In 1906 a German neurologist named Alois Alzheimer recognized an early-onset form of senile dementia in one of his patients, and described a characteristic brain pathology associated with the condition. Today, two to four million Americans are affected by Alzheimer's Disease (AD), which is the fourth leading cause of death in the United States (1). AD is a complex syndrome characterized by generalized and progressive cognitive dysfunction (2). Specific clinical manifestations include short-term memory impairment, personality alteration, deterioration of abstract thinking and judgment capabilities, and attentional, linguistic, and visuospatial orientation deficiencies (3). Histopathologically, AD is characterized by the accumulation of insoluble fibrous material called amyloid b protein (Ab P) in the brain. Furthermore, specific pathological structures called neuritic plaques, neurofibrillary tangles, and neuropil threads develop inside brain neurons (4,5). These pathologies are associated especially with neocortical and limbic structures, accounting for the characteristic cognitive manifestations of the disease. There is evidence that the development of AD is both genetically and environmentally determined. Three genes have been identified which induce familial AD when they are mutated. These are called the b -amyloid precursor protein gene (APP), the presenilin 1 (PS-1) gene, and the presenilin 2 (PS-2) gene. In addition, possession of the e 4 allele of a gene called apolipoprotein E (ApoE) increases the risk of developing the disease (6). Most researchers now believe that defects in all four genes exert their pathology by the same mechanism: they elevate the production and/or deposition of amyloid b protein in brain tissue (11). (Interestingly, it has long been observed that Down's syndrome patients frequently exhibit neuropathology which is virtually identical to that observed in AD. This observation lead to the hypothesis and subsequent verification of the fact that the b -amyloid precursor protein gene is found on chromosome 21.) The only factors which are consistently associated with AD in all epidemiological studies are age and family history of dementia. Certain agents have recently been identified which may protect against the development of the disease or ameliorate its progression. These include estrogen, nonsteroidal anti-inflammatory drugs (NSAIDs), and, as discussed subsequently, antioxidants such as vitamin E (7). For instance, epidemiological studies and clinical trials demonstrate that the hormone estrogen "improves memory in both healthy women and female patients with Alzheimer's disease, and may even stave off that disease if given to women after menopause" (12). An inflammatory component of AD has also been identified. It has been demonstrated that Ab P initiates an inflammatory response by binding to surface receptors on microglia, leading to neuronal death. Preliminary research suggests that NSAIDs reduce the risk of AD (13). One AD researcher recently envisioned four possible avenues for future treatments: i) inhibitors of enzymes which cleave Ab P from its precursor, ii) inhibitors of Ab P aggregation, iii) anti-inflammatory drugs, and iv) antioxidants, calcium channel blockers, and antiapoptotic chemicals which would conceivably interrupt the pathways of neuronal damage induced by Ab P (11). Nevertheless, despite these promising possibilities, currently there is no cure nor any effective therapy for AD.

The precise biochemical mechanisms underlying neuronal damage in AD remain ambiguous. However, certain findings in pathological specimens suggest that at least a portion of the damage may be oxidative in origin. It is believed that certain neuronal regions may become selectively vulnerable to attack by highly reactive free radical molecules such as superoxide anion, hydroxyl radical, and peroxynitrite. These species are produced during mitochondrial metabolic and enzymatic activity. Their effects are normally neutralized by natural antioxidants such as vitamins C and E, uric acid, beta carotene, and bilirubin, or they are transformed by enzymes such as superoxide dismutase, peroxidase, and catalase. Oxidative damage can be especially deleterious to the lipid bilayer of cells (lipid peroxidation), but it can also affect most other proteinaceous and nucleic cellular components (8). It has been demonstrated that as brain cells age, a greater fraction of their proteins are damaged by oxidation. This effect is particularly noted in the frontal cortex, which is a susceptible region in AD. Furthermore, "Alzheimer's patients accumulate even higher levels of oxidized proteins in their frontal lobes, compared with age-matched controls" (8). Finally, it has been proposed that a variety of age-related degenerative conditions, including AD, "may be the direct upshot of oxidative damage to mitochondrial DNA" (8).

In 1996 further advances were made in elucidating the connection between AD and oxidative stress. Researchers recognized that oxidation induces free carbonyl formation from lipids, proteins, and nucleic acids, and devised a sensitive immunocytochemical technique to detect regions of carbonyl accumulation, thereby isolating areas affected by oxidative stress. The technique was performed on hippocampal brain tissue from six AD cases, three age-matched controls, and three younger controls. The AD and control samples showed significant differences. For instance, the AD samples showed carbonyl accumulation in

neuronal cytoplasm, as well as in neuronal and glial nuclei. Moreover, carbonyl accumulation was strongly detected in the AD neurofibrillary tangles, establishing a relationship between this important pathological characteristic and oxidative damage. The researchers concluded: "In Alzheimer's disease, carbonyl-reactivity is not only specifically increased in association with the neurofibrillary alterations characteristic of the disease, but also is increased in neuronal cytoplasm and glial and neuronal nuclei. This is further evidence for the notion that oxidative stress, as manifested in oxidative modifications, is associated with the pathogenesis of Alzheimer's disease" (10).

Given the apparent association between AD and cellular oxidative damage, interest has recently arisen in the hypothesis that compounds with antioxidant properties might be used therapeutically in the prevention and treatment of the disease. An antioxidant has been defined as "any substance, often an organic compound, that opposes oxidation or inhibits reactions brought about by dioxygen or peroxides" (2). Antioxidants are usually readily oxidized themselves; indeed, antioxidants usually exert protective effects by being oxidized preferentially over another substance being protected. Antioxidant substances interrupt reactions which can lead to biological damage by trapping free radical molecules.

The list of antioxidant compounds is fairly extensive, and some examples have been given previously. Vitamin C, or ascorbic acid, is an example of a water-soluble compound with antioxidant activity. Vitamin E is another of the well-known antioxidants; since it is fat-soluble, vitamin E can interact with and pass through cell membranes and effectively trap free radicals, prevent lipid peroxidation, and forestall cellular damage. Vitamin E is a fascinating substance whose chemical properties and biochemical effects are still being elucidated. It is a member of a class of compounds known as tocopherols, and another name for vitamin E is a -tocopherol. This vitamin can be found in vegetable-seed oils, meat, and dairy products (2). Vitamin E supplementation has been associated with decreased risk of cardiovascular disease and cancer (9). Research is continuing into the efficacy of vitamin E in assuaging oxidative stress. Nevertheless, the assessment of one reviewer of the relevant data is that "the knowledge available to date, largely based on animal studies and human epidemiology, suggests that tocopherols carry out essential functions in slowing or preventing degenerative disease processes" (9).

It is evident, therefore, that the pathology of AD is related to neuronal oxidative damage, and that vitamin E can function as an antioxidant and free radical scavenger. But has any research been conducted regarding the specific effect of vitamin E in AD pathology? This is a quite recent area of research, but some preliminary studies do suggest a connection. One of the first investigations of this question concluded that vitamin E does indeed protect neurons from amyloid b protein toxicity (14). This study found that at concentrations greater than 10-7 M, a specific segment of Ab P containing amino acid residues 25 through 35 killed 80% of a sympathetic nerve cell colony in 24 hours. The Ab P segment acted by enhancing glutamate toxicity in the cells. (Interestingly, however, at lower concentrations Ab P actually protected the neurons from glutamate death; that is, at lower concentrations Ab P actually has neurotrophic effects in the CNS.) When the experiment was repeated in the presence of vitamin E, the cells were "almost completely protected from peptide toxicity" (14). The authors interpret these results as supporting the hypothesis that Ab P "induces or potentiates oxidative damage occurring with the culture conditions employed and that antioxidants such as vitamin E can provide effective protection in vitro" (14). The researchers also suggested that vitamin E may slow the clinical progression of AD.

Another study completed last year arrived at similar conclusions. Eleven pairs of postmortem AD samples and control cases were matched using various parameters, and the temporal neocortices were analyzed by a chemiluminescence technique for the development of lipid peroxidation. Oxidative damage was significantly (130%) greater in the AD samples compared to the controls (15). The authors also present an interesting case study of an 85 year old AD patient who had taken vitamin E for four years before his death. When this temporal cortex tissue was subject to the chemiluminescence analysis, it showed a very slow initiation and progression of lipid peroxidation compared to controls. The study also determined that the lipophilic antioxidant butylated hydroxytoluene, which has activity similar to vitamin E, protects against in vitro lipid peroxidation. The authors believe that the presented case study "suggests that oral use of antioxidants in humans may be able to protect tissue at risk for ROS [reactive oxygen species]-associated pathology" (15).

The results of the most comprehensive clinical trial of vitamin E and AD were published last year in the New England Journal of Medicine (16). This double-blind, randomized, multicenter study consisted of 341 patients with moderate AD. Over a period of two years the patients were given the drug selegiline (a monoamine oxidase inhibitor with antioxidant activity), vitamin E (2000 IU/day), both selegiline and vitamin E, or a placebo. The primary outcome parameter was the time to death, institutionalization, severe dementia, or the loss of basic self-care capabilities. Each of the treatments resulted in longer times to primary outcome than the placebo. The vitamin E group showed a significant delay in time to institutionalization compared to the other groups. "There were also significant delays in the deterioration of the performance of activities of daily living and the need for care" (16). In short, in this particular trial, vitamin E was shown to slow the deterioration of patients with AD of moderate severity: "Our findings suggest that the use of selegiline or alpha-tocopherol may delay clinically important functional deterioration in patients with Alzheimer's disease….Both selegiline and alpha-tocopherol delay functional deterioration, particularly as reflected by the need for institutionalization, and should be considered for use in patients with moderate dementia" (16).

Much has been learned about AD since Dr. Alzheimer first described the condition over 90 years ago. But this complex disease remains quite incompletely understood, and effective therapies remain elusive. It has been shown that AD has a component of neuronal oxidative damage, and some recent and preliminary evidence suggests that vitamin E may ameliorate the progression of the disease. There is evidence that these findings have already begun to be incorporated into clinical practice. After reviewing the previously described NEJM article, Dr. Alan Adelman of the Department of Community and Family Medicine at Penn State University remarked: "I would consider trying vitamin E in patients with moderately severe AD since it can be obtained over the counter, and is relatively nontoxic and inexpensive. It is hoped that more effective agents will be developed in the years to come" (17). Only further research will be able to verify the therapeutic efficacy of vitamin E in the treatment of Alzheimer's disease.

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