The Pathogenesis of Alzheimer's Disease

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Despite consensus on clinical and neuropathologic definitions of Alzheimer's disease, limited information is available on its causes and pathogenesis. Current data suggest interactions among the various possible biological and environmental influences that result in a common pathway leading to the disease. Biological influences include genetic mutations causing the disease phenotype and polymorphisms contributing to disease risk. Alterations in immune or inflammatory responses may also represent biological influences. Various environmental influences that may interact with endogenous biological factors include education, traumatic injury, oxidative stress, drugs, and hormone replacement. The author describes some recent findings that suggest possible pathogenic mechanisms, which may eventually have important treatment implications. *(J Clin Psychiatry 1998;59[suppl 9]:7–14)*

At the turn of the century, the German psychiatrist and neurologist Alois Alzheimer first described a middle-aged patient suffering from a progressive deterioration of language, memory, and behavior. After the patient's death, Alzheimer applied a new staining technique to the patient's autopsied brain tissue and showed neuropathologic features now considered pathognomonic for the disease: neurofibrillary tangles and neuritic plaques in the neocortex and other brain regions. A definite diagnosis of Alzheimer's disease[1] still can be made only by histopathologic examination of brain tissue after the patient's death.

Gradual onset and progressive decline in cognition with sparing of motor, behavioral, and sensory functions until later stages characterize the clinical course of Alzheimer's disease. Patients suffer from memory impairment in the earliest stages and have difficulty learning new information and retaining it for more than a few minutes. In more advanced stages, they have even greater difficulty learning and retrieving information. Patients also develop aphasia, apraxia, disorientation, visuospatial dysfunction, impaired judgment, behavioral disturbances such as aggression, anxiety, and agitation, and a deterioration in the ability to perform basic and instrumental activities of daily living.

Despite consensus on both clinical[2,3] and neuropathologic[4] definitions of the disease, only limited information is known about its etiology and pathogenesis. Technological advances have led to several breakthrough discoveries in recent years, particularly in the area of genetics. The underlying pathogenic mechanisms, however, are not yet defined. Methods for inferring etiology vary, and may involve neuropathologic and neurochemical observations, in vitro and animal model experiments, observations from epidemiologic case control studies, and controlled clinical trials. Disparate information and theories are sometimes posited, and the notion that Alzheimer's disease is perhaps a group of diseases[5,6] or a syndrome has been considered in order to explain the complex observations.

The various possible causes and predisposing factors probably reflect an interaction of biological and environmental influences. Examples of biological influences include genetic mutations causing the disease phenotype and polymorphisms contributing to disease risk. Alterations in immune or inflammatory responses may also represent biological influences. Various environmental influences that may interact with endogenous biological factors include education, traumatic injury, oxidative stress, drugs, and hormone replacements. In this article, I will describe some of the new findings that suggest possible pathogenic mechanisms, which may eventually lead to specific treatments.

GENETICS OF ALZHEIMER'S DISEASE

Genetic Epidemiologic Studies

Many possible risk and protective factors for Alzheimer's disease (Table 1) have been explored in epidemiologic studies, including those related to environment

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Table 1. Risk Factors and Protective Factors for Alzheimer's Disease

Status	Risk Factors	Protective Factors
Definite	Advanced age	Unknown
	Family history	
	Apolipoprotein E-4	
	Down syndrome	
Possible	Other genes	Estrogen replacement
	Head trauma	Nonsteroidal anti-inflammatory drugs
	Lower educational level	
	Depression	Antioxidants

(e.g., head trauma, heavy metal exposure), social context (e.g., depression, educational level), biology (e.g., age, hyperthyroidism), and family history (e.g., Alzheimer's disease, Parkinson's disease).[2,7] Efforts to clarify genetic heterogeneity will likely contribute to an increased understanding of the role of these risk factors. One approach to uncovering the genetic component is to assess the risk to relatives of patients with Alzheimer's disease. Family studies show that from 25% to 50% of relatives of patients with Alzheimer's disease become afflicted, compared with only about 10% for control groups.[8] Life-table methods, which take into account the late, age-dependent disease onset, have estimated risks by age 90 years ranging from 24% to 50%.[9,10]

Another way to assess the degree of genetic influence on a disease is to determine concordance rates for twins (i.e., rate that both twins are affected in a pair). One limitation of such studies is that they require longitudinal follow-up, since age at dementia onset often varies. Studies of twins with Alzheimer's disease indicate that monozygotic (identical) twins have concordance rates ranging from 40% to 50%, while dizygotic (fraternal) twins have rates ranging from 10% to 50%.[11]

Genetic Loci Identified for Alzheimer's Disease

Segregation analysis (i.e., analysis of whether a genetic marker segregates during meiosis along with a disease) of families with Alzheimer's disease further confirms a genetic component. Results are particularly informative when families are subgrouped according to mean age at onset. Early-onset families show autosomal dominant inheritance with age-dependent penetrance. For late-onset families, the pattern is more complicated: mode of inheritance is probably heterogeneous, and nongenetic factors are likely involved in the disease process.

The genetic heterogeneity referred to in Alzheimer's disease is generally at the locus level (i.e., different genes in different genomic regions), but different mutations in the same gene may also occur. As a result of the Human Genome Project, investigators have available numerous, highly polymorphic marker loci for Alzheimer's disease linkage studies. The initial genetic studies demonstrated autosomal dominant inheritance in just a few large pedigrees. These findings stimulated the search for responsible genes.

Because Down syndrome (trisomy 21) patients invariably develop Alzheimer's disease neuropathology and dementia by their 40s and the rate of Down syndrome is increased in families with Alzheimer's disease, geneticists initially focused their search on chromosome 21. Significant linkage to chromosome 21 was discovered in some early-onset families but not in others.[12,13] The excitement concerning the chromosome 21 findings grew after it was discovered that the gene coding for the amyloid precursor protein (APP) found in senile plaques was localized to the same chromosome 21 region.[14] In studies of additional families, however, APP mutations very rarely caused Alzheimer's disease. During the past few years, genetic mutations causing most cases of early-onset familial Alzheimer's disease have been identified. Most early-onset families not segregating APP mutations show mutations of a chromosome 14 gene (presenilin 1).[15] In addition, chromosome 1 mutations (presenilin 2) have been found to cause an additional form of early-onset Alzheimer's disease in families of Volga German origin.[16]

Determining genetic influences for the common late-onset Alzheimer's disease (dementia beginning after age 60) posed a challenge, since an actual genetic effect or a chance event from a common disease in large families could cause the familial aggregation of late-onset Alzheimer's disease. Such problems as diagnostic ambiguity and unclear mode of inheritance have slowed progress in this research area.

A genomic screen demonstrated evidence for linkage, association, or both for a chromosome 19 region.[17] Apolipoprotein E (APOE) became a candidate gene for susceptibility to Alzheimer's disease, in part because APOE and antisera to APOE stain senile plaques and neurofibrillary tangles.[18] Apolipoprotein E also localized to the same region of chromosome 19 identified in linkage studies.

Apolipoprotein E has 3 allelic variants (2, 3, and 4). Everyone inherits 1 allele from each parent, so that 5 genotypes are possible (2/3, 3/3, 2/4, 3/4, and 4/4). In the general population, approximately 3% of individuals have the 4/4 genotype, 20% have the 3/4 genotype, while most people have the 3/3 genotype. The APOE-4 allele increases risk and decreases age at dementia onset in a dose-related fashion; i.e., risk of Alzheimer's disease is lowest for the 3/3 genotype, higher for the 3/4 genotype, and highest for the 4/4 genotype.[19] By contrast, the APOE-2 allele may have a protective effect, so that risk of Alzheimer's disease is lower for people with the 2/3 genotype than for those with the 3/3 genotype.[20]

Many laboratories have confirmed the influence of the APOE gene on susceptibility to Alzheimer's disease.[21,22] Apolipoprotein E-4 associations have been demonstrated in late-onset familial Alzheimer's disease, but also in late-onset sporadic Alzheimer's disease (no family history). In sporadic early-onset Alzheimer's disease, APOE may have a similar effect.[23]

Genetics and Environment

Although the comparisons of Alzheimer's disease concordance rates for monozygotic and dizygotic twins suggest a genetic component for Alzheimer's disease, the 50% concordance rate in monozygotic twins also points to environmental factors. The environment may either accelerate or retard genetic expression.

An example of such an interaction has been reported for head trauma and APOE-4. Meta-analysis of epidemiologic studies of prior head trauma leading to unconsciousness for an hour or more suggests that such trauma results in a 2-fold increased risk for Alzheimer's disease. Mayeux and associates[24] found a 10-fold increased risk of head trauma in patients with Alzheimer's disease only if the patients also had at least 1 APOE-4 allele, suggesting a synergistic effect between the 2 risk factors.

Transgenic Mice

Researchers in academic centers and industry have been focusing efforts on developing new drugs to treat Alzheimer's disease. Several strategies have been used, including cholinesterase inhibition, anti-inflammation, and efforts aimed at interfering with amyloid deposition and processing. Clearly, a better understanding of the pathogenic mechanisms involved in Alzheimer's disease and neurodegeneration is needed to develop more definitive therapies.

Understanding of the pathogenesis of Alzheimer's disease would certainly be improved by the availability of a small-animal model that shows both brain degeneration characteristic of Alzheimer's disease and the accompanying memory deficits. Several groups have produced new mouse strains by introducing into the animals a mutant version of the human gene encoding the APP. Early models produced amyloid plaques without accompanying behavioral changes or the memory deficits without the accompanying plaques. Most recently, however, scientists produced a mouse strain manifesting plaques containing β-amyloid along with age-related learning and memory impairments.[25] They found a correlation between impairment in learning and memory and increased β-amyloid and senile plaque formation. Other research teams are developing mouse models using other human mutant genes, such as the presenilins. Although the model is not perfect in that it does not contain neurofibrillary tangles, it is a major improvement over previous models.

Clinical Relevance of APOE Genotyping

Comprehensive assessments of people with age-associated memory impairment may be useful in ruling out depression or dementia as a cause of the cognitive dysfunction. Use of APOE genotyping in asymptomatic persons, however, provides little useful information and is not recommended until results from further studies are available.[26] Apolipoprotein E-4 is neither necessary nor sufficient to cause Alzheimer's disease, and cognitively normal centenarians have been reported with the 4/4 genotype. Apolipoprotein E genotype results of asymptomatic persons, therefore, can be misleading. The presence of APOE-2 or APOE-3 may falsely reassure persons that they are protected against developing Alzheimer's disease, and the presence of APOE-4 may falsely alarm them that they will develop Alzheimer's disease. Instead, APOE genotyping may be useful in increasing the likelihood of a diagnosis of Alzheimer's disease if a patient already has dementia.[26]

Apolipoprotein E is probably not the only gene that increases susceptibility to late-onset Alzheimer's disease; in fact, it is estimated that the genes identified thus far account for only 50% of the genetic variability in Alzheimer's disease. Several additional genetic sources have been investigated but not confirmed as potential genetic risk factors for Alzheimer's disease, including the very low-density lipoprotein receptor,[27] α_1-antichymotrypsin,[28] and the D_2 dopamine receptor A1 allele.[29] Recent work suggests an association between the major histocompatibility complex allele HLA-A2 and age at Alzheimer's disease onset.[30]

POSSIBLE PATHOGENIC MECHANISMS

β-Amyloid

One of the major neuropathologic hallmarks of Alzheimer's disease, especially in the hippocampus and association cortex, is the amyloid plaque. β-Amyloid is a protein (39 to 43 amino acids) that aggregates into a fibrillar, β-pleated structure; it is the principal component of the amyloid plaque. Recent studies point to β-amyloid as either a cause of Alzheimer's disease or a by-product corresponding to neurodegenerative disease progression. Because β-amyloid deposition may be one of the earliest neuropathologic markers in Alzheimer's disease and related disorders such as Down syndrome,[31] such patterns of deposition preceding other disease changes suggest a causal relationship, although only indirectly. Other indirect evidence includes the finding that β-amyloid is toxic to cultured neurons.[32] Moreover, autopsy studies of patients with Alzheimer's disease and elderly controls demonstrate a high correlation between β-amyloid load in entorhinal cortex and cognitive performance prior to death.[33] Perhaps the most compelling evidence that β-amyloid represents a cause rather than an epiphenomenon of Alzheimer's disease is the finding that missense mutations in APP genes cause a rare form of early-onset familial Alzheimer's disease.[34] These results are further supported by the recent finding that APP transgenic mice develop plaques and age-related memory loss.[25] However, even this evidence does not prove causality, since some other APP-related mechanism rather than β-amyloid itself may be the critical pathogenic event.

Apolipoprotein E

The strong association of APOE-4 with risk and age at Alzheimer's disease onset suggests an APOE model to ex-

plain Alzheimer's disease pathogenesis; several such models have been described.[35–37] One model proposes that APOE seeds a reaction augmenting amyloid production, somehow stabilizes β-sheet formation, or both. The known associations of the 3 alleles suggest that APOE-4 would be the most efficient of the APOE proteins in this process. In vitro experiments are supportive of this model, but concentrations used may not be physiologically relevant.[38] An alternative model holds that APOE mediates β-amyloid clearance, and APOE-2 is more efficient than APOE-3 and APOE-4.

A third model proposed by the group that originally discovered the APOE association with Alzheimer's disease posits APOE involvement in cytoskeletal stability.[35] Tau protein binds and stabilizes microtubules, and, in this model, intraneuronal APOE-3 binds the microtubule-associated tau, which prevents the abnormal hyperphosphorylation that causes acceleration of paired helical filament formation and neurofibrillary tangle assembly. In this way, it is the ineffectiveness of APOE-4 that contributes to the APOE genetic associations in Alzheimer's disease. Such interactions between APOE and cytoskeletal proteins lead to the assumption that APOE enters the cytoplasmic compartment, is in contact with cytoplasmic proteins, and is not contained within membrane vesicles. Yet, cytoplasmic localization of APOE has not been confirmed.

Other known functions of APOE suggest additional possible interactions, such that APOE may mediate cholinergic function, immune regulation, and response to nerve injury. The precise pathogenic mechanism involving APOE is complex and remains unknown.

Presenilins

The discovery of the presenilin mutations on 2 different chromosomes (1 and 14) is certainly consistent with the viewpoint that several pathogenic mechanisms can lead to 1 common phenotype. Both protein products of the mutations contain roughly 450 amino acids, with amino acid sequences that are 67% identical and share 7 transmembrane regions. The high homology between these 2 genes is striking, and such similarities in sequence suggest similarities in function.[39] One clue to their function is the observation that cells from patients with presenilin mutations make abnormally large amounts of β-amyloid ending at residue 42.[40] Moreover, this form of β-amyloid is deposited early and selectively in the disease process and is particularly likely to aggregate into fibrils. Such findings support the view that the presenilins initiate increased β-amyloid production, which then triggers the disease process; this is the so-called "amyloid cascade hypothesis."

Immune and Inflammatory Mechanisms

Support for immune and inflammatory mechanisms in Alzheimer's disease comes from a large body of literature derived from basic scientific research. For example, amyloid plaques contain activated microglia, complement proteins, acute-phase reactants, and inflammatory cytokines, which amplify and sustain inflammatory and immune response.[41,42] Active microglia also express the major histocompatibility glycoproteins, including HLA-A, HLA-B, HLA-C, and HLA-DR.[43,44] Complement proteins may induce microglia migration and synthesis and release of such inflammatory intermediaries as interleukin-1 and prostaglandins. Neurodegeneration may result from chronic release of cytotoxic host defense factor from activated microglia. Nonsteroidal anti-inflammatory drug (NSAID) actions, including the interference with activation of complement proteins and the formation and release of chemical mediators that inhibit cyclooxygenase and prostaglandin production, may influence the inflammatory process.[45]

Many population-based, case-control, and cross-sectional studies suggest that patients taking anti-inflammatory drugs or suffering from such inflammatory diseases as arthritis have a reduced risk for developing Alzheimer's disease.[42,46] For example, McGeer and colleagues[47] reviewed hospital discharges of older patients and found that a concomitant diagnosis of rheumatoid arthritis and Alzheimer's disease occurred at a rate 6 to 12 times lower than that expected if the 2 diseases are assumed to be independent. As a result of such observations, McGeer and Rogers[48] have proposed the sustained use of NSAIDs or other anti-inflammatory agents as a potential treatment for Alzheimer's disease. Not all studies confirm an association.[49,50] For example, Sturmer and colleagues[49] found no substantial effect of aspirin use on cognitive decline, but their data were compatible with a modest benefit, especially with intermittent use. Recent reviews[46] of this literature highlight the various methodological limitations of these studies, including ascertainment biases, inadequate dosing, and sample heterogeneity, which may result in misleading conclusions regarding associations and causality. Although encouraging, such observational studies do not prove efficacy.

In an attempt to control for genetic effects, Breitner and colleagues[51,52] studied older twin pairs and siblings and found that 1 year of sustained exposure to NSAIDs had a significant preventive effect on Alzheimer's disease onset. Apolipoprotein E genotyping in these subjects revealed a trend for the greatest NSAID effect in those without APOE-4. More recently, data from the Baltimore Longitudinal Study of Aging[45] found that people with 2 or more years of NSAID use had a relative risk for Alzheimer's disease of 0.40 (95% confidence interval [CI] = 0.19 to 0.84) compared with 0.65 (95% CI = 0.33 to 0.129) for those with less than 2 years of use. No significant associations between Alzheimer's disease risk and either aspirin or acetaminophen use were found.

Cholinergic and Other Neurotransmitter Changes

Cholinergic deficits represent a key component of the Alzheimer's disease dementing process. A well-established

defect in Alzheimer's disease is the deterioration of cholinergic basocortical projections. In support of this defect are findings of reduced choline acetyltransferase activity of the cerebral cortex.[53] This enzyme is necessary to synthesize acetylcholine, the neurotransmitter thought to be critical for memory function. In addition, cholinergic cell body loss has been demonstrated in the nucleus basalis.[54] Other studies show correlations between cortical choline acetyltransferase reduction or nucleus basalis cell reduction and cortical plaque density.[55] Cognitive decline, as measured by the Blessed-Roth Dementia Rating Scale, has been shown to correlate with cholinergic deficits in Alzheimer's disease.[56] Moreover, the pharmacologic augmentation of cholinergic transmission through the inhibition of acetylcholinesterase, the enzyme that catabolizes acetylcholine, has been shown to enhance the cognitive performance of patients with Alzheimer's disease in clinical trials. Indeed, an increased cholinergic transmission resulting from available pharmacotherapy is the only approach shown to be efficacious for treatment of Alzheimer's disease symptoms.

The cholinergic system, however, is not the only neuronal system affected by Alzheimer's disease. For example, deficits in the noradrenergic system, including the nucleus locus ceruleus (LC),[57] also have been demonstrated. Patients with Alzheimer's disease and depression prior to death have significantly greater neuronal loss in the nucleus LC than nondepressed patients with Alzheimer's disease.[58] In addition, patients with Alzheimer's disease and concurrent major depression have a 10-fold norepinephrine reduction compared with nondepressed demented patients.[59] Some symptoms observed in Alzheimer's disease, therefore, may be modulated through nucleus LC function, similar to what is observed in primary depression and anxiety.

Other neurotransmitter deficits in patients with Alzheimer's disease involve the serotonergic system and include decreased serotonin and 5-hydroxyindoleacetic acid concentration in various brain regions, as well as cell loss and neurofibrillary tangles in the median raphe nuclei, perhaps also associated with depressive symptoms.[59] Finally, somatostatin, corticotropin releasing factor, and peptide Y are other reported neurotransmitter systems showing deficits in patients with Alzheimer's disease.

The observation that cholinergic mechanisms partly control APP processing suggests that cholinergically based therapeutic strategies may modify disease progression, in addition to relieving symptoms. This possibility suggests that future studies of cholinergic system enhancers might include monitoring of amyloid burden as an outcome measure. The noradrenergic or serotonergic deficits noted also suggest rationales for use of antidepressant drugs in patients with Alzheimer's disease, particularly those with symptomatic behaviors. Cholinergic deficits are clearly not the exclusive neurotransmitter alteration, but they are consistent and occur early in the disease process.

Oxidative Mechanisms

The fact that age is the major risk factor for Alzheimer's disease suggests that cellular and molecular mechanisms of normal aging may be relevant to the pathogenesis of Alzheimer's disease. The "free-radical" hypothesis posits that reactive oxygen species (ROS) accumulate in tissues and damage the major cellular components—proteins, nucleic acids, and lipids.[60] Several sources of evidence support this hypothesis. For example, various ROS and ROS-modified proteins, lipids, and DNA accumulate as a result of aging and disease, and cellular systems involved in ROS metabolism are altered. Interventions that suppress ROS accumulation, moreover, extend life span or diminish age-related functional decline of specific organ systems.[61] Other compelling evidence includes observations that dietary restriction in rodents and primates reduces oxidative stress in many organ systems and extends maximum life span.[62] Antioxidants also can increase life span in a variety of species.[60]

In Alzheimer's disease, age-associated oxidative stress and alterations in antioxidant enzyme systems are enhanced. Other evidence supports a link between alterations in APP metabolism and dysregulation of free-radical metabolism, further supporting oxidative mechanisms as a component of Alzheimer's disease pathogenesis. β-Amyloid may initiate oxidative damage to neurons, or neurons under oxidative stress may be particularly vulnerable to β-amyloid neurotoxicity.

Further evidence supporting oxidative mechanisms comes from a recent antioxidant-controlled clinical trial.[63] A study of 341 moderately impaired patients with Alzheimer's disease found that treatment with vitamin E (alpha-tocopherol) or the selective monoamine oxidase-B inhibitor selegiline (available for Parkinson's disease treatment, but also an antioxidant) showed decreased rates of functional decline compared with placebo treatment, but no evidence of improvement. Although the results are promising, methodological issues limit the degree to which they can be generalized, and additional studies are needed. It is possible, but certainly not proved, that antioxidants delay Alzheimer's disease progression. Oxidative injury is not likely to be the sole cause, but may contribute to Alzheimer's disease pathology.

Estrogen

Estrogen has numerous effects on brain function, and many of them have implications for cognitive function and Alzheimer's disease pathogenesis.[64] Estrogen receptors are present in hippocampus, a brain region involved in memory function and affected by Alzheimer's disease. Estrogen also increases choline acetyltransferase, and animal studies show that estrogen can enhance synaptogenesis in CA1 hippocampal pyramidal cells.[65] Other relevant mechanisms involving estrogen include possible reductions in β-amyloid deposition and modulation of glucose

metabolism and cerebral blood flow.[66] Observational epidemiologic studies suggest a role for the protective effects of estrogen against Alzheimer's disease,[67] and preliminary treatment studies show estrogen may reverse cognitive impairment in patients with Alzheimer's disease.[68] However, estrogen use may be associated with increased risk of breast cancer.

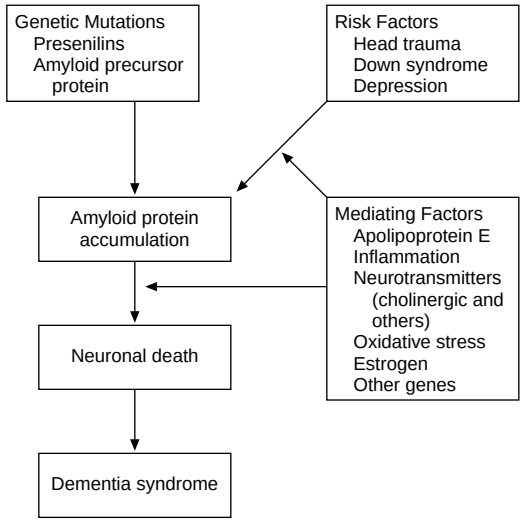
Psychosocial Risk Factors

People with lower levels of educational achievement show increased risk for developing Alzheimer's disease. Prencipe and associates[69] found in a door-to-door population survey that subjects with less than 3 years of schooling had a significantly higher prevalence of dementia (14.6%) than subjects with 3 or more years of schooling (5.9%), and the risk related to a low level of education was still present after adjustment for age and sex. By contrast, Cobb and colleagues,[70] in the Framingham Study, found that after age adjustment, low educational attainment was not a significant risk factor for the incidence of dementia generally, or of Alzheimer's disease specifically. Low educational attainment, however, was associated with increased risk of non–Alzheimer's disease dementia.

Stern and colleagues[71] studied nondemented persons aged 60 years or older over a 4-year period to estimate the relative risk of incident dementia associated with low educational and occupational attainment. Of the 593 subjects, 106 became demented, and all but 5 had Alzheimer's disease. The risk of dementia was increased in subjects with either low education or low lifetime occupational attainment. They concluded that increased educational and occupational attainment may reduce the incidence of Alzheimer's disease, either by decreasing ease of clinical detection of Alzheimer's disease or by imparting a reserve that delays the onset of clinical manifestations. This latter explanation would suggest a "use it or lose it" theory, wherein neuronal activity somehow extends neuronal survival. An alternative explanation is that education represents an epiphenomenon, i.e., a marker for some other precipitating event. For example, educated people may have less exposure to environmental toxins, which could increase risk for their dementia. The finding of Cobb and associates[70] that non–Alzheimer's disease dementia is increased in less-educated people is consistent with this latter explanation: deleterious smoking habits and other risk factors for stroke in persons with fewer years of education could increase the risk of non–Alzheimer's disease dementia.

Another possible risk for dementia is depression. Devanand and associates[72] evaluated baseline depressed mood and the incidence of dementia and Alzheimer's disease in 1070 community-dwelling elderly. Baseline depressed mood was associated with an increased incidence of dementia, an effect that remained after adjustment for other relevant variables. They concluded that depressed mood moderately increased the risk of developing dementia, primarily Alzheimer's disease.

Figure 1. Possible Pathogenic Mechanism in Alzheimer's Disease



Speck and colleagues[73] used a case-control design to assess the strength of the association between reported history of depression and onset of Alzheimer's disease. They found a modest association of depression with Alzheimer's disease. When these data were stratified by depression onset year, they observed an odds ratio of 2.0 (95% CI = 0.9 to 4.6) for depression occurring more than 10 years prior to the onset of dementia symptoms, but a lower odds ratio of 0.9 (95% CI = 0.2 to 3.0) for depression beginning within 10 years of the onset of dementia. They concluded that depressive episodes beginning years before dementia onset may increase the risk of developing Alzheimer's disease. Whether depressed mood is a very early manifestation of Alzheimer's disease or instead increases susceptibility through another mechanism is not clear. Moreover, both psychological and physiologic aspects of depression may augment the risk for Alzheimer's disease.

INTEGRATIVE THEORIES AND CONCLUSIONS

The above examples of potential risks and causes for Alzheimer's disease are just a sampling of possible contributing factors. Attempts to integrate the available, yet incomplete, information and knowledge are theoretical but useful in formulating potentially meaningful hypotheses and explanations (Figure 1). A variety of risks and causes may serve as initiating factors, including genetic mutations (presenilins, APP) and polymorphisms (APOE, HLA), head trauma, or Down syndrome. Age, in some way, then, promotes the disease process. With disease progression, neuritic plaques, neurofibrillary tangles, and

neuronal and synapse loss progress, perhaps mediated by an inflammatory response and oxidative stress. Numerous neurotransmitter systems are involved, and other factors such as estrogen exposure, education, and depression appear to contribute to the process. Clearly, the disease is heterogeneous, and uncovering various etiologies will most likely lead to a better understanding of the underlying pathogenic mechanisms. Such mechanisms, moreover, should eventually lead to specific treatments.

Drug name: selegiline (Eldepryl).

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