* more than *APOE3* in supporting neurite outgrowth [36]. These experiments confirmed the Mahley group findings that human *APOE3* is more neurotrophic than *APOE4* by more efficient lipid delivery [37, 38]. Furthermore, we must consider other differences between human and chimpanzee *APOE*. Of the 8 residues that show evidence of positive selection in human *APOE*, half are in the lipid-binding C-terminus [39]. While *APOE4* is likely to be the human ancestral isoform, the unknown effect of

Table 19.1 Apolipoprotein E residues for contemporary human, Denisovan, and Chimpanzee alleles

	Amino acid 61	112	158
Human E2	R	C	C
Human E3	R	C	R
Human E4	R	R	R
Denisovan	R	R	R
Chimpanzee	T	R	R

C Cysteine; *R* Arginine; *T* Threonine; [33]

these other amino acid differences in lipid binding could also have influenced lipophilic steps in host defense.

Thirdly, the *APOE* alleles show regional geographic gradients. Within Europe, for example, *APOE4* shows a fourfold longitudinal cline, from 5 to 10 % below 30° latitude north [40] to 20–30 % at higher latitudes [34]. Longitudinal gradients of APOE4 are found in China [41] and India [42]. Latitudinal gradients are also seen, e.g., 41 % *APOE4* in Aka Pygmies of western Congo versus 33 % for Zairians [43].

Fourth, the *APOE4* allele is associated with resistance to certain infectious agents. A case is building for a role of *APOE* alleles in malarial resistance, because Plasmodium parasites are dependent (auxotrophic) on cholesterol as a nutrient during the blood and liver stages of replication [44]. A population from Gabon highly infected with *Plasmodium falciparum* showed evidence for an epistatic gene interaction of *APOE4* with sickle-cell hemoglobin (HbAS, malarial resistant vs. HbAA): The HbAS carriers who were also *APOE4* had a 40 % lower infection index than HbAA carriers, while *APOE3* carriers did not differ [45, 46]. In vitro, plasma from *APOE4* carriers, but not from homozygotes for the E3 allele, inhibited the growth of the parasite *P. falciparum* [47]. There is some evidence that *APOE4* carriers also have higher blood levels of IL-13 [48], a cytokine with antiparasitic activity. Moreover, *APOE4* carriers have greater induction of TNFα in response to bacterial endotoxins, suggesting greater innate immune activation [49]. Another example may be the resistance of *APOE4* carriers to progressive fibrosis in chronic hepatitis C [50, 51]. Contrarily, *APOE4* may increase susceptibility to HIV [52, 53] and herpes simplex virus [53], as discussed below.

Besides their potential roles in host defense, *APOE* alleles may also influence brain development. An MRI observational study of normal children showed that the entorhinal cortex was consistently thinner in *APOE4* versus *APOE3* carriers [54]. A thinner temporal cortex was also found in neonatal *APOE4* carriers [55]. Because of neurodegeneration in this brain region during the early stages of AD, the thinner cortex implies a smaller neuronal reserve in *APOE4* carriers. In mice transgenic for human *APOE* alleles, the E4 mice have synaptic deficits relative to E3 mice [56]. Frustratingly, we lack cell-level details for *APOE* alleles at stages of human brain development. A trade-off in *APOE4* carriers between resistance to infections and brain development is suggested for Brazilian slum children who commonly suffer diarrhea: The *APOE4* carriers had better cognitive responses to micronutrient supplementation than the *APOE3* carriers [57, 58]. Thus, under conditions of infection that differ from privileged healthier populations, the APOE4 protein could be advantageous for brain development. This association is also shown in the resistance of malnourished mice to cryptosporidial infections, a common cause of diarrhea, in which E4 mice grew best [59].

Lastly, we note a very recent report that blood progesterone levels are higher in *APOE4* carriers during the luteal phase of the ovulatory cycle [60]. The women in this study from Poland were healthy and not carrying a burden of infections. These authors proposed that the potential increase of fecundability in *APOE4* carriers because of elevated progesterone during the luteal phase represents the beneficial component in its antagonistic pleiotropy.

19.2.3 Trade-Offs from Variegated Gene Expressions as a Form of Bet-Hedging

Evolutionary biologists use the term "bet-hedging" in several different ways [61]. A simple way to think about it is the old adage "don't put all your eggs in one basket"! Our use of the term here fits best with the notion of a "probabilistic diversification of the phenotypes expressed by a single genotype" [61]. We would include stochastic variations in gene expression (transcriptional, translational or post-translational in origin) among populations of otherwise identical cell types. For example, in the *C. elegans* nematode, in which all individuals are genetically identical, individual worm-to-worm variations in expression of the heat-shock gene hsp-16.2 predicted survival over a fourfold range [62].

Martin [63] used the term "epigenetic gambling" to describe such phenomena, implying a strong conceptual bias in favor of a transcriptional origin for such variegated gene expression. Furthermore, while such bet-hedging may have evolved as an adaptive trait as it ensures phenotypes that could survive in the face of unpredictable environmental challenges, the phenomenon of "epigenetic drift" [64, 65] when extended to the post-reproductive period of the life course would partially escape the force of natural selection, thus contributing to diverse geriatric pathologies, including AD and other later-onset dementias [66] (Fig. 19.2). Such a scenario could represent the action of antagonistic pleiotropic genes. A similar role of epigenetic drift in the pathogenesis of AD was independently proposed, together with supporting data [67]. Gerontologists have become aware that stochastic events during development are important determinants of individual outcomes of aging [20, 68], but this topic remains underdeveloped in theory and experiment.

19.2.4 Mutations and Polymorphisms Which Are not Phenotypically Expressed Until the Post-reproductive Period

Peter Medawar's influential book An Unsolved Problem in Biology [69] clearly delineated this major mechanism of biological aging. However, it was J.B.S. Haldane who first developed the fundamental concept based upon Huntington's disease [70]. Haldane was puzzled by the unusual high frequency of this severe autosomal dominant disorder (about 1/18,000 in the British population). He concluded that the disease represented a late-acting mutation that had escaped the force of natural selection. Medawar elaborated upon this idea. Specifically, he hypothesized that for deleterious mutations and polymorphisms to be maintained, suppressor alleles at various loci are likely to have evolved such that deleterious mutations could partially escape the force of natural selection if the associated adverse phenotypes emerged later in life. According to Medawar, many such mutations associated with

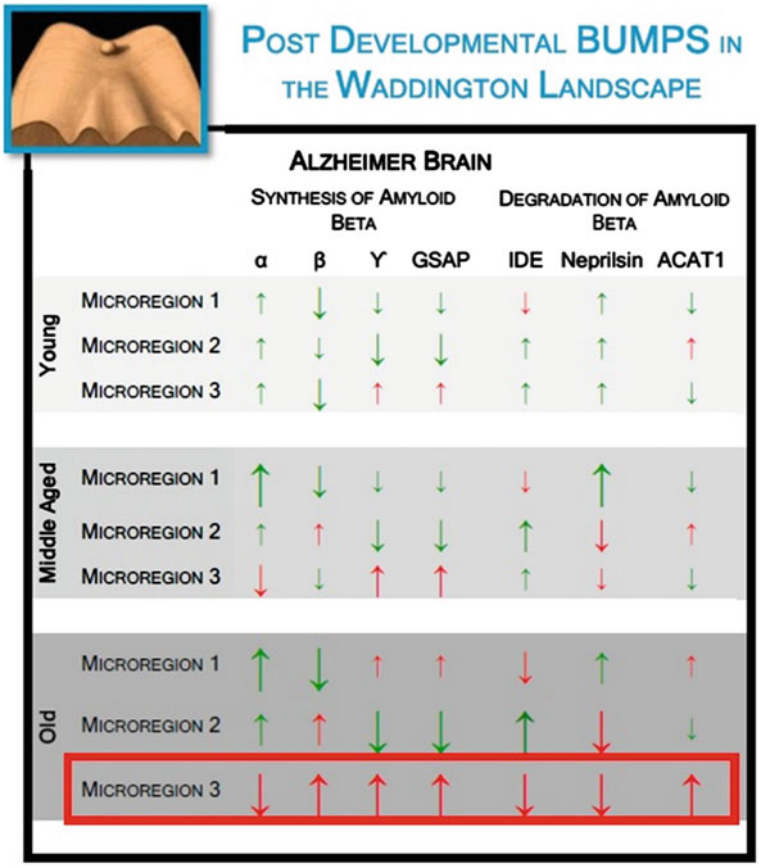

Fig. 19.2 This figure illustrates what might be described as the genesis of "A Perfect Storm" of age-related drifts in gene expression, sufficient to lead to the quasi-stochastic multifocal distributions of neuritic plaques in the hippocampus of patients with LOAD. We imagine a series of "bumps" in the Waddington landscape, which eventually become sufficient to produce localized fibrillary deposits of amyloid beta that create neuritic plaques. The left set of columns illustrate variable degrees of drift (either increased or decreased gene expression) for four loci involved in the *synthesis* of Aβ peptides, while the right set of columns illustrate variable degrees of drift for four loci involved in the *degradation* of Aβ. GSAP is a gamma secretase activating protein [110]. ACAT1 (Acyl-CoA:cholesterol acyltransferase) exemplifies how the down-regulation of an enzyme can enhance Aβ clearance via autophagy-mediated lysosomal proteolysis in microglia [111]. The diagram is an oversimplification, as other loci, including APOE, are involved. An earlier draft of this figure was published in [112]

late adverse phenotypes could collectively contribute to biological aging. This theory predicts that the patterns of mutations and phenotypes are likely to be idiosyncratic among populations, consistent with the views of geriatricians and pathologists that no two human beings age in precisely the same ways.

19.2.5 Evolutionary Biology and the Common Sporadic, Late-Onset Forms of Alzheimer's Disease (LOAD)

To varying degrees, all phenotypes are the products of diverse interactions between alleles at multiple loci (Gene × Gene) and between genes and changing environments (Gene × Environment). For complex phenotypes like AD, with its diverse spectrum of neuropathological lesions and highly variable times of onset, rates of progression, and patterns of clinical presentations, one would anticipate large numbers of genetic contributions and environmental interactions. This is particularly valid for LOAD, given the Medawar proposition of selection for suppressor loci that push the times of expression later in the life course. Indeed, large-scale genome-wide association studies (GWAS) and other emerging genomic approaches, although far from having exhausted its potential for the discovery of both rare and common variants, have already identified more than 20 loci, each with variations associated with LOAD risk. These loci can be functionally grouped as lipid metabolism, inflammation/immune response, endocytosis/intracellular trafficking, tau metabolism/microtubular structure function, synaptic plasticity, and metabolism of the β-APP [71–75].

A speculative but heuristic attempt to integrate these various discoveries in terms of evolutionary biology and antagonistic pleiotropic gene action invokes a range of host responses to challenges by infectious agents. We have outlined above our hypothesis according to which the *APOE4* allele has a protective role against pathogens, including agents that rely upon host lipids for their replication. In addition, a protective role conferred by both the immune system and the inflammatory response would seem obvious, and similarly, it could be argued that genes associated with endocytosis and intracellular trafficking have a protective role against certain intracellular pathogens. Given recent evidence for "infectious proteins" in AD [76, 77], microtubular-associated proteins such as tau could be incorporated in such a theory. The fact that different molecular forms or "strains" of tau aggregates exhibit different efficiencies of spread within the brain and that they can be transmitted via retrograde axonal transport from peripheral nerves has attracted a review by a specialty journal in virology [78].

Lastly, we note intriguing findings that the Aβ peptide, implied as a neurotoxic factor in AD, also has antimicrobial activities in vitro against Gram-negative and Gram-positive bacteria and yeast [29] and for replication of the influenza A virus [79]. As noted earlier, the Aβ42 peptide sequence is remarkably conserved in vertebrates. Because *APOE* isoforms have differential binding to APP [80], novel human *APOE* isoforms could have been selected for host defense against infections, as may have been the case for *APOE4*. We anticipate progress in the biology of *APOE* with the powerful new genomic techniques to identify novel infectious agents with the potential to cause LOAD. Indeed, a role for the herpes simplex virus in AD was suggested decades ago [81, 82] and an association with the E4 allele was shown twenty years ago [83]. Although some viruses appear to require host fatty acid synthesis, there is as yet no evidence that Herpes simplex is a lipophilic agent.

An enhanced susceptibility to AD in *APOE4* carriers might be related to a deficient delivery of lipids following neuronal damage to the host [37, 38, 84]. Another infectious candidate detected in AD brains is *Chlamydia pneumonia*, a spirochetal bacteria, which a meta-analysis associated with fourfold higher risk of AD [85]. The role of infections remains controversial in AD, as it is for atherosclerosis, where infectious agents have also been associated with arterial lesions [86].

19.3 Implications for Policy and Practice: Brain Aging Is Highly Plastic

Our discussion of evolution in brain aging and AD-like processes shows a huge range of plasticity, i.e., a dissociation from any strict clock of aging. While there is no systematic evidence to link the rates of AD-like processes to species-specific life spans, it is clear for humans that aging remains by far the major risk factor for AD. Continued research on fundamental processes of aging warrants high priority.

We anticipate that even for early-onset familial AD, there is untapped plasticity. As noted earlier, monkeys restricted to small cages exhibit higher brain amyloid burdens and less synaptic protein [13]. The restricted social interactions and limited mental challenge may be a model for the strong inverse association of AD risk with education levels [87–89]. Corresponding evidence for the impact of cognitive activity on brain structure and chemistry is emerging, based on small clinical studies from brain imaging with PiB binding. In healthy elderly, the brain Aβ load varied inversely with life-time cognitive activity by >50 %, specifically in cortical regions with multimodal nodes (lateral–medial prefrontal and parietal cortex; lateral temporal cortex) [90]. Other aspects of brain plasticity are given by Stern's analysis of cognitive reserve [91, 92].

Thus, we propose that the human environment will prove to influence most if not all risk factors for AD. Those risk factors are likely to include exposures to infectious diseases. While we have argued that *APOE4* is likely to have evolved because of the protection, it confers against certain pathogens, the evidence of an association of *APOE4* with a herpes zoster virus provides a rationale to search for pathogenetic roles for this and other viral agents using the emerging power of next-generation genome sequencing. We anticipate that new drugs such as the apoE peptide mimetics [93] will be used in concert with environmental interventions to delay the ages of onset and slow down the rates of progress to LOAD.

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Glossary

Amyloids and Aβ peptides	Amyloid refers to a large group of proteins or peptides that are rich in β-helical sheets of amino acids and are prone to form insoluble aggregates within tissues. The aggregates that are among the classical diagnostic features of Alzheimer's disease are known as Amyloid beta, or Aβ. There are several varieties, all of which are derived from a much larger precursor protein (APP, or the β-APP). The two Aβ peptides that have been most investigated are Aβ 1–40 (with forty amino acids) and Aβ 1–42 (forty-two amino acids). The name amyloid is derived from a chemical test for starch (an iodine test) used by the famous pathologist Rudolph Virchow in the mid-nineteenth century to determine the nature of waxy material he found in livers of some autopsied subjects. Virchow was prescient in using the suffix "–oid" (like starch), as this and all other types of amyloids turned out to be proteins. Amyloids, however, co-precipitate with hyaluronan sulfate proteoglycans, hence the positive iodine test!
Aging	Aging can be defined as a collection of gradual and insidious declines in multiple cellular physiological functions, which reduce responses to stress, increase the risk of chronic disease, and accelerate the probability of death during later adult ages
Amino acid residues	Proteins consist of strings of amino acids. When amino acids are linked, molecules of water are lost and the resulting amino acids are referred to as amino acid residues
APOE	This is the accepted abbreviation for a gene that codes for the apolipoprotein E protein. By convention, the abbreviations for genes are both capitalized and italicized; the related protein is also capitalized, but not italicized. Human populations have three different forms (alleles) of this gene, each differing slightly by amino acid sequence. The most common allele is E4, where E stands for epsilon. The least common allele, E2, is associated with lesser risk for Alzheimer's disease. E4 is the major risk factor for late-onset Alzheimer's disease
APP	Abbreviation for β-amyloid precursor protein (see Aβ peptides, above)

Astrocytes	The name of this major brain cell represents its typical star-like shapes. They provide neurons with lipids carried by apolipoprotein E
Entorhinal cortex	This is the part of the medial temporal cortex of the brain that connects the hippocampus to other areas of the cerebral cortex and is therefore an essential hub in the networks involved in learning and memory
Epigenetic drift	Epigenetics literally means "on top of" the genes. It involves chemical changes to the basic nucleotide base pairs of the DNA and of its associated proteins known as histones. In so doing, these chemical alterations change the expression of genes during cell differentiation and in certain pathological conditions. These chemical marks and their associate alterations in gene expression gradually change during aging, a process known as epigenetic drift
Epistatic gene interaction	Genes do not work in a vacuum. They are dependent upon interactions with other genes, variations at which can modulate the phenotype of the organism. For a fuller account of the origins and evolution of this concept, its terminology and its classifications, consult [94]
Lipid-binding terminus	Proteins and fatty substances (lipids) can be bound together in the same molecule. Characteristic sequences of amino acids have evolved to provide specificity for such interactions. These sequences can occur at different regions of the protein. For the case of apolipoprotein E (APOE), this binding occurs near the carboxyl end (C-terminus)
Neurite	A neurite is a projection from a neuron. These can be axons, the long neurites along which impulses are conducted from the cell body to other cells, or they can be dendrites, the short, branched extensions that transmit signals across the synapse
PiB	Abbreviation for Pittsburgh (Pi) Compound B, a radioactive compound related to a dye that has long been used to stain deposits of amyloid for the microscopic detection of amyloids. When used with positron emission tomography (PET scans), PiB detects deposits of amyloid in the brains of living patients and thus can help with the diagnosis of Alzheimer's disease in very early stages. Thus, PiB can also document the effects of therapies designed to reverse or slow the rate of progression of the disease

Plasticity	In evolutionary biology, plasticity usually refers to the process of one genotype leading to various phenotypes depending on the environment. A broader use has developed among biogerontologists to represent the different timing of aging processes within phylogenetic clades, as shown in Fig. 19.1
Public allele system	This term represents a polymorphic gene (one with several variants, each of which has frequencies greater that $\sim 1\ \%$) that is widely found in different human populations. Its effects upon a given phenotype are generally predictable, as in the classic example of sickle-cell hemoglobin (see trade-offs)
Selective advantage	This term applies to alleles or groups of alleles or to certain phenotypes whose gene actions lead to a greater probability of survival in a given environment
TNFα	This gene encodes a multifunctional proinflammatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily
Trade-offs	This term is used here to refer to gene actions that can exhibit differential effects on phenotypes depending upon the environment or the stage of the life cycle. A classic example is sickle-cell hemoglobin, in which heterozygotes have resistance to malaria, whereas homozygotes suffer painful tissue damage

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