she uses both hands equally well. Her patellar reflexes are present. Her pupils react. Somewhat rigid radial arteries, on auscultation no enlargement of the heart, no albumin.

During the progression of her disease, symptoms which must be considered focal in nature appear more or less clearly They are always minor. In contrast, the general loss of intellectual capacity progresses continuously. Death occurs after a four and a half year duration of the illness. The patient ended up lying in bed completely mindless, with her legs drawn up, incontinent, and suffering from decubitus in spite of diligent care.

Autopsy revealed a uniformly atrophic brain without evidence for macroscopic foci. The larger cerebral vessels show arteriosclerotic changes.

Preparations obtained by using the silver-method of Bielschowsky show peculiar changes of the neurofibrils Inside an otherwise still seemingly normal cell, one or more fibrils become more conspicuous due to their exceptional thickness and due to their exceptional stainability. During further stages, parallel arrays of these fibers show similar changes. Then they join together as dense bundles and gradually appear at the cell surface. Ultimately, the nucleus and the cell disintegrate, and only a tangled bundle of fibrils indicates the site where once the neuron had been located.

As these fibrils can be stained with other dyes than normal neurofibrils, a chemical transformation of the fibril substance must have taken place This may well be the reason why the fibrils survive the destruction of the cell. It seems that the transformation of the fibrils goes hand in hand with the storage, within the neuron, of an as yet not closely researched, pathological metabolic product Approximately one quarter to one third of all the neurons of the cerebral cortex show such alterations. Numerous neurons, especially in the upper cell layers, have totally disappeared.

Dispersed over the entire cortex, and predominantly in the upper layers, small miliary foci are found which are caused by the deposition of a peculiar substance in the cerebral cortex. This substance can already be seen without staining, but it is refractory towards staining

The glia has formed abundant fibers; in addition, many glia cells show large bags of fat.

There is not a hint of infiltration of the vessels However, the endothelial layers show proliferative changes, and at some sites one notes the formation of new vessels.

Altogether, we are obviously dealing with a peculiar disease process An increasing number of such peculiar disease processes has been noted during the past years. This observation must suggest to us that we should not be content to force any clinically ambiguous case into a category of diseases that is familiar to us There is no doubt that a greater number of mental diseases exist than is listed in our textbooks In a number of such instances, the ultimate histological examination will reveal the peculiar nature of a given case. Then we will gradually reach the stage in which we will be able to separate certain diseases from the major disease categories of our textbooks, and to delineate such diseases with much greater clinical precision.

Pathogenetic mechanisms in dementias of the Alzheimer's type

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This review addresses two of the most intellectually challenging and socially important problems of contemporary biology and medicine: 1) *Why* do aging cohorts of many populations of human beings become so extraordinarily susceptible to the set of pathologies that currently define dementias of the Alzheimer's type? 2) *How* do these lesions develop – i.e. what are the detailed mechanistic steps that lead from etiology or etiologies to phenotypic expression? A plausible answer to the first question can be provided by the current conclusions of evolutionary biologists concerning nonadaptive mechanisms for the evolution of senescence. The second question has at least a partial answer in that, in a few rare pedigrees, there is compelling evidence that a specific gene mutation, involving the β-amyloid precursor protein, is the primary cause of an early onset of the disease. Thus, we now have a metabolic pathway that serves as a working hypothesis for a candidate pathogenetic mechanism for all forms of the disorder. The major challenge is to elucidate how intrinsic biological aging impacts upon this pathway. An additional challenge is to discover environmental agents that can modulate the rates of development of specific

components of the pathology, including β-amyloidogenesis. While candidate agents include head trauma, stress, various neurotoxins and novel infectious agents, there is as yet no proof that these or other exogenous factors are of major significance.

IN developed and in developing societies, in which we are witnessing unprecedented increases in the proportions of the population over the age of 65, an 'epidemic' of a debilitating dementing illness, Alzheimer's disease (AD), is fast becoming a major public health problem all over the world. Aging is by far the most potent risk factor, resulting in exponential increases in prevalence and incidence, the rates doubling approximately every 5.1 years[1,2]. Thus, we shall have to turn to the science of gerontology in order to gain a deep understanding of pathogenetic mechanisms. In the meantime, medical geneticists have provided a powerful clue via investigations of rare familial forms of the disorder that result in comparatively early onsets of symptoms in association with what appear to be single major mutant genes inherited as autosomal dominants.

We shall begin our discussion at the most basic level, that of the evolutionary biology of aging, in order to appreciate that there is a potential role for a great variety of mutant genes in the modulation of rates of development of particular aspects of the senescent phenotype within a given species or in individual members of a species. We shall then briefly review the status of our knowledge of gene action in rare families with familial forms of the disorder. The emphasis will be upon the hypothesis that one particular metabolic pathway, that leading to altered forms of processing of the β-amyloid precursor protein (βPP) and the associated generation of deposits of β-amyloid (Aβ), may constitute the basic pathogenetic mechanism of all forms of AD. Finally, we shall consider a few broad categories of exogenous environmental agents that may interact with intrinsic genetic susceptibilities and with intrinsic biological aging processes in order to either increase or decrease the rates of progression of components of the pathology, including the deposition of Aβ.

Evolutionary biology of aging

Evolutionary biologists believe that they can provide a cogent explanation as to *why* we age, although not *how* we age [3–5]. Put in simple terms, we age because of the failure of natural selection to act upon phenotypes that predominate after the peak of reproductive activity. Thus, there is ample opportunity for many different types of constitutional mutations or allelic variations to accumulate if deleterious effects of such mutations only reach phenotypic expression postreproductively. Such mutations may have either neutral effects upon reproductive fitness or, paradoxically, even beneficial effects early in the life course, when natural selection is efficient. This latter idea has been referred to as 'antagonistic pleiotropy'[3,6]. The neuropathology of AD, as reviewed elsewhere in this issue, involves lesions that are probably only quantitatively different from what can be observed in virtually all brains of human subjects if they live well into their eighties and nineties[6–15]. Thus, the genome of *Homo sapiens* appears to harbor genetic information that eventually results in the emergence of neurofibrillary tangles, dystrophic neurites, neuritic plaques, Aβ, granulovacuolar degeneration of hippocampal pyramidal neurons, and the regional loss of neurons and of neuronal synapses. The fact that at least half of all human subjects over the age of 85 appear to escape from clinically significant degrees of cognitive decline[16] suggests that there are important nature–nurture interactions modulating the rates of development of such pathologies. Let us first consider the 'nature' (genetic) component of such potential interactions and then the 'nurture' (environmental) component.

Formal genetic analysis in familial forms of Alzheimer's disease: A brief overview

This subject has been discussed in some detail by G. D. Schellenberg in this issue. Here we give only the salient conclusions. 1) In a few rare families around the world, a single major autosomal dominant mutation at the β-amyloid precursor protein locus (APP) (localized to band 21 of the long arm of chromosome 21) appears to cosegregate with susceptibility to a comparatively early onset of AD (onset prior to age 60) (reviewed in ref. 17). Mutation at this locus can also lead to a hemorrhagic encephalopathy in a few Dutch pedigrees (reviewed in ref. 17). These subjects typically die of cerebral hemorrhages, presumably before parenchymal lesions can lead to a dementing type of illness[18]. 2) In another subset of families, the evidence being greatest for a kindred of southern Italian origin, mutation at a *different* locus on the long arm of chromosome 21, one that is closer to the centromere, appears to play a major role[19]. 3) A third potential gene mutation, localized to the long arm of chromosome 19, may have a major effect in the genesis of AD in families in which the mean onset of symptoms of AD begins after the age of 60 (ref. 20). 4) In other subsets of families with early onset disease and pedigrees that are indicative of autosomal dominant inheritance, there is strong evidence against linkage at any of the above loci (see related article by Schellenberg, this issue). Thus, even at this early stage of our knowledge of the formal genetics, it is clear that allelic variation at multiple genetic loci may play major pathogenetic roles. Given the predictions of

evolutionary theory discussed above, this conclusion is not surprising. It would be of great interest to learn if any of these mutations fall into the class of antagonistic pleiotropy – i.e. have such mutations provided some reproductive advantage to the carriers? Unfortunately, this is an exceedingly difficult question to answer.

β-Amyloid precursor proteins and their amyloidogenic derivatives

Amyloid is a generic term for a class of highly insoluble proteins that are generally detected by pathologists in extracellular locales within a variety of tissues, depending upon the type of amyloid. At the light microscopic level, they give characteristic dichroic (two color) birefringence when they are stained with the Congo red dye and examined with rotating polarized light. The textbook explanation for this physical chemical behaviour is a β-pleated sheet conformation of aggregated polypeptides[21] but this is based upon X-ray diffraction studies of dried proteins. Recent X-ray diffraction data of hydrated materials, however, suggest that this feature may not be essential[22]. The electron microscope reveals an irregular mesh of straight filaments of about 5 nanometers in diameter[23]. The deposits of aggregated amyloid polypeptides are typically associated with a variety of other molecules, including high concentrations of a glycoprotein and of certain proteoglycans[24]. The monomeric amyloid units are 39–42 amino acid proteolytic products of a large variety of larger precursor proteins[25]. For the case of the amyloid associated with AD, called β-amyloid (Aβ), the precursor is one or more of a family of isomeric proteins collectively known as β-amyloid precursor proteins (βPP). The functions of these proteins are unknown, but are clearly of fundamental importance, given the fact that homologues are widely dispersed in the animal kingdom, including even *Drosophila melanogaster*, an invertebrate[26]. The gene is expressed early in development within the nervous system[27] and may also play a trophic role[28]. The proteins are encoded by a structural gene (APP) located at chromosome band 21q21, as noted above. The several different isoforms of mRNA are the result of differential splicing of gene transcripts[29]. The three major moieties are βPP695, βPP751 and βPP770, the numbers corresponding to the numbers of constituent amino acids. The larger proteins include sequences coding for a Kunitz type acidic protease inhibitor domain[30]; they predominate in non-neuronal tissues. The major form in neurons is βPP695. Posttranslational modifications of these proteins include glycosylations, phosphorylations, and tyrosine sulphation[31–33]. The structure of the major isoforms is consistent with their categorizations as plasma cell membrane proteins, with short intracytoplasmic tails and long extracellular N-terminal segments[34]. The amyloidogenic sequence (Aβ) maps partially within the membranous domain and partially extracellularly (Figure 1). The usual mode of proteolytic cleavage clips the protein within the Aβ sequence, precluding the possibility of amyloidogenesis. The resultant secretory products include a previously described protease inhibitor, Nexin II, bearing the Kunitz type protease inhibitor domain. How then can amyloid deposits develop?

Figure 1 summarizes one plausible hypothesis. There is now evidence, both *in vitro* and *in vivo*, that alternative, minor modes of proteolytic processing are possible[35–38] (Figure 1). These appear to involve an intracellular, lysosomal pathway. Given the usual circumstances of a wild-type gene structure, normal gene dosage, normal regulatory circuitry and the absence of any unusual degree of either endogenous or exogenous agents that might upregulate levels of expression and/or

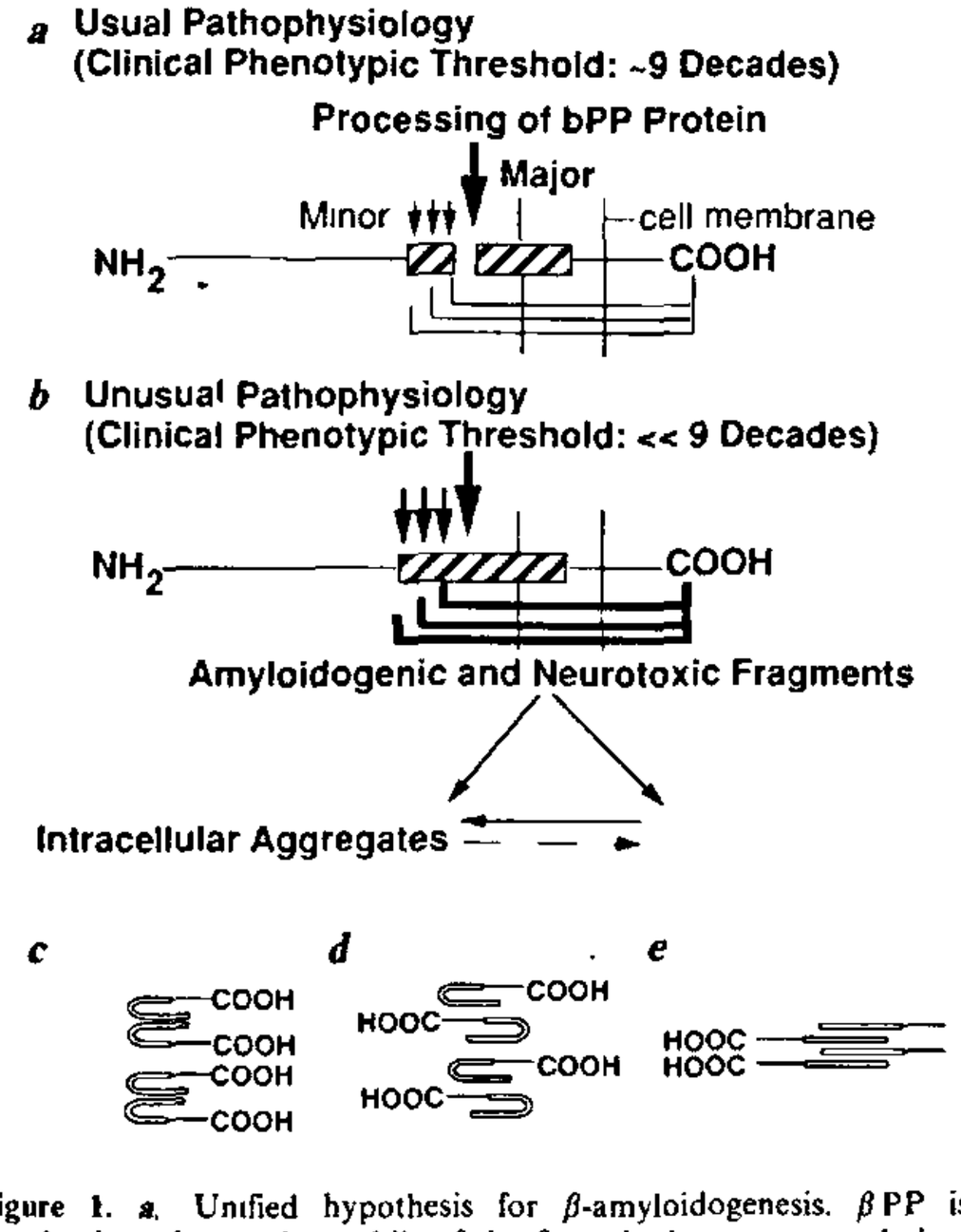

Figure 1. ***a***, Unified hypothesis for β-amyloidogenesis. βPP is mostly cleaved near the middle of the β-amyloid sequence, excluding this proteolytic pathway as a source of the β-amyloid protein. ***b***, Altered metabolism of βPP, such as the overproduction of βPP, mutation in the βPP gene, or an imbalance of proteases and protease inhibitors, may lead to an increased rate of amyloidogenic proteolysis. These amyloidogenic fragments may be associated with neurotoxicity. Our experimental results[37] suggest that C-terminal fragments of βPP are involved in the intracellular formation of amyloid protein aggregates and are associated with neurotoxicity. ***c***, ***d*** and ***e***, Three schematic models for the aggregation of the C-terminal fragments are deduced from observations in Kirschner *et al.*[66], Hilbich *et al.*[67], Dyrks *et al.*[68] and Fukuchi *et al.*[37].

influence the modes of processing, it would presumably require most of a human life span to begin to reach some phenotypic level of significance. A variety of genetic and environmental variables might alter this equation, however, resulting in higher rates of the alternative and amyloidogenic modes of processing. These could include: 1) heritable increases in gene dosage for the structural gene, as in the case of the Down syndrome (trisomy 21), in which the lesions of AD are universally detectable by the age of 40 (ref. 39); 2) mutation in the structural gene, as mentioned above; 3) mutations in regulatory domains of the gene; 4) structural, regulatory or gene dosage mutations involving the several proteases or protease inhibitors capable of influencing either major or minor modes of processing; 5) various environmental agents capable of enhancing the rates of synthesis of the precursor proteins or its modes of processing.

The above scenario is based upon the still unproven proposition that either the aggregate of Aβ, or some polypeptide associated with its development, is indeed neurotoxic. While there is good evidence that this can occur *in vitro*[37], the results of *in vivo* experiments have so far been inconsistent. These have been of several types: 1) direct injection of various amino-acid sequences[40-42] of Aβ; 2) the synthesis of neurotransplantation chimeras[43]; 3) the synthesis of transgenic mice[44-48]. It will take some time before the story becomes clarified. Of particular concern is the fact that current standard methodologies for the creation of conventional transgenic mice fail to adequately control for effects of the genetic background upon the expression of the transgene. This is because the yield of transgenics is substantially reduced if one injects DNA into zygotes derived from a single inbred genotype; the economic advantages of hybrid vigor have led investigators to inject zygotes of various F2 or F1 crosses and then to backcross to some particular genotype in order to establish a variety of transgenic founders of differing but unknown genotypes. The effects of genetic background on transcription of a transgene are now well established[49]. It is quite likely that important effects also obtain at the levels of translation and posttranslational modifications and processing, important variables in the genesis of Aβ.

The proposition that *all* forms of AD can be related to the metabolism of the βPP (Figure 1) can also be challenged. Mammalian tissues have a limited morphological repertoire of reactions to injury. It is entirely possible that a variety of different pathogenetic mechanisms can lead to what morphologically looks like AD. At this juncture, however, the most heuristic hypothesis is that of the primacy of the amyloidogenesis pathway. The discovery of mutations at the APP locus as a primary event in susceptibility to AD leads us to take such a position.

The role of the environment

All phenotypes are the result of interactions between the genotype and the environment. One should not expect the phenotype of AD to behave otherwise. Perhaps the most compelling line of evidence leading us to invoke a role for environmental factors in the pathogenesis of AD comes from studies of discordant identical twins. Cook *et al.*[50], for example, have described identical twin sisters, both of whom eventually developed AD, but with a difference of 15 years in the respective times of onset of the disease. Such a difference could reflect the stochastic nature of the underlying pathology and, indeed, of the underlying aging processes. It is even conceivable that, for the case of *female* twins, who are somatic mosaics for genes on the X chromosome, there are indeed underlying cellular genetic differences. The most reasonable hypothesis, however, is that environmental factors were responsible for the marked difference in susceptibility. What could these factors be?

First, let us consider environmental factors that could potentially modulate the metabolism of the βPP, since we have concluded above that this pathway is currently the prime candidate for a unifying pathogenetic mechanism. Given the proposition that overexpression of βPP will lead to acceleration of rates of β-amyloidogenesis, what evidence is there that environmental factors might lead to such overexpression? We should first, however, consider what might be a rational molecular basis through which such factors could operate. This leads us to a consideration of the structure and function of regulatory domains of the APP gene, about which some detailed information is only available for its promoter. The promoter includes domains that are under either positive or negative regulatory controls. Such domains include nucleotide sequences characteristic of AP-1, heat-shock factor, Sp1 and AP-4 regions[51]. One gene product that can act on a regulatory sequence to decrease gene expression has been identified as one of the mammalian homeobox genes (Hox-3.1)[52]. Thus, it seems quite likely that a complex regulatory network exists to regulate the levels of APP gene expression at the transcriptional level and that these could well include genes responsive to environmental factors. Moreover, there are likely to be mechanisms of regulation of mRNA splicing, mRNA transport, translation, modification, and turnover, all of which could, in principle, be responsive, in part, to exogenous stimuli.

One such agent may be physical trauma, particularly repetitive or chronic trauma. While still controversial, there is epidemiological evidence supporting a role for head trauma (reviewed ref. 53). More persuasive evidence, in my opinion, comes from newer histopathological evaluations of the brains of ex-boxers[54]. It now

appears that the pathology of dementia pugilistica is quite comparable to what is observed in AD. Altered hemodynamic factors may also lead to an enhanced probability of developed Aβ, since it is deposited in vascular malformations of the spinal cord and brain[55]. Given the structure of the promoter noted above, it is not surprising that another physical agent, heat shock (treatment of cultured human lymphoblastoid cell lines at 42°C for 30 min), can result in an upregulation of mRNA expression of the APP locus[56]. It is quite likely that a variety of other cell injuries may also result in such upregulation.

A number of exogenous chemical agents may act, in different ways, to enhance or to alter, for better or for worse, APP gene expression. Aluminium, long suspected as a factor in the pathogenesis of AD (reviewed in ref. 53) appears to be one of these, although there is no evidence of a dose-response relationship[57]. The drug colchicine, which inhibits axonal transport via depolymerization of microtubules, has been shown to lead to an accumulation of the βPP within neurons[58]. Chloroquine, a commonly used antimalarial agent, has been shown to inhibit the intracellular, lysosomal degradation of the mature βPP holoprotein[31]; it thus might be expected to decrease the rate of deposition of Aβ, although there is as yet no evidence that such is the case.

Does aging *per se* result in an increased expression of the APP gene? To the extent that one believes in the *in vitro* model of cellular aging, the answer appears to be a qualified yes. Human fibroblasts that have been serially passaged, with concomitant loss of proliferative potential, exhibit a higher steady state level of APP mRNA and, to some extent, an increase in protein product[59]. A number of lines of evidence point to the generality that aging is associated with a decline in protein synthesis and protein turnover, with an associated increase in a variety of posttranslationally modified proteins[60]. It remains to be seen how such metabolic changes may enhance susceptibility to the lesions of AD. This is indeed the greatest challenge for the future, since the major risk factor for the disease is intrinsic biological aging.

Turning away from the paradigm of the primacy of amyloidogenicity in the pathogenesis of AD, what other environmental modulators might be considered? Two particularly intriguing possibilities derive from the findings of behavioral neurobiologists. If one accepts the view that the most fundamental parameter leading to dementia is a loss of synaptic connectivity, then it is conceivable that environmental enrichments of synaptic networks could serve as a buffer to counter losses related to endogenous and exogenous factors. There is indeed neuroanatomical evidence in experimental rodent populations that 'rich' environments result in increased cortical thickness and, presumably, increased synaptic reserve[61]. This notion of the potential importance of variable 'reserve' function has been invoked to explain the surprising findings of subsets of older subjects with neuropathological changes of AD but who, in life, did not have dementia[62]. It might also explain epidemiological evidence pointing to protective effects of comparatively high educational levels, although it is difficult to sort out the confounding variable of such effects upon the performance of subjects on standard psychometric tests[63]. A second field of relevant behavioral research has to do with evidence that various modalities of stress may result in damage to hippocampal neurons (reviewed in ref. 64). This is thought to be mediated via the feedback of glucocorticoid hormones to hippocampal cells with appropriate receptors, and to result in cell injury via pathways related to a cell's energy metabolism. The most vulnerable hippocampal cells, however, are not those that are most vulnerable in human AD. Nevertheless, the hypothesis is currently receiving a great deal of attention and doubtlessly will undergo various refinements in the near future.

The question of the cellular and subcellular loci of activity is also a problem for an otherwise attractive environmental model of neurotoxicity. It is now well established that the ingestion of shellfish that have, in turn, fed upon particular populations of algae, can result in dramatic hippocampal pathology, with permanent loss of memory and, in some cases, death (reviewed in ref. 65). The responsible agent has been shown to be domoic acid, an analog of glutamic acid, a physiological neurotransmitter. Domoic acid is member of a family of 'excitotoxins' that produce postsynaptic lesions in subsets of vulnerable neurons. The early lesions of AD, however, are currently thought to be predominantly presynaptic and, moreover, preferentially involve different subsets of hippocampal neurons. Nevertheless, the model of environmental neurotoxins is extremely attractive and is deserving of a high priority for comparative cross-cultural research, something we hope will emerge from the present collection of papers.

Conclusions

In 1992, the simplest integrative hypothesis for the pathogenesis of AD is based upon minor modes of processing of products of the APP gene, with resulting neurotoxicity (Figure 1). In most individuals, this presumably occurs at relatively low rates, such that a phenotypic threshold for clinical AD may never be achieved, or may be achieved only after some nine decades. Earlier onsets may rarely result from a structural mutation at the APP locus or from other constitutional mutations, such as the increased gene

dosage associated with trisomy 21. Environmental agents may also play a role by either upregulating the synthetic rates of βPP or by altering processing of the protein molecules. Intrinsic differences in the 'reserve' of neurons and neuronal synapses may also determine variations in rates of achieving phenotypic expression of AD.

An alternative view is that a variety of distinct pathogenetic mechanisms can lead to the lesions of AD, with Aβ depositions as epiphenomena in a proportion of these mechanisms.

Regardless of which view prevails, the greatest challenge for the future will be to obtain a detailed understanding of the underlying molecular events of intrinsic biological aging, which appears to be the single major risk factor for the developing of Aβ and AD.

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Recognition of Alzheimer's disease as a major public health problem: An historical account of the American experience

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As late as the early 1970s, most US physicians considered Alzheimer's disease to be an esoteric neurological disorder. The American public was essentially totally unaware of its existence. Elderly individuals with cognitive impairment or senility were thought to have 'hardening of the arteries' or 'little strokes.' This view was shared by many specialists in the aging field. Fewer than a half a dozen laboratories were involved in research on Alzheimer's disease. By 1990, the situation has changed dramatically. Today, it is recognized that up to four million Americans have Alzheimer's disease and that 35–45% of those of the age of 85 are afflicted, a figure of special importance because the over-85 age group is the fastest-growing segment of the US population. The National Institutes of Health, during 1991, spent more than 230 million US dollars to fund biomedical research addressed to Alzheimer's disease. The lay organization, the Alzheimer's Association, now has over 100 chapters and many hundreds of 'support' groups. The national Alzheimer's Association itself has raised more than $18 million in 1991 to support education, care, and research in Alzheimer's disease, and a similar amount will be raised by the individual chapters. How has this remarkable change in recognition of the importance of Alzheimer's disease occurred in the United States?

Following Alzheimer's description in 1907[1] of the typical pathological changes – the brain atrophy, the neuritic plaque, the neurofibrillary tangle – in the case of a woman who died in her fifties following a several-year course of progressive memory loss, difficulty in naming, and delusions, the existence of this disorder as a presenile dementia was immediately recognized and the eponym was widely accepted. A number of cases of elderly individuals with so-called senility who had the same pathologic changes as described by Alzheimer in his presenile case were reported. But there was not unanimous agreement about the relationship of Alzheimer pathology and 'senile dementia.' In particular, other authors emphasized the occurrence of multiple strokes, particularly small strokes, in brains of older individuals who died at state hospitals in a senile condition[2], although as early as 1948, Newton[3] had noted that the clinical course of Alzheimer's disease and that of senile dementia was quite similar, but not much attention was paid to this prescient report. When I was an intern and resident in the early 1950s, the general medical teaching was that elderly demented individuals had 'hardening of the arteries', 'cerebral arteriosclerosis' and that this hardening was inevitable and that nothing could be done about it. On the other hand, Alzheimer's disease as a presenile condition was considered to be a markedly uncommon but interesting disorder that I, a neurology resident, observed from time to time on the neurology wards of my teaching hospital. This state of affairs was further abetted by the nomenclature that had been adopted by the American Psychiatric Association in 1952 in the first addition of its *Diagnostic and Statistical Manual*[4], in which dementia *in the elderly* was subsumed under the title of Organic