Alzheimer's Disease: Advances in Theory and Treatment

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Abstract

New strategies for disease-modifying treatment of Alzheimer's Disease are being developed as a result of advances in the understanding of the pathogenesis and underlying neurodegenerative processes. Identification of the heterogenous genetics of Alzheimer's Disease has demonstrated autosomal dominant and susceptibility genes which operate in different forms of the disease. Disease-modifying treatments involve neurotrophic factors, protein-processing modulators, antioxidants, anti-inflammatories, and estrogen. Nerve growth factor improves the survival of neurons. The control of oxidative stress and destructive inflammation may decrease the rate of neurodegeneration. Modulation of protein processing has the goal of decreasing the formation of neuritic plaques and neurofibrillary tangles. Basic research and clinical trials of candidate drugs may soon lead to more effective biologically-based treatments for Alzheimer's Disease. (Alzheimer's Disease: Advances in Theory and Treatment, Clinical Project, Susan Gonzalez)
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In 1906, Alois Alzheimer described the case of a woman with progressive cognitive decline and behavioral changes which he associated with certain pathological features. On close examination of the brain, Alzheimer found dense deposits, now known as neuritic plaques. Inside the cells were twisted strands of fibers which are currently identified as neurofibrillary tangles. The findings of neuritic plaques and neurofibrillary tangles are the hallmarks of Alzheimer's Disease, a disease that is a widespread and rapidly increasing health problem. Recent advances in neuroscience provide an improved understanding of the underlying mechanisms and pathological features of AD with the goal of identifying and treating certain factors that turn on destructive processes in the brain, as manifest in neuritic plaques and neurofibrillary tangles. The National Institute on Aging (NIA) estimates that 4 million Americans have Alzheimer's disease. The disease causes 100,000 deaths per year and is the fourth leading cause of death in the U.S. (Advisory Panel on Alzheimer's Disease, 1996; Evans, 1990). The course of the disease is approximately 4-8 years from onset to death though the course can run 20 years or more (National Institute on Aging (NIA), 1995). The disease is terminal and has no known cure. Nineteen million adults report that they have a relative with the disorder, a fact which has enormous implications for family caregiving. Ten percent of the population over age 65, and between one-quarter and one-half of the U.S. population over 85 has the disease (NIA, 1995). The NIA (1995) projects that 31 million Americans will be 85 or older in the year 2050 which will lead to a three-fold increase in the number of cases of AD in the next 50
years. In terms of the economic impact, the annual cost of caring for a person with AD is approximately $35,000 per patient in the U.S. (Ernst & Hay, 1994).

Diagnosing Alzheimer’s Disease

Dementia is broadly defined as the development of multiple cognitive deficits, including memory impairment. Alzheimer’s Disease accounts for approximately 70% of the cases of dementia. The main risk factor for AD is advancing age, with a prevalence of 1% at age 60, doubling every 5 years to reach 30% to 50% by age 85 (Geldmacher & Whitehouse, 1997). The relationship of AD to age leads to the belief that if each of us lives long enough we will succumb to AD though this has not been definitively established. Physicians and family members may attribute slipping mental performance to the normal aging process (Small, 1997). The brain usually shows mild atrophy or shrinkage and there are mild changes in memory and rate of information processing. However, these changes do not have significant effects on daily functioning and are not progressive, nor are they expressed in multiple areas of cognitive deficit (Whitehouse, 1993).

Small (1997) suggests that AD is often misdiagnosed especially in the early stages which is perhaps due to a gap in our understanding of normal and abnormal aging in the brain. Geldmacher (1997) proposes that when AD is viewed as a terminal disease without a cure, there is a tendency to defer the diagnosis. The failure to diagnose AD in the early stages has important implications since treatment and management techniques to improve quality of life for the patient and family are most effective if they are started in the early stages of the disease. Biologically-based treatments have only recently been introduced so there is reason for hope
but this will rely on an accurate and timely diagnosis. It is also important to consider that an early diagnosis gives the patient an opportunity to clarify end-of-life plans while judgement and personality are largely intact.

A discussion of the differential diagnosis of AD was recently reviewed by Geldmacher and Whitenhouse (1997). Diagnosis is by exclusion of other diseases. Dementia must be differentiated from delirium and depression, while recognizing that all three disease entities can coexist (American Psychiatric Association, 1994). Dementia can be grouped into two categories: those that present with prominent motor signs such as vascular dementias and Parkinson’s disease. These are distinct from those forms that present without prominent motor signs, such as AD and Pick’s disease. Routine diagnostic steps should include a careful history, baseline and follow-up mental status screening, laboratory and imaging studies, and neuropsychological studies. Laboratory testing can reveal dementias with treatable causes such as B-12 deficiency, neurosyphilis, and hypothyroidism. There are certain tests which claim to diagnose AD in patients utilizing cerebrospinal fluid (CSF), and another in development which is a urine test (Nymox; 1997). Genetic testing is also available, but its use is controversial and raises complex ethical questions (Roses, 1997).

In distinguishing dementia from delirium and depression certain key points should be considered. Dementia is a syndrome of progressive cognitive and emotional impairment that is severe enough to interfere with daily functioning and quality of life. Delirium is an acute state of fluctuating consciousness which is most often induced by drugs, illness,
dehydration, pain, cerebral hypoperfusion and infection in the elderly (Geldmacher & Whitehouse, 1997). With depression, the patient may complain of somatic problems or cognitive difficulties. In AD, a relative is more likely to seek medical attention for the patient during an visit for a medical problem. Depression usually has a fairly well-defined onset, and the duration of depression is measured in weeks or months. Dementia has an insidious onset, and the duration is usually longer than depression, marked by plateaus in the course of progression of the illness. The clinician must distinguish pseudodementia characteristics of depression, frequently found in the elderly, from AD. With the understanding that depression and AD have frequent comorbidity, the diagnostic process can be quite complex, requiring time and multidisciplinary assessment.

Psychiatric clinical features associated with dementia include depression, delusions, hallucinations, illusions, verbal, emotional or physical outbursts, insomnia, disorientation in space, and agitation. Seizures and neurological abnormalities, such as increased muscle tone, may be present in advanced AD. It is noteworthy that the prevalence of AD is higher in patients with Parkinson’s disease and Down’s syndrome or trisomy-21 (NIA, 1995).

Pathology of Alzheimer’s Disease

Since the time of Alzheimer’s first clinical description of AD in 1906, most of the century went by with few advances in the understanding of pathology of AD. Our current understanding of AD is due in large part to the research support of the NIA AD program which began in 1978.
Treatment advances have been enabled by a better understanding of the pathology and genetics of AD.

Researchers have described a theory that AD begins in the entorhinal cortex, which is an important waystation in memory formation, and proceeds to the hippocampus, which controls memory formation (Kandel, Shwartz and Jessel, 1991; NIA, 1995). The pathology gradually spreads to other regions of the brain, particularly the cerebral cortex, which is involved in higher functions such as language and reason. In the affected areas, neurons degenerate, losing their synapses with other neurons, resulting in neuronal death. Short-term memory falters with the loss of hippocampal functioning, and higher cognitive function declines with disease progression. Each of the components involved in the neurodegenerative process are thought to have important roles in the development of the pathology of AD.

The Neuron and Neurotransmission

It has been established since the mid 1970's that levels of the neurotransmitter acetylcholine (ACTH) fall precipitously in people with AD (Davies & Maloney, 1976). Acetylcholine is used throughout the body and it is an important neurotransmitter of the hippocampus and cerebral cortex (Kandel et al. 1991). Levels of ACTH fall somewhat in normal aging, but in AD patients ACTH levels drop by approximately 90% (Davies & Maloney, 1976; Geula & Mesulam, 1994). Acetylcholine is critical in the ability to reason, and in the process of forming memories (Kandel et al. 1991). Low ACTH levels may also be implicated in behavioral disturbances associated with AD (Bodick, 1997). Treatment strategies have been developed to boost ACTH, including the two approved treatments in the U.S.
The decline of ACTH may be due in part to problems at the receptor and cell membrane level. Abnormalities have been detected in neuron membrane phospholipids which are situated next to the receptor in the cell membrane. Phospholipid abnormalities in neurons affected by AD might impair the receptor's ability to perform the critical role of neurotransmission (Horsburgh & Saitoh, 1994).

**Tau and Neurofibrillary Tangles**

There is a key protein called tau, which was only recently found to be the major component of neurofibrillary tangles inside neurons (Lee, Balin, Otvos, and Trojanowski, 1991). In healthy neurons, tau proteins form part of the microtubule system which serves to pass nutrients from the neuron body down to the ends of the axons (Kandel et al. 1991). The neurofibrillary tangles, made up of tau protein, disrupt the neuron by twisting into paired helical filaments, as in the twisting of two threads together. The physical shape and function of the neuron is distorted and the resulting collapse and cell death is a sign of AD (Kosik & Greenburg, 1994).

**Beta-Amyloid and ApolipoproteinE**

Neuritic plaques, also known as senile plaques, are composed of protein fragments, known as beta-amyloid, mixed with other proteins. Beta-amyloid is a string of approximately 40 amino acids from a larger protein called amyloid precursor protein or APP. In forming beta-amyloid, APP protrudes through the neuron membrane, and is replenished by new APP molecules formed within the cell and the beta-amyloid fragment is cleaved from APP (Kandel et al. 1991).

It is proposed that certain substances bind to the beta amyloid and
It is proposed that certain substances bind to the beta amyloid and keep it in solution, preventing it from forming plaques (Cotman & Pike, 1994). In AD, this balance is disturbed and beta-amyloid drops out of solution and forms insoluble plaques. Beta-amyloid may ultimately cause neuronal death by forming tiny channels in neuron membranes, allowing uncontrolled and lethal amounts of calcium through the membrane. In addition, it is thought to reduce choline in neurons, thereby reducing the amount of choline that is needed to synthesize acetylcholine, vital to the maintenance of cholinergic neurons (Cotman & Pike, 1994).

ApolipoproteinE (apoE) is a protein that binds to beta-amyloid. There are three known versions of the apoE gene and corresponding protein: apoE2, apoE3 and apoE4 (Evans et al., 1997). Apolipoprotein is known to be a carrier of cholesterol in the blood, but it was only recently linked to AD, specifically, the late-onset type (Corder, Sanders, and Strittmatter, 1993). ApoE3 is the most common in the general population and apoE2 the least common. ApoE4 is found in about 40% of patients with late-onset AD (Farrer et al., 1997). In AD, researchers examine how tau and beta amyloid react with apoE in each of its three forms. ApoE4 binds strongly to beta amyloid rendering it insoluble while the apoE3 protein does not. This may explain the formation of neuritic plaques (Corder et al. 1993). In addition, it appears to regulate the formation of beta-amyloid by controlling amyloid precursor protein or APP. ApoE4 is also implicated in the formation of neurofibrillary tangles by causing the distortion of the tau protein in the neuron’s microtubules (Kosik & Greenberg, 1994).
Recent discoveries of the genes involved in AD have shown that AD is a disease with heterogenous genetics (Roses, 1997). Some of these genes are mutations and are autosomal dominant, while others indicate a risk or susceptibility to AD. The defects associated with AD occur on chromosomes 1, 14, 19, and 21 with other areas under investigation. The gene on chromosome 19 indicates susceptibility to late-onset AD, a form of the disease occurring after age 65 (Post et al. 1997). Chromosome 19 produces three different versions of apoE. People who inherit two apoE4 genes from their parents are considered to be about eight times more likely to develop late-onset AD than those who inherit two apoE3 genes. ApoE2 is associated with the lowest risk of all (Farrer et al. 1997). However, one-third of the patients with AD lack apoE4 and approximately 50% of the people who are homozygous for apoE4 and survive to age 80 do not have AD (Farrer et al, 1997). While the genetic risks are known, genetic tests lack specificity and sensitivity for late-onset AD. Because it is not a consistent biological marker for late-onset AD, the National Institute of Aging and the Alzheimer’s Disease and Research Association recommend that predictive genetic tests not be used for people without symptoms (Post et al, 1997).

Three of the genes involving chromosomes 1, 14, and 21 are determinant, or autosomal dominant, and relate to early-onset familial AD or FAD. Early-onset familial AD begins in the early 40s and mid 50s and accounts for 1%-5% of all AD cases. Chromosome 14 represents most of the cases of FAD and 1 the fewest, while chromosome 21 abnormalities occur in about 5% of early-onset FAD (Lopera et al. 1997). Specific AD genes called
presenilin 1 and presenilin 2 are mapped to chromosomes 14 and 1, respectively. These mutation genes result in aberrant nucleotide sequencing. Chromosome 21 is also involved in Down’s syndrome, in a trisomy or extra version of the chromosome. Down’s syndrome patients develop plaques and tangles as they age, much like AD patients (Kandel et al. 1993; Lopera et al. 1997). As with other autosomal dominant neurodegenerative disorders, genetic counseling is an essential part of the testing program (Post et al. 1997). Since it is likely that there are autosomal dominant genes yet to be discovered, a negative screen does not mean that the mutation does not exist.

Metabolic and Brain Blood Flow Studies

Another focus of research is in metabolic studies using Positron Emission Studies (PET) that study the brain’s use of oxygen and glucose. These studies produce images that show which areas of the brain are active, i.e. utilizing oxygen and glucose. By comparing these images over time, researchers can follow the progression of the disease as glucose metabolism declines with neuronal degeneration. It is not clear if the decline in glucose metabolism leads to cell death, or the process of cell death leads to glucose metabolism decline (Rapoport & Grady, 1993).

The transport of glucose within the brain is also an area of research in AD pathology. Studies demonstrate that levels of blood glucose transporters are low in the cerebral cortex in AD (Rapoport & Grady, 1993). These regions are vital to cognition, language and reason which are gradually wiped out by the disease. Besides glucose transport, enzymes within the mitochondria may be altered in AD (Rapoport & Grady, 1993). Any problem with glucose metabolism impairs the integrity of cell
function and the cell’s ability to form neurotransmitters such as acetylcholine.

Calcium is carefully regulated in all cells (Kendal et al. 1991). Calcium channels admit specified amounts, at certain times, and proteins store or remove calcium from the cell. The cell’s response to an excitatory or activating neurotransmitter called glutamate may be altered in AD (Landfield, Thibalt, and Mazzanti, 1992). When glucose metabolism-impaired neurons are stimulated by glutamate, the neuron’s response is over-stimulated and the neuron floods itself with calcium in a state of excitotoxicity that may lead to cell death. Khachaturian (1994) proposes that after several series of biological events, the final blow to the neuron is a rise in cellular calcium levels. There may be an increase in calcium channels in AD, or a defect in the structures that store calcium or pump it out of the cell.

Other theories related to problems of brain blood flow suggest that deposits of minerals, amyloid, or cholesterol may be implicated in AD (NIA, 1995). Within this focus are studies of the condition of capillary flow through the brain. Snowdon et al. (1997) has shown that numerous small strokes or lacunar infarcts are related to the development of AD in the Nun Study, a longitudinal study of aging and AD in a population of Catholic sisters. Snowdon et al. (1997) concludes that cerebrovascular disease plays an important role in determining the presence and severity of AD. It is of note that the prevalence of both diseases increases with age. If cerebrovascular disease is a risk factor for AD, then the identification and treatment of risk factors for stroke would possibly reduce the risk for AD.
Environmental Factors

Environmental factors that contribute to the development of AD have been studied. These environmental agents include zinc, aluminum, foodborne poisons and viruses (Markesbery & Ehmann, 1994). When researchers found traces of aluminum in the brains of patients who had AD, aluminum became a target of research and controversy. The results have not been consistent or compelling and Markesbury & Ehmann (1994) suggest that high level of aluminium may be an artifact of laboratory handling of the brain specimens. Likewise, zinc levels which are either too high or too low have been studied in relation to AD, and research continues. Rare foodborne toxins leading to dementia have been traced to seeds which contain harmful amino acids found in certain legumes eaten in India, Africa and Guam (Kandel et al. 1991). These amino acids augment glutamate and cause excitotoxicity. This is not a common cause of dementia, but the reactions involved at the neuronal level could reveal important information to AD.

Risk and Protective Factors

The two known risk factors for AD are: (a) Age, with the risk of AD rising exponentially, doubling each decade after age 65; and (b) family history and genetic disposition (NIA, 1995). Possible risk factors are head injury, female gender and educational level (Gatz, Lowe & Berg, 1994). It may be that the higher rate of the disease in women may be a function of longevity (NIA, 1995). The risk of head injury seems to interact with apoE4. It is thought that the mechanism might be related to free radical damage associated with head injury, and this increases the risk of AD, though possibly only in those with apoeE4 (Corrada, Costa and
Kawas, 1997). The risk of higher educational level requires further examination as it may be an artifact related to how and who is diagnosed with AD.

Possible protective factors include long-term anti-inflammatory use, smoking, and estrogen administration (Birge, 1997; Ford, Mefouche, Friedland, and Kalariá, 1996). It is not known how anti-inflammatory and immune system alterations are involved in AD. Regarding the possible protection conferred in smoking, there may be a relation to nicotine's action as a cholinergic agonist or augmenter. It is thought that cigarette smoking, by way of increased and prolonged exposure to nicotine, increases nicotinic cholinergic receptors and compensates for the reduced number of nicotinic receptors found in AD patients on autopsy.

Women who take estrogen have a lower incidence of AD. As a clue to treatment, studies indicate that estrogen has a positive effect on cognition in both healthy women and women with AD (Birge, 1997). It has been suggested that estrogen exerts a trophic or growth effect on structures that are damaged by AD, such as the cholinergic basal forebrain and the hippocampus.

Treatment of Alzheimer's Disease

Treatment strategies for AD can be divided in two groups: those that are designed to enhance cognition but do not treat the underlying disease process, and those that have the ambitious target of disease-modification (Aisen & Davis, 1997). This division is not clear-cut, as it is uncertain which agents will ultimately modify the disease. The discussion of palliative treatments will begin with tacrine (Cognex), and donepezil (Aricept), before turning to the topic of novel compounds.
**Tacrine and Donepezil**

Tacrine (Cognex, Parke-Davis) has been approved since 1993 and donepezil (Aricept, Pfizer) was approved by the Food and Drug Administration in 1996. The focus of these drugs is in symptom reduction and facilitation of daily functioning in mild to moderate AD. Both of these drugs are cholinesterase inhibitors, acting to prevent the breakdown of acetylcholine to make up for the loss of cholinergic neurons in the AD (Geldmacher & Whitehouse, 1997). Both drugs have demonstrated improvements in cognition and overall functioning compared to placebo. Donepezil has an improved safety profile over tacrine, as tacrine is associated with a 30% risk for hepatotoxicity. Because of this, patients taking tacrine should have periodic blood tests of the liver enzyme aminotransferase or ALT (Miller, 1994).

There are different cholinesterases in the body, one is more active in the brain while another is more active in the gastrointestinal system. Tacrine acts on both while donepezil is highly specific for cholinesterase activity in the brain. This explains why tacrine is associated with higher gastrointestinal symptoms. This activity also results in a shorter half-life of tacrine, requiring a four times a day dose schedule compared to donepezil’s once-daily dose schedule (Geldmacher, 1997). Because both of these drugs are cholinesterase inhibitors, they will interfere with the activity of anticholinergic drugs. A synergistic activity would be expected with cholinergic agonists like succinlycholine-type muscle relaxers. Neither donepezil or tacrine should be used with monoamine oxidase inhibitors. Tacrine interacts with numerous drugs including cimetidine and theophylline, whereas donepezil does not significantly
interact with these drugs (Eisai Pfizer 1997; Miller, 1994).

Since neither tacrine or donepezil alters the disease process, the patient’s functioning will decline, despite treatment, as neurons continue to die. Patients and families should be counseled regarding realistic expectations and the drug’s role in improving cognition by temporarily forestalling the decline and the inevitable progression of AD. A typical response to the drug are subtle improvements in attentiveness, daily functioning, and conversational language which may help delay institutionalization. In clinical trials of tacrine, patients showed improvement on standardized assessments through the 18th-24th week, but deterioration in functioning occurred by the 30th week (Miller, 1994).

There are clinical drug trials in progress that attempt to boost available ACTH with different approaches. Some of these involve cholinergic agonist properties (arecoline and physostigmine), another compound (xanomeline) has both acetylcholine substitution and agonist properties (Asthana et al. 1996; Bodick et al. 1997). Aceyt1-L-carnitine (Alcar) may provide both nerve cell protection and cholinergic agonism (Thal et al. 1996). A Chinese herbal remedy prepared from the moss Huperzia serrata (HupA) and used traditionally for fever and inflammation is receiving attention as a treatment for AD. A derived and purified compound is available as a prescription drug for dementia in China (Skolnick, 1997). Initial studies indicate it may be more potent and more selective in the activity of aceylcholinesterase inhibition though this will require further study.

Research of Disease-Modifying Treatments

The current research of disease-modifying treatment can be divided
into 4 categories as follows: (a) Neurotrophic factors, (b) protein-processing modulators, (c) antioxidants, (d) anti-inflammatories and estrogen.

**Neurotrophic Factors**

Neurotrophic factor interventions are based on the fact that cells require certain factors for development and survival. Neurons degenerate prematurely in AD. This has led to the idea that an absence of these sustaining factors leads to cell death (Aisen & Davis, 1997). Several neurotrophic factors have been studied in animal studies and clinical trials with positive results. The most promising of these is nerve growth factor (NGF) due to its association with cholinergic neurons in the entorhinal cortex and the hippocampus (Aisen & Davis, 1997; Kendal, 1993). There are several problems with delivering the NGF to the brain as it is a relatively large molecule and thus will not pass through the blood-brain barrier. In addition, NGF may exert toxicity in other organs and cause harmful proliferation of neurological tissue.

One possible solution around the blood-brain problem may be found in the drug AIT-082. AIT-082 is an oral agent that stimulates the brain to form NGF and readily crosses the blood brain barrier (Aisen & Davis, 1997). Animal studies found that rats regenerated lesioned neurons within seven days of oral ingestion of AIT-082. Initial trials have been shown to be safe and well-tolerated in humans, according to the developer, and further human trials are being planned (Neotherapeutics, 1997). It may be possible that this approach would be effective across different models of the pathology of AD.
Protein Processing

The approach of modulating protein processing centers on the fact that the neuropathologic changes of amyloid plaques and neurofibrillary tangles are composed of protein. This area of research attempts to alter the process of pathological protein formation. Apolipoprotein precursor protein, or APP, has a critical role in AD which is highlighted by three findings: (a) AD develops at a young age in Down's syndrome and this is linked to the presence of an extra APP gene on chromosome 21; (b) the correlation between AD and APP gene mutations in familial genetic studies; and (c) AD-type neuropathology and behavior deterioration in animal models with APP mutations (Aisen & Davis, 1997).

Apolipoprotein precursor protein is not yet well understood, but it is thought that treatment interventions may be developed to regulate the generation of beta-amyloid. The goal would be to prevent the formation of amyloid plaques. Focus has been on modulating the different versions of the cleaving, or splitting, protein enzymes called secretases which are a kind of protease (Checler, 1995). These drugs, called protease inhibitors, would be designed to stop faulty protein splitting (Gandy & Greengard, 1992). The problem lies in designing protease inhibitors that would be highly specific for their targets. None are in clinical trials although this is a promising avenue of research.

There are efforts to modify the mechanisms that create the aberrant tau protein of neurofibrillary tangles. Special proteins, called kinases, that are instrumental in this process would be targeted to inhibit or reverse the process of tau formation (Lee, 1996). This area of research is also in the preclinical discovery stage.
Antioxidants

Oxidative stress occurs when highly reactive by-products of metabolism, called free radicals, are released. Free radicals are molecules with unpaired electrons. The body has a host of mechanisms to both utilize and protect itself against free radical damage (Sano et al. 1997). The vulnerability of the cell’s protein and lipid constituents to free radical damage, particularly of the cell-membrane, has been well-documented (Benzi & Moretti, 1995; Sano et al. 1997). In addition, free radicals may impair the delicate balance of calcium in the cell. Free radical damage is thought to be an underlying process of atherosclerosis and cataract formation, as well as other diseases common in advancing age. This indicates a general decrease in the body’s ability to contain free radical activity.

From the free-radical theory, it follows that antioxidant strategies may yield answers in AD. Numerous antioxidant compounds are in preclinical and clinical trials. The Alzheimer’s Disease Cooperative Study (ADCS) consortium, sponsored by the National Institute on Aging, recently completed a multi-center trial of alpha-tocopherol (vitamin E) and selegiline (Eldepryl). Results suggest that antioxidants delay the decline of the AD though the underlying pathology continues (Sano et al. 1997).

There has been popular interest in an herbal preparation of ginkgo biloba, a plant that has long been used in Chinese medicine. Ginkgo biloba has found popularity in the U.S. and Europe as a purported cognitive enhancer. Recent positive results in mild to moderate AD were reported in the Journal of the American Medical Association (Le Bars,
1997). It is possible that its beneficial effects may be due to antioxidant properties though the mechanism of action is not fully understood. As herbal preparations are very popular, it is important to ask patients and families about their use.

**Anti-Inflammatory Drugs and Estrogen**

When epidemiological studies showed some benefits of estrogen and anti-inflammatory drugs in treating AD, the National Institute of Aging launched pilot studies through the ADCS to provide additional data. Consideration of free-radicals overlaps that of the inflammatory process because free radicals are produced in the inflammatory response and some anti-inflammatories have antioxidant properties. Converging lines of evidence point to inflammatory mechanisms, including the finding that the inflammatory response may be associated with the production of beta-amyloid (Aisen & Davis, 1994). Numerous other histopathologic constituents associated with neuritic plaques also relate to the inflammatory process. One area of research focuses on interventions with glial cells as they are thought to mediate an inflammatory response that contributes to AD (Gliatech, 1997). Scientists who characterized glial cell involvement in AD have identified compounds which suppress detrimental glial cell activity. These studies are in clinical trials.

A recent study using data from the Baltimore Longitudinal Study on Aging (Stewart, Kawas, Corrada, and Metter, 1997) found that regular use of NSAIDs may reduce the risk of AD by as much as 60%. In addition to other anti-inflammatory agents, a current ADCS trial of prednisone is underway. The ADCS started with prednisone because it shows the most activity in the central nervous system over other anti-inflammatories.
If positive results are found, trials will be started in nonsteroidal anti-inflammatory (NSAIDS) which would be safer than steroids for long term use (ADSC, 1997).

Estrogen is a female hormone and it also has an important role in the brain. It is thought that estrogen is used in areas of the brain that are affected in AD, including the cerebral cortex and hippocampus. It also interacts with nerve growth factor (NGF), and promotes survival of nerve cells that use acetylcholine (Birge, 1997). With the linkage of AD to cerebral vascular disease, estrogen's role in preventing vascular disease and improving blood flow in diseased vessels provides another focus for AD research (O'Brien, 1994). It is known that estrogen, through hormone replacement therapy, is associated with reducing the risk for cerebral vascular strokes and cardiovascular disease by approximately 50% (Birge, 1997). This may relate directly to the reduced risk of AD with estrogen replacement. The research on estrogen's role in AD is still preliminary, and is offset with the knowledge that as is, estrogen would not be used in men, nor is not recommended for all post-menopausal women.

Conclusion

It is hoped that the rapid pace of research in Alzheimer's Disease will lead to the availability of disease-modifying treatments in the near future. The search for AD treatment is a long process that includes basic laboratory research and complex clinical trials. The goal of the research is to develop safe and effective treatments for AD. Patients and families await new treatment to ease the symptoms of the disease and to modify its course. For them it is an immediate concern.
The paper approaches a disease entity on the physical level of neuroscience. It is the author's view that such knowledge, paired with a therapeutic understanding of the lived experience of an individual in health and wellness is integral to nursing. The strength of nursing is found in the ability to translate into practice a holistic understanding that includes both phenomenologic and scientific knowledge. Psychiatric nursing is strengthened by advances in neuroscience as mental illness is recognized in terms of its physical reality, with the advent and development of biological treatments in psychiatric illness. This does not eclipse the importance of the nurse’s therapeutic use of self in working with the individual and family. Alzheimer’s Disease has always been treatable by way of innovative strategies aimed at preserving a sense of self in the face of disease and neurodegeneration. Oliver Sachs commented on the "neural embodiment of self" and its tenacity in the face of Alzheimer’s Disease with the idea that memories and will are embedded in the self, which has both a phenomenologic and physical reality. In this manuscript I have reviewed advances in the theory and treatment of Alzheimer’s Disease in a reductionistic exploration of the disease in terms of genetics, neurons and neurotransmitters. This is in keeping with my interest and background in drug research and development. The clinical aspect of this project involved facilitation of a caregiver support group as part of a large, multicenter study on caregiving sponsored by the National Institute on Aging and the National Institute of Nursing Research. The manuscript and clinical experience articulate my view of nursing with its foundation and strength in both science and practice.
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