Advances in Alzheimer's Disease: A Report

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Summary

Alzheimer's disease (AD) continues to present a formidable problem with many facets of the disorder largely unknown or proven. Investigations are continuing into the etiology and biochemistry of AD and possible treatments are being considered as well. This article reviews some pertinent papers presented at the fourth meeting of The International Study Group on the Pharmacology of Memory Disorders Associated with Aging held in Zurich in January, 1987. Investigators met and discussed the latest findings on Alzheimer's disease.

A report was issued previously on the Zurich III meeting held in January, 1984[6]. That conference, and the more recent Zurich IV meeting of The International Study Group on the Pharmacology of Memory Disorders Associated with Aging, focused on Alzheimer's disease (AD). Basic and clinical researchers met and discussed recent advances in AD.

The etiology of Alzheimer's disease has not yet been specifically identified; however, we do know that usually it occurs in later life but sometimes manifests in middle age. AD is characterized by progressive deterioration of memory and cognitive impairment. Neuropathological conditions appear in the brains of AD patients and show numerous neurofibrillary tangles and senile plaques. Furthermore, many large neurons are lost in the neocortex[42] and in the nucleus basalis of Meynert[44], diagonal band of Broca and medial septal nucleus. Degeneration of these cholinergic neurons, and specifically the nerve terminals, correlates with the lower levels of choline acetyltransferase (CAT), acetylcholinesterase (AChE) and acetylcholine (ACh) found in AD patients. Several review articles can be referred to for a more detailed discussion of the theoretical aspects and history of [2 3 8 12 15 18 19 20 46].

1. Advanced Nutritional Technology, Inc., Elizabeth, NJ 07207.

Etiology of Alzheimer's Disease

Epidemiologic Contributions with Emphasis on the Genetic Hypothesis (Rocca, 1987)

Epidemiologic studies have been utilized to define the etiology of clinically diagnosed AD. Host and environmental factors have been studied[36].

The first factor identified was genetics. A number of studies have indicated a significantly higher risk for AD in relatives of patients than for the general population. However, other studies have suggested that there is no genetic correlation. Furthermore, some studies have indicated an association between Alzheimer's disease and Down's syndrome. Other findings have suggested no correlation.

A second factor investigated was the immune system. A link has been demonstrated between AD and immunologic factors which has been attributed to impairment of the immune system in older individuals and the amyloid nature of senile plaques. Early studies have indicated some correlation between AD and lymphoma, lymphosarcoma, Hodgkin's disease and immune system disorders but those findings have not been replicated.

Another factor studied for association with AD was viral infection. No definitive correlation was suggested.

Toxic exposures was a fourth factor. Environmental and occupational exposures have not specifically been identified to correlate with the presence of AD.

Head trauma was a fifth factor studied. Because trauma has been known to cause neurofibrillary tangles, it was suggested as a possible association with AD. Statistically significant data to confirm the relationship has not been presented.

Data presented to date has offered potential clues to the etiology of AD. Further investigation is needed to confirm these results.

Familial Alzheimer's Disease Gene

(St. George - Hyslop et al., 1987).

Studies of Alzheimer patients have indicated that there may be a genetic basis. Several reports have been published which described pedigrees showing autosomal dominant inheritance of AD. Patients with AD in those pedigrees exhibited a strong family history of AD and did not differ significantly from cases not traced genetically with respect to features determined clinically or by laboratory or pathology.

The familial Alzheimer's disease (FAD) gene has been identified and located on chromosome 21. Alzheimer-like neuropathology has been found frequently in the brains of elderly people having trisomy 21. That finding has suggested that genetic material encoded in chromosome 21 might contribute to a critical role in AD pathogenesis and possibly be the locus of the FAD gene. A genetic map of this autosome has shown the long distal arm of chromosome 21 to be linked to FAD. Down's syndrome is characterized by triplication of this area. Because the FAD gene was found to be located in a region different from that associated with Down's syndrome, we could understand the occasional reports of trisomy 21 that were not involved with Alzheimerlike neuropathology. Further work will clear the inconsistency.

Definition of the loci for the FAD gene would provide a significant advance in the study of Alzheimer's disease. First, it would provide a means to identify individuals at risk and enable application of potential preventive and curative treatments prior to advanced degeneration from the disease. Second, characterization of a genetic origin for AD would help define its etiology and also help in identifying preventive measures and treatments for the disorder.

Neurofibrillary Tangles Labeled by Ganglioside Monoclonal Antibody A2B5

(Freyetal., 1987)

Alzheimer's disease is characterized by the degeneration of neurons and presence of neurofibrillary tangles (NFT), especially in the temporal and frontal cortex. NFT are of special interest as they are associated with the clinical severity of dementia. Furthermore, AD is characterized by loss of neuronal processes, loss of choline acetyltransferase (CAT) activity and proliferation of fibrous astrocytes. However, some ganglio-sides are known to be neurotrophic and neuritogenic, to raise CAT levels and inhibit astrocyte proliferation. Therefore, knowledge of ganglioside changes in AD is important to understand the etiology of the disease.

Techniques using monoclonal antibody and staining of tangles have demonstrated that AD seems to change the ganglioside composition of adult neurons such that the NFT share common properties with fetal neurons. The indicated ganglioside alteration in AD may be associated with neuronal degeneration. The evidence indicates that gangliosides should be studied further for their role in AD.

Other Factors: Heterogeneity — Relation to Down's Syndrome

Previously in this report, we mentioned that AD is characterized by a selective loss of cholinergic neurons in some regions of the brain, especially the projections from cholinergic cell bodies in the basal forebrain, i.e., nucleus basalis of Meynert, to the neocortex and projections from the medial septum to hippocampus. That description was reemphasized[26]. Furthermore, the specific explanation for the selective vulnerability of cholinergic neurons in Alzheimer's disease has not been demonstrated. One hypothesis has described vulnerability as the result of competition for available choline, between phospholipid metabolism in cell membrane structure and acetylcholine synthesis[45]. It has been postulated that the competition might be stimulated by inherited or acquired traits, possibly affected by age and might produce failure in synaptic transmission'and/or cell membrane repair.

Another report[30] explained that AD patients have been characterized into distinct subgroups based on qualitatively different impairment profiles. AD does not affect the total brain but instead seems to involve specific cortical and subcortical regions selectively more than other regions. AD does not produce common symptoms in *ill* patients. Acceptance of differences among patients can help in diagnosing AD and understanding concomitant anatomical and psychological changes.

Rossor[37] reported that histological and

neurochemical heterogeneity in AD had been studied. Two subgroups had been identified with significant variation in choline acetyltransferase activity, noradrenalin concentration and number of senile plaques and neurofibrillary tangles. It was indicated that further studies should continue to draw conclusions on disease heterogeneity.

Patients with Alzheimer's disease and Down's syndrome (DS) seemed to exhibit certain similarities in immunologic dysfunction, as indicated by Singh[39]. That deficit could be a possible etiology of at least one subset of AD.

Down's syndrome, a chromosomal anomaly of trisomy 21, has been shown to be a high risk factor for predisposition to AD. The DS brain contains neurofibrillary tangles and neuritic plaques also, but fewer in number than the AD brain.

Etiological factors in AD have been suggested and certainly further studies are needed to provide definitive evidence.

Biochemical Changes in Alzheimer's Disease

Neuropeptides (Beal et al, 1987).

Several different experimental approaches have been undertaken in studying the biochemical changes produced by AD. Neurotransmitter alterations is one course which has provided a good deal of information on the pathology. Earlier it was hoped and anticipated that replacement therapy would correct neurotransmitter deficiency. This has not occurred probably because of the complexity of AD.

Another abnormality found in AD is loss of neuropeptide activity in somatostatin, neuropeptide Y and substance P. Histo-chemical and immunohistochemical techniques have related neuropeptide deficits to AD pathology. Morphologic alterations of neuropeptide neurons have been identified and associated with senile plaque and neurofibrillary tangles. Somatostatin, neuropeptide Y neurons and substance P fibers were shown to be shrunken and irregular in shape. Also, cell density was reduced in some cases.

Nicotinic and Muscarinic Cholinergic Receptors (Whitehouse and Kellar, 1987). A number of neurotransmitter systems have been shown to be altered in AD. These include systems of the cholinergic forebrain, noradrenergic and serotonergic. Furthermore, several neuropeptides have been shown to be of lowered activity in AD. Abnormalities were demonstrated in somatostatin and corticotropin releasing factor as well as neuropeptide Y and substance P. However, there has not been consistency in that AD has not affected all neurons the same. Research is continuing to investigate the selective vulnerability of different neurons. In addition, it is important to better characterize anatomical, physiological and clinical conditions within each neurotransmitter system.

Loss of cortical acetylcholinesterase and also choline acetyltransferase activity in AD is known. Furthermore, reduction in cholinergic markers has been traced to neuronal dysfunction in the cholinergic basal fore-brain, including nucleus basalis of Meynert, nucleus of the diagonal band of Broca and septal nuclei. Severity of the cholinergic neuronal loss has been related to senile plaque density, increased number of neuro-fibrillary tangles and reduced number of presynaptic cholinergic markers, therefore correlated with severity of neuropathology.

Some studies have suggested that modification of the cholinergic system can produce some improvement in cognitive function[41]. In order to evaluate cholinergic pathology in Alzheimer's disease, it is important to characterize the changes in cholinergic receptors. Changes in muscarinic receptors have not been demonstrated consistently due to the complexity of different subtypes of these receptors. Whitehouse has demonstrated more consistent abnormalities in nicotinic receptors. These changes have been shown also in Parkinson's disease.

AD is known to affect multiple neuronal systems. It is important to identify the neuronal populations affected by the disease and also the pathological neurochemical changes in neurotransmitter systems. An understanding of receptor changes will provide clues to potential therapies.

Phosphatidylcholine as a Precursor of Choline (Blusztajn et al , 1987).

The selective vulnerability of specific cho-linergic neurons located in the brain has been reported to occur in AD[8]. The finding has suggested that these neurons may utilize

choline as a precursor to the neurotransmitter acetylcholine and also as a constituent of the phospholipids found in cell membrane, i.e., phosphatidylcholine (PC). Continuous utilization of choline from the diet for acetylcholine synthesis or inadequate dietary intake will result in choline being split off from PC in cell membrane. This can result in membrane function impairment followed by cell degeneration and death if adequate choline stores are not provided.

It has been shown that long-axon cholinergic neurons which originate in the basal forebrain and project to the neocortex and hippocampus are altered in AD, at their neuronal terminals. This has resulted in cholinergic transmission impairment in the brain, evidenced by cognitive dysfunction. From these reports and data, AD is being studied vis-a-vis etiology, pathology and treatment.

The current study followed the path that all cells have the ability to synthesize PC and incorporate it as a component of the cell membrane. Cholinergic neurons also use their membrane PC as a source of choline for synthesis of acetylcholine. If supplies of free choline (such as from the diet) are inadequate to maintain proper acetylcholine levels, then cholinergic neurons seem to draw on PC in their membranes. That alters the membrane phospholipid composition and can lead to neuronal loss of activity and even death. The degradation process has been called "auto-cannabalism". On the other hand, administration of supplemental choline (or PC) to AD patients may enhance acetylcholine synthesis and provide proper membrane composition of phospholipids. This can possibly slow the disease process and correct deficits in brain functions.

Dietary Choline and Phosphatidylcholine Induces Dendritic Growth

(Mervis et al, 1987).

It has been demonstrated that the cholinergic system is impaired in memory dysfunction associated with old age and also in AD[2]. These findings have suggested that dietary choline may be of therapeutic value. The rationale for choline therapy is twofold; first, as a precursor for synthesis of the neurotransmitter acetylcholine and second, in phospholipid synthesis and replacement for neuronal membrane integrity[8] [33]. Supplementation with PC provides this second important role in maintaining the composition and fluidity of neuronal membranes by providing the structural component of the membrane and which can also be used as a source of choline for acetylcholine synthesis thus preventing PC depletion from the membranes. Over the years of investigations, choline has been provided either as choline chloride or phosphatidylcholine (PC) from lecithin.

There are some age-related membrane lipid changes which can cause loss of neuronal function and cell death. In this regard, the present study was initiated to examine the effect of choline supplementation on dendritic branching in neurons of the aging mouse neocortex.

The choline-enriched diets contained either 4.8 mg choline/g of chow or 10.8 mg/g chow compared to the control diet of 2.3 mg/g chow. Enrichment was accomplished using 95% PC from lecithin. The study was conducted based on feeding for 11 months. Results indicated that the choline-enriched diets repressed or reversed the trend towards normal age-related loss of dendritic branching by inducing new dendritic growth. The diets exhibited a dose-response relationship.

Increases in the Concentration of Brain Nicotinic Receptors by Dietary Choline

(Morley and Garner, 1987).

Study of the effects of dietary choline on nicotinic cholinergic receptors (nAChRs) in rats found that dietary choline increased the number of nAChRs. The increase was shown to occur quickly within 24 hours, with age and dose dependency. Furthermore, withdrawal of choline supplementation resulted in a decrease in number of nAChRs. The increase in nAChRs with choline supplementation seemed to be dependent on a high-affinity choline uptake system. Choline was supplied as choline chloride 7.5 mg/kg/day.

Studies such as this will provide information to help understand AD. Supplementation with dietary choline alone has not been very successful in treating AD patients. This can be explained as dietary choline by itself may not be utilized by the brain in activation of existing cholinergic receptors because choline uptake is retarded in AD. However,

other treatments such as drugs not dependent on choline uptake might be effective, and perhaps even more effective in combination with choline supplementation.

Aluminum, Alzheimer's Disease and Neurofibrillary Tangles
(Perl and Good, 1987).

The neurofibrillary tangle seems to represent neuronal reaction to injury which may be initiated by genetic, metabolic, toxic, infectious or immunologic factors. Some data has indicated that accumulation of aluminum is related to formation of neurofibrillary tangles. More research is needed as little is known of the relationship between long-term aluminum exposure and AD.

Platelet Membrane Changes
(Brammer et al , 1987).

Membrane microviscosity and phospholipid composition of platelets from AD patients have been studied. This group was compared to multi-infarct demented patients and healthy controls. Membrane microviscosity was reduced significantly in the Alzheimer group as compared to the others. No significant difference in phospholipid composition was noted.

Platelet membrane changes can be useful as possible peripheral markers for AD, if correlation can be established. Changes in membrane fluidity, for example, may illustrate effects on membrane function such as ligand-receptor binding and secretory activity.

Potential Treatments for Alzheimer's Disease

Nerve Growth Factor
(Hefti and Will, 1987).

Studies have shown that nerve growth factor (NGF) behaves as a neurotrophic factor for cholinergic neurons in the mammalian forebrain. NGF receptors are located on these neurons. NGF is known to affect forebrain cholinergic neurons in supporting survival, fiber elongation and expression of transmitter enzymes. Therefore, NGF is investigated as a treatment to relieve the loss of cholinergic neuronal activity as in AD.

We say that growth and survival of developing neurons are influenced by what are called "neurotrophic factors". NGF represents a protein of specific amino acid sequence and structure and whose gene has been identified. Other neurotrophic factors have been identified and characterized also. Proper neuronal development, differentiation and maintenance of function require specific neurotrophic factors. NGF appears to act as a neurotrophic factor for basal forebrain cholinergic neurons.

Furthermore, studies have indicated that NGF can reduce lesion-induced degeneration of basal forebrain cholinergic neurons. As AD is related to loss of activity in these neurons, NGF may have a relationship to AD. Decrease in cholinergic activity has been correlated to the intensity of plaques and clinical demonstration of dementia.

Intracerebroventricular Cholinergic Drug Administration (Harbaugh, 1987).

Intracerebroventricular (ICV) cholinergic drug infusion in AD patients is presented as a potential therapy. A double-blind, placebo-controlled crossover study showed significant improvement, during drug infusion, in some neuropsychological tests. However, clinical application still has not been determined. Another double-blind study is in progress to evaluate daily living activities and neuropsychological tests in order to elaborate upon the possibility of this treatment in AD, to study safety and efficacy. The drug being utilized is bethanechol chloride.

The therapeutic system being investigated incorporates several factors to be considered. For ICV drug infusion, there must be understanding of surgical technique, methods of tissue diagnosis, drug selection criteria and mechanism for the implantable infusion system and neurosurgical catheter placement. This treatment scheme can surmount some problems faced with delivering drugs to the brain. By infusing drugs directly into the cerebrospinal fluid, certain problems are overcome such as systemic drug side effects, peripheral drug Inactivation, poor absorption, protein binding and interference, poor blood-brain barrier crossover and poor patient compliance. However, there are risks to overcome which include hemorrhage, infection and neurotoxicity.

This system offers potential as an improved method of administration for drugs

that are effective in treating AD. Cholinergic replacement therapy seems to be the best course to follow at the current time but there are not many cholinomimetic drugs available presently.

Oral Administration of Highly Purified Phosphatidylcholine (PC) in Capsules
(Lopez and Berry, 1987).

Highly purified PC was given orally in softgels* (soft gelatin capsules) to study the effects on levels of plasma choline. Doses were 3, 6, 9 and 18 grams of PC. It was demonstrated that a 9 g dose would double plasma choline levels after 2 hours.

It was demonstrated previously that dietary intake of choline, precursor to the neurotransmitter acetylcholine, increases brain choline content and release of acetylcholine[10 11 18 20 24 25 47]. Furthermore, increased blood choline levels can influence brain PC synthesis and enhance the structural integrity of neuronal membranes. Oral administration of highly purified PC may reduce the abnormal movements seen in tardive dyskinesia, as evidenced in studies using less pure PC — the early investigations being reported by Growdon et al[19] and Davis[13 14].

Although dose response studies have not been performed to determine the ideal dosage regimen for phosphatidylcholine, it is generally agreed upon that doubling of blood choline levels can be significant in treatment for tardive dyskinesia. The same application is considered for other cholinergic disorders such as AD.

Use of Oral Tetrahydroaminoacridine
(Summers et al, 1987).

This program administered tetrahydro-aminoacridine (THA), a centrally active anticholinesterase, to 17 AD patients with moderate to severe conditions[41]. All subjects were requested to follow dietary supplementation with commercial lecithin at 9 or more capsules of 1200 mg, or their equivalent, daily. In the first phase of the study which was non-blinded, significant improvement was noted in subjects who received THA based on global assessment, Orientation Test and Names Learning Test. Dosage was 25 mg for the first day, increased to a peak dose of 150-200 mg over 7-10 days. The second phase covered 14 subjects in a double-blind, placebo-controlled cross-over study. Again, patients receiving the drug showed significant improvement as in the three tests above and, additionally, the Alzheimer's Deficit Scale. The optimal dosage determined in phase I was administered for 3 weeks. The third phase is continuing with long-term administration of the optimal dose THA determined in phases I and II on 12 subjects. The average length of treatment reported was 12.6 months with symptomatic improvements and no serious side effects noted.

These data suggest that THA may be helpful in long-term treatment of AD. Studies are continuing to confirm these observations.

Noradrenergic Mechanism in Cognitive Decline
(Arnsten and Goldman-Rakic, 1987).

Clonidine, an alpha-2 agonist, was shown to improve spatial working memory performance. Data indicated improvement in 13/13 old rhesus monkeys with demonstrated memory impairment. The response seemed to occur at post-synaptic alpha-2 receptors in the cortical area responsible for spatial working memory, the principal sulcal cortex. It may be concluded that noradrenergic mechanisms are important to frontal association cortex function and that alpha-2 agonists may help restore this activity in AD patients with norepinephrine loss.

Failure of Long-Term High-Dose Lecithin
(Heymanetal, 1987).

A double-blind trial of lecithin (PC) therapy in early AD was conducted. The study ran for 5 months on 16 patients with 21 placebos of 9 g** twice daily. It was expected that the treatment would retard the clinical and neuropsychological indications of AD. Lecithin (PC) treatment re-sulted in an increased mean plasma choline level from 15.9 baseline to 28.8 nmol/ml. Data indicated that 6 lecithin-treatment patients were stable or improved as compared to 12 of the placebo patients. Conclusion

* Each softgel (soft gelatin capsule) contains 900 mg pure phosphatidylcholine.

** PC administered was greater than 90% purity.

of this study was that lecithin (PC) alone showed no significant therapeutic effect in early AD.

A number of similar studies have been reported previously, some with improvement in some patients[27] [28] [43]. Problems have been the methods of patient evaluation, purity of lecithin (PC) used, dosage and duration of treatment, compliance and differentiation between early-onset or late, senile form of AD.

Study with Oxiracetam

(Bergamasco et al, 1987).

Oxiracetam, a cognition enhancer, was studied in 30 patients with cognitive disturbance possibly caused by benign senescent forgetfulness or to early dementia. Treatment was 800 mg oid or placebo for four weeks following a double-blind protocol.

Significant improvement was noted after oxiracetam but not placebo using the Gibson Test and Toulouse-Pierron Test. There were few, if any, and inconsequential side effects.

Further trials should be done.

A Novel Ml Agonist

(Fisher et al, 1987).

A novel selective muscarinic agonist called AF102B was synthesized. The drug was studied in rodents and showed no adverse side effects in doses approaching lethal regimens. In the studies performed, drug AF102B reversed cognitive impairment using the AF64A-treated rat, an animal model that mimics cholinergic hypofunction in AD. Furthermore, AF102B seems to offer a broader therapeutic window than does phy-sostigmine. Additional studies are continuing on the drug.

Currently available cholinergic compounds have several limitations including short duration of action, pronounced side effects and narrow therapeutic index. An ideal muscarinic agonist to be used in AD treatment should exhibit cognitive function synapse selectivity, long duration of action, wide therapeutic index, flow across the blood-brain barrier, limited or no side effects and minimal tolerance under chronic administration.

Considerations for the Future

Continued research on Alzheimer's disease is necessary to study and evaluate etiology, biochemistry and treatment programs. The most promising avenue to date has been evaluation of the cholinergic system, which is the neurotransmitter system affected most in dementias, including AD. This "cholinergic hypothesis of geriatric memory dysfunction" has created a battery of potential therapies[2]. The theory of "auto-cannabal-ism" has suggested the importance of phosphatidylcholine as a source of choline in synthesis of the neurotransmitter acetylcholine and as a phospholipid integral to membrane structure for proper membrane function and cell integrity — also important for cholinergic system function[8]. A promising need is for a cholinergic agonist that crosses the blood-brain barrier and interacts with postsynaptic receptors, perhaps with concomitant phosphatidylcholine administration.

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