

**A REVIEW ON ALZHEIMER'S DISEASE (A. D.)**

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**ABSTRACT**

Major depression in late life and Alzheimer's disease (AD) are disorders of enormous and increasing public health significance. In addition to early physical and intellectual challenges, individuals with Down syndrome are at a high risk for developing the symptoms characteristic of Alzheimer's. People with Down syndrome develop the two hallmarks of Alzheimer's disease amyloid plaques and tau tangles in their 30s and 40s. Due to improved clinical care, people with Down syndrome are now regularly living into their sixth decade of life, causing many to develop dementia due to Alzheimer's. The high incidence of the symptoms characteristic of Alzheimer's in people with Down syndrome is thought to be due to the extra copy of chromosome 21, which contains the gene that encodes the amyloid precursor protein (APP). APP is cleaved to form the amyloid-beta peptide; the primary component of plaques. It has been presumed that the extra copy of the gene produces an abnormally high amount of amyloid-beta. The cholinergic hypothesis was initially presented over 20 years ago and suggests that a dysfunction of acetylcholine containing neurons in the brain contributes substantially to the cognitive decline observed in those with advanced age and Alzheimer's disease (AD).

**KEY WORDS:** Down syndrome, amyloid plaques and tau tangles, tretment.

**INTRODUCTION:**

Alzheimer's disease, the most common form of dementia characterized by widespread loss of brain cells called neurons, is a complex, multifactorial, progressive, neurodegenerative disease primarily affecting the elderly population is estimated to account for 50.60% of dementia cases in persons over 65 years of age. The disease is

characterized by loss of memory and impairment of multiple cognitive and emotional functions. Pharmacotherapy is focussed on symptomatic benefit and slowing disease progression, but a number of possible disease modifying and preventive strategies based on current understanding of AD pathophysiology are under investigation.<sup>[1-5]</sup>

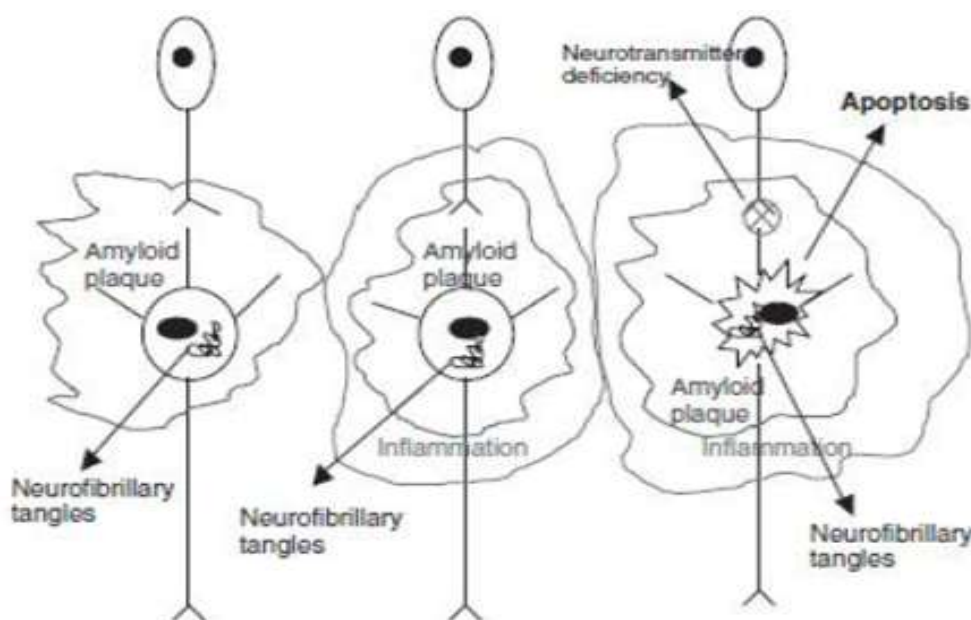


fig.1. neuronal changes in A.D.

Abnormal processing and extracellular deposition of A $\beta$  (1-42), a proteolytic derivative of the larger amyloid precursor protein (APP) is a key step in the pathogenesis of Alzheimer's disease<sup>[6]</sup>. The current therapeutic efforts are directed towards developing drugs that reduce A $\beta$  burden or toxicity by inhibiting its production, aggregation or misfolding, toxicity, A $\beta$ -metal interactions or by promoting A $\beta$  clearance by neutralizing or removing the toxic aggregate or misfolded forms of these proteins<sup>[7,8]</sup>. Also immunization with A $\beta$  (1-42) has been shown to decrease brain A $\beta$  deposition and improve cognitive performance in the transgenic mouse models of AD<sup>[9]</sup>. India has the traditional Ayurvedic system of medicine in which a number of plants are used for the treatment of variety of diseases. Over the last 4000 years, Ayurvedic medical practitioners across India have been using some of the plants which are classified as "medhyarasayanas" or nootropic cerebral activators for treating disorders of the central nervous system (CNS) and also to improve the memory and intellect. While pharmaceutical companies continue to invest enormous funding and time on identifying agents that could be useful for treating AD, these Ayurvedic phytochemicals would appear to have significant benefits without causing any side effects that have yet to be fully exploited. Experimenting with novel therapeutic molecules becomes relevant and this study is an attempt to shortlist a few plant based compounds which might interfere with the disease pathology either by preventing or slowing the progress of AD. Plants included in the present study are: Bacopamonniera, Centellaasiatica, WithaniaSomnifera, Acoruscalamus, Nardostachysjatamansi, Convolvulus pluricalis, Glycirrhizaglabra, Emblicaofficinalis, Punicagranatum, Terminaliachebula, Coriandrumsativum, Saussurealappaand Tinisporacordifolia. These plants have been shown to have anti-anxiety activity, anti-fatigue and memory enhancing effects<sup>[10,11]</sup>. Among these, bacosides from Bacopamonnieraextract have been shown to reduce the amyloid plaque levels in PSAPP mice<sup>[12]</sup>. Asiaticoside from Centellaasiaticahas been reported to have protective effects from A $\beta$  induced neurotoxicity<sup>[13]</sup>. Extracts from Withaniasomniferahave reversed AD pathology in APP/PS1 transgenic mice by enhancing low density lipoprotein related receptor levels in the liver<sup>[14]</sup>. Our current study focused on identifying whether A $\beta$  is the molecular target of these phytocompounds in exerting their beneficial effects. This was achieved by evaluating the ability of the methanolic extracts of the useful parts from the above 13 nootropic plants on;

- (i) Prevention of aggregation of A $\beta$  and;
- (ii) Dissociation of preformed A $\beta$  fibrils.

## **HISTORY:**

In 1901, a 51-year-old woman, Auguste D, was admitted to the state asylum in Frankfurt. She was suffering from cognitive and language deficits, auditory hallucinations, delusions, paranoia and aggressive behavior, and was studied by Alois Alzheimer (1864–1915), a doctor at the hospital.

Alzheimer moved to the Munich medical school in 1903 to work with Emil Kraepelin – one of the foremost German psychiatrists of that era – and when Auguste D died in April 1906, her brain was sent to him for examination. In November of that year, Alzheimer presented Auguste's case at a psychiatry meeting, and he published his talk in 1907.

In 1910, Kraepelin coined the term 'Alzheimer's disease' – a term still used to refer to the most common cause of senile dementia. But had Alzheimer actually discovered a new disease, and was Kraepelin justified in calling it suchAlois Alzheimer (1864–1915).

## **THE CONCEPT OF DEMENTIA:**

During the eighteenth century, the term 'dementia' had a clinical and a legal usage, referring to states of psychosocial incompetence regardless of age, reversibility or pathological antecedents. This broad view was gradually narrowed down, culminating at the end of the nineteenth century with what I have called the 'cognitive paradigm' the view that dementia is an irreversible disorder (mainly in the elderly) of intellectual functions (particularly memory).

This paradigm is still in place today, although it was partially modified during the 1980s when it was accepted that non-cognitive features such as hallucinations, delusions and behavioural deficits – were part of the disease. Before the adoption of the cognitive paradigm, such symptoms actually formed part of the definition of senile dementia.

In his original presentation, Alzheimer discussed Auguste D's cognitive and non-cognitive deficits, and reported that, on post mortem, he had found plaques, tangles and arteriosclerotic changes in her brain. Two important issues emerge here: were these markers new, and why, in his announcement, did Kraepelin omit to mention Auguste D's arteriosclerotic changes, hallucinations, delusions and other psychiatric symptoms.

## **THE MARKERS OF THE NEW DISEASE:**

All the markers that Alzheimer reported were well known at the time, and it is clear from his writings that he never meant to say that they were new. For example, it was the prevalent view before 1906 that in senile dementia "the destruction of the neurofibrillae appears to be more

extensive than in the brain of a paralytic subject". Indeed, five months before Alzheimer's report, the American worker Fuller whose contribution to this field has been neglected had drawn attention to the presence of "neurofibrillar bundles in senile dementia".

Nor was the association between plaques and dementia a novelty, as it had been reported in 1887 by Beljahow, and confirmed by Redlich and Leri a few years later. Oskar Fischer, the neglected researcher from Prague, had also pointed out, in June 1907, that 'miliary necrosis' should be considered as a marker of senile dementia. Kraepelin's announcement

At the end of the section on 'senile dementia' in the eighth edition (1910) of his Handbook of Psychiatry, Kraepelin wrote: "the autopsy reveals, according to Alzheimer's description, changes that represent the most serious form of senile dementia" the Drusen were numerous and almost one-third of the cortical cells had died off. In their place instead we found peculiar deeply stained fibrillary bundles that were closely packed to one another, and seemed to be remnants of degenerated cell bodies. The clinical interpretation of this Alzheimer's disease is still confused. While the anatomical findings suggest that we are dealing with a particularly serious form of senile dementia, the fact that this disease sometimes starts already around the age of 40 does not allow this supposition [i.e. it should be considered as a new disease]. In such cases we should at least assume a 'senium praecox' if not perhaps a more or less age-independent unique disease process."

Neither the biological markers nor the symptom constellation reported by Alzheimer were new, and he was fully aware of it. In fact, states of persistent cognitive impairment affecting the elderly, and accompanied by delusions and hallucinations were well known at the time. The likely answer is that he did not. His surprise at Kraepelin's claim must have been tempered, however, by his knowledge that the continuation of research grants depended upon the Munich department performing well and 'discovering' new diseases every year.

A conservative interpretation of the primary data suggests that Alzheimer's only intention was to point out that senile dementia could occur in younger people (in this case, in a woman of 51). In this regard, Perusini (a man who worked with him) wrote that, for Alzheimer "these morbid forms do not represent anything but atypical form of senile dementia.

#### **THE RECEPTION OF ALZHEIMER'S DISEASE:**

Others also expressed surprise at Kraepelin's announcement. In Russia, Hakkeboutsch and Geier referred to Alzheimer's disease as a variety of the

involution psychosis and Simchowicz considered it as only a severe form of senile dementia. Ziehen does not mention Alzheimer's disease in his major review of the senile dementias. Lastly, Lugaro wrote: "For a while it was believed that a certain agglutinative disorder of the neurofibril was considered as the main marker of the pre-senile form [of senile dementia], and that this was hurriedly baptised as Alzheimer's disease." He went on to state that he believed that the latter was only a variety of senile dementia.

At a meeting of the New York Neurological Society, Ramsay Hunt asked Lambert, the presenter of a case of 'Alzheimer's disease' that "he would like to understand clearly whether he made any distinction between the so-called Alzheimer's disease and senile dementia, other than...in degree and point of age". Lambert stated that, as far as he was concerned, the underlying pathological mechanisms were the same<sup>[15]</sup>.

#### **CAUSES:**

The cause of Alzheimer's disease is unknown. Several competing hypotheses exist trying to explain the cause of the disease. The oldest, on which most currently available drug therapies are based, is the cholinergic hypothesis<sup>[16]</sup>, which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency have not been very effective. In 1991, the amyloid hypothesis postulated that amyloid beta (AB) deposits are the fundamental cause of the disease.<sup>[17,18]</sup> Support for this postulate comes from the location of the gene for the amyloid beta precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who thus have an extra gene copy almost universally exhibit AD by 40 years of age.<sup>[19,20]</sup> Another hypothesis asserts that the disease may be caused by age related myelin breakdown in the brain. Demyelination leads to axonal transport disruptions, leading to loss of neurons that become stale. Iron released during myelin breakdown is hypothesized to cause further damage. Homeostatic myelin repair processes contribute to the development of proteinaceous deposits such as Amyloid-beta and tau.<sup>[21,22,23]</sup> Alzheimer's appears to be caused to a large degree by oxidative damage.<sup>[24]</sup> There is mounting evidence that antioxidant factors may help prevent or delay the onset of the disease. Signs and Symptoms Although the course of Alzheimer's disease is unique for every individual, there are many common symptoms.<sup>[25]</sup> The earliest observable symptoms are often mistakenly thought to be 'age-related' concerns, or manifestations of stress.<sup>[26]</sup> In the early stages, the most

commonly recognized symptom is inability to acquire new memories, such as difficulty in recalling recently observed facts. As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long-term memory loss, and the general withdrawal of the sufferer as their senses decline.<sup>[26,27]</sup> gradually, bodily functions are lost, ultimately leading to death.<sup>[28]</sup> Alzheimer's disease has been classified into three stages. Stage One usually lasts two to four years. It involves confusion, forgetfulness, disorientation, recent memory loss, and mood changes. Stage Two often lasts two to ten years. It typically is characterized by decreased memory functioning, reduced attention span, hallucinations, wandering, restlessness, muscle spasms, reduced ability to perform logic, increased irritability, and an increased inability to organize thoughts. Stage Three generally lasts one to three years. This period most often involves the increased inability to recognize family members, a progressive inability to recognize their own image in the mirror, weight loss, incontinence, swallowing difficulty, the development of skin infections, and seizures.

#### **PATHOPHYSIOLOGY:**

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. The disease usually becomes clinically apparent as insidious impairment of higher intellectual function with alteration in mood and behavior. Later, progressive disorientation, memory loss, and aphasia become manifested, indicating severe cortical disfunction. Eventually in 5-10 years, the affected individual becomes profoundly disabled, mute, and immobile. Patients rarely become symptomatic before 50 years of age, but the incidence of the disease rises with age and the prevalence roughly doubles every 5 years, starting from a level of 1% for the 60-64 years old population and reaching 40% or more for the 85-89 years old cohort. This progression increase in the incidence of the disease with age has given rise to major medical social and economic problems in countries with a growing number of elderly individuals. Most cases are sporadic, and although 5%-10% are familial, the study of such familial cases has provided important insight into the pathogenesis of the more common sporadic form. While pathogenic examination of the brain tissue remains necessary for the definitive diagnosis of Alzheimer's disease, the combination of clinical assessment and modern radiological methods allows accurate diagnosis in 80%-90% of cases. The neuropathological hallmarks of AD include "positive" lesions such as amyloid plaques and cerebral amyloid angiopathy, neurofibrillary tangles and glial responses, and "negative" lesions such as neuronal and synaptic loss. Clinic pathological correlation studies have been crucial to

generate hypotheses about the pathophysiology of the disease, by establishing that there is a continuum between "normal" aging and AD dementia, and that the amyloid plaque build-up occurs primarily before the onset of cognitive deficits, while neurofibrillary tangles, neuron loss, and particularly synaptic loss, parallel the progression of cognitive decline. Amyloid plaques: Extracellular protein deposit in the cortex of AD patients. The major protein in neuritic plaques is amyloid  $\beta$ - peptide ( $A\beta$ ), which is a 40-42 amino acid peptide derived from a membrane protein, the  $\beta$ -amyloid precursor protein (APP) after sequential cleavage by enzymes. APP encoded by gene on chromosome 21. APP interact with extracellular matrix and supports the growth of neuritis in neuronal culture, Its physiological role is likely related to the modulation of synaptic activity although still controversial. Genetic evidence implicates  $A\beta$  in the pathogenesis implicated  $A\beta$  in the pathogenesis of Alzheimer's disease, Almost all patients with trisomy (Down syndrome) develop pathologic changes indistinguishable from those seen in Alzheimer's disease, suggesting that having an increased copy of the APP gene increases the metabolism of APP to  $A\beta$ . Neurofibrillary tangles (NFT): intraneuronal aggregates of hyperphosphorylated and misfolded tau that become extraneuronal ("ghost" tangles) when tangle-bearing neurons die. Tau protein is a microtubule-associated protein normally located to the axon, where it physiologically facilitates the axonal transport by binding and stabilizing the microtubules. In Alzheimer's disease, tau is translocated to the somatodendritic compartment and undergoes hyperphosphorylation, misfolding and aggregation giving rise to neurofibrillary tangles and neuropil threads.<sup>[29,30,31]</sup>

#### **DIAGNOSIS**

Alzheimer's disease is the most common form of dementia in the elderly. Dementia is commonly recognized with use of the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).<sup>[32,33]</sup> The diagnosis of Alzheimer's disease is most often based on the criteria developed by the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),<sup>[34]</sup> according to which the diagnosis is classified as definite (clinical diagnosis with histological confirmation), probable (typical clinical syndrome without histological confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histological confirmation). Typical sensitivity and specificity values for the diagnosis of probable Alzheimer's disease with the use of these criteria are 0.65 and 0.75.<sup>[35]</sup> The classic clinical features of Alzheimer's disease are an

amnesic type of memory impairment,<sup>[36,37]</sup> deterioration of language,<sup>[38]</sup> and visuospatial deficits.<sup>[39,40]</sup> Motor and sensory abnormalities, gait disturbances, and seizures are uncommon until the late phases of the disease.<sup>[34]</sup> Functional and behavioral disturbances are characteristic of the disease. Patients progress from the loss of higher-level activities of daily living, such as check writing and the use of public transportation, through abnormalities of basic activities of daily living such as eating, grooming, and using the toilet, as the disease enters advanced phases.<sup>[35]</sup> Behavioral disturbances also progress over the course of the illness.<sup>[33]</sup> Mood change and apathy commonly develop early and continue for the duration of the disease. Psychosis and agitation are characteristic of the middle and later phases of the disease.<sup>[41]</sup> As part of the assessment of dementia, laboratory studies are necessary to identify causes of dementia and coexisting conditions that are common in the elderly. Thyroid-function tests and measurement of the serum vitamin B12 level are required to identify specific alternative causes of dementia. A complete blood count; measurement of blood urea nitrogen, serum electrolyte, and blood glucose levels; and liver-function tests should be performed.<sup>[42]</sup> Specialized laboratory studies such as a serologic test for syphilis, the erythrocyte sedimentation rate, a test for human immunodeficiency virus antibody, or screening for heavy metals are indicated when historical features or clinical

circumstances suggest that infections, inflammatory diseases, or exposure to toxins may be contributing to the dementia. Neuroimaging plays an important role in the diagnosis of Alzheimer's disease and is particularly helpful in excluding alternative causes of dementia. It is currently recommended that patients undergo structural imaging of the brain with computed tomography (CT) or magnetic resonance imaging (Fig. 1A) at least once in the course of their dementia.<sup>[43]</sup> Functional imaging with positron-emission tomography (Fig. 1B) or single-photon-emission CT may be helpful in the differential diagnosis of disorders associated with dementia.<sup>[44]</sup> The low rates of recognition of dementia by family members and physicians<sup>[45,46]</sup> constitute a major barrier to appropriate care for many patients with Alzheimer's disease. (Rates of such "failure to recognize" are reportedly 97 percent for mild dementia and 50 percent for moderate dementia.) Patients with complex presentation or challenging management tissues should be referred to a specialist with expertise in dementia. fig.2. Scans of Patients with Probable Alzheimer's Disease.

In Panel A, a magnetic resonance image shows cortical atrophy and ventricular enlargement. In Panel B, a positron emission tomographic scan shows reduced glucose metabolism in the parietal lobes bilaterally (blue-green) as compared with more normal metabolism in other cortical areas (yellow).

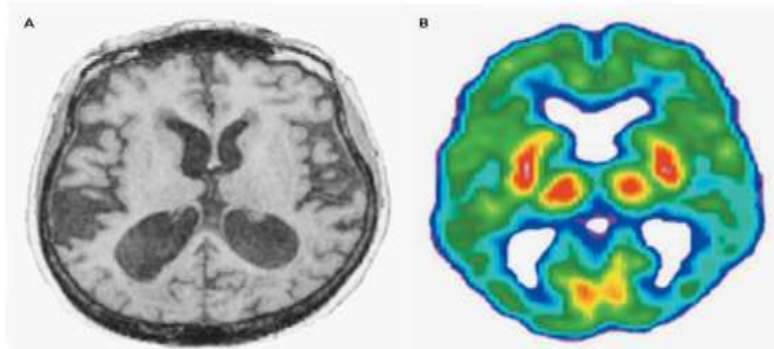
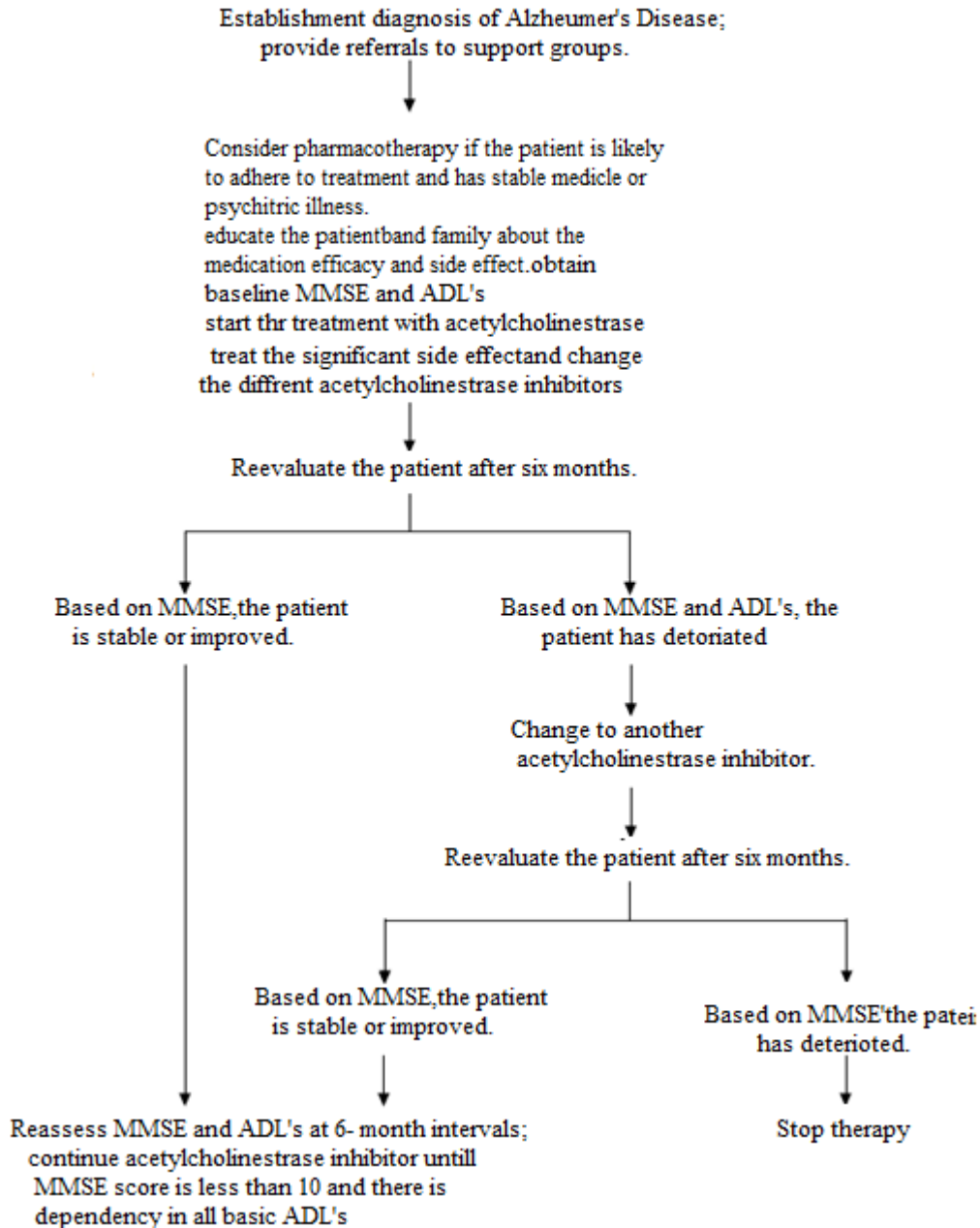


Figure 2: Scan of patient with probable A.D.

In panel A, A magnetic resonance image shows corticle atropy and ventricular enlarement. In panel B apositirin emission tomographic scan reduced glucose metabolism in

the parietal lobes bilaterally (blue-green) as compared with more normal metabolism in other corticle areas (yellow).

**MANAGEMENT OF ALZHEIMER DISEASE:**



**Figure 3: Algorithm for the management of patients with Alzheimer's disease. (MMSE = Mini-Mental State Examination; ADLs = activities of daily living.)**

Alzheimer's disease an algorithm for the management of patients with Alzheimer's disease is presented in fig.3. The patient who is selected for acetyl cholinesterase inhibitor therapy should have stable medical or psychiatric illnesses. An unstable illness will cause deterioration of functional ability and predispose the patient to delirium, which will minimize the benefits of therapy and complicate the assessment of a drug's effectiveness. Age should not be the only factor in patient selection; co morbid diseases and functional ability may be more important factors. Acetylcholinesterase inhibitors must be taken regularly and in a dosage sufficient to benefit the patient. Prolonged interruptions of therapy will result in

sustained and irreversible cognitive decline. A patient who is unlikely to adhere to therapy or who has an illness that frequently interrupts therapy will not benefit from treatment and will be exposed to cholinergic side effects. The manufacturers of the acetylcholinesterase inhibitors recommend slow titration to avoid cholinergic side effects. If a target dosage cannot be achieved with one drug, it may be worthwhile to try a different medication. Antiemetics may alleviate some of the gastrointestinal side effects associated with acetylcholinesterase inhibitors, but frail patients taking medications with anticholinergic actions may be predisposed to delirium. If significant weight loss occurs, an

appetite stimulant may be taken temporarily, although no clinical evidence supports this use. Acetylcholinesterase inhibitors do not necessarily have to be withdrawn if a patient develops disturbed behavior. Treatment with nonpharmacologic strategies or even psychotropic medication may be required if the behavior upsets the patient or causes potential harm to family, caregivers, or others. Disturbed behaviors are common in patients with Alzheimer's disease and often precede the diagnosis of dementia. Clinical trials do not suggest that Acetylcholinesterase inhibitors worsen or precipitate such behaviors. Periodic monitoring and assessment of a patient's functional ability and Mini-Mental State Examination score are useful. The results may encourage the patient's family, and the rate of change can guide the physician, patient, and family in future planning. The assessments also can help in deciding whether to continue therapy or change to another Acetylcholinesterase inhibitor.<sup>[47-50]</sup>

#### TREATMENT OF ALZHEIMER'S DISEASE:

##### ANTIAMYLOID THERAPIES:

No anti-amyloid therapies are currently available. A program to vaccinate humans was implemented after the observation that immunization with *Ab* reduces pathological signs of Alzheimer's disease in transgenic mice that have the amyloid precursor protein mutation.<sup>[52]</sup> This clinical trial was interrupted when encephalitis developed in 6 percent of the patients.<sup>[53]</sup> Post hoc analyses of a subgroup of 30 patients observed at a single site within the trials suggested that those patients who generated *Ab* antibodies had a reduction in disease progression.<sup>[51]</sup> Passive immunization represents an alternative and perhaps a safer vaccination strategy.<sup>[54]</sup> The enzymes responsible for liberating a toxic fragment of 42 amino acids, from the amyloid precursor protein are and secretases. Inhibitors of these enzymes are under active study.<sup>[55]</sup> The metabolism of cholesterol is intimately involved in the generation of *A* and preliminary evidence suggests that statins may be beneficial in reducing the accumulation of *Ab*.<sup>[56]</sup> Metal-binding compounds such as clioquinol may reduce oxidative injury associated with *Ab* and may inhibit the aggregation of the *Ab* peptide.

High blood glucose levels may increase the levels of insulin and insulin-degrading enzymes, redirecting the latter from an alternative role in the metabolism of *Ab*. Some investigators suggest that analogues of insulin-degrading enzymes might represent therapeutic options. Strategies aimed at reducing the aggregation of *Ab* offer another therapeutic avenue to be explored. The

identification of valid targets and potential treatments suggests that disease-modifying therapies will emerge from this research arena.<sup>[57,58,59]</sup>

##### NEUROPROTECTIVE APPROACHES:

*Ab* protein seems to exert its neurotoxic effect through a variety of secondary mechanisms, including oxidative injury and lipid peroxidation of cell membranes, inflammation, hyperphosphorylation of tau protein, and increased glutamate excitotoxicity (fig. 4). Neuroprotective strategies have targeted these mechanisms in an effort to reduce the cell injury associated with the generation and aggregation of *Ab*. Proof that these approaches are neuroprotective in humans is lacking; available data from animal models make this mechanism of activity most plausible.

##### ANTIOXIDANTS:

The principal antioxidant strategy has involved treatment with alpha-tocopherol (vitamin E). A randomized, placebo-controlled trial compared the effect of vitamin E, selegiline, the two drugs together, and placebo in patients with Alzheimer's disease.<sup>[60]</sup> The results of unadjusted comparisons showed no significant difference among the four groups in the study. However, when the severity of cognitive decline at baseline was included as a covariate, a significant delay in the primary outcomes (time to death, placement in a nursing home, development of severe dementia, or a defined severity of impairment of activities of daily living) was observed for patients in the selegiline, alpha-tocopherol, and combination-therapy groups, as compared with the placebo group. The increase in median time to one of the primary outcomes, as compared with the time in patients receiving placebo, was 230 days for patients receiving alpha-tocopherol, 215 days for those treated with selegiline, and 145 days for those receiving both agents. No differences in cognitive function were evident among the four groups. No statistically significant differences in vital signs, weight change, laboratory values, or 49 categories of adverse events emerged among the groups. On the basis of this study, many practitioners have added high-dose vitamin E supplements (2000 IU daily) to their standard treatment regimen for Alzheimer's disease. One retrospective study compared patients treated with a cholinesterase inhibitor plus vitamin E with historical controls and interpreted the results as indicating that the combination treatment is safe and beneficial. Several but not all epidemiologic studies provide evidence supporting the concept that vitamin E, as well as vitamin C, has a role in delaying the onset of Alzheimer's disease.<sup>[61-63]</sup>

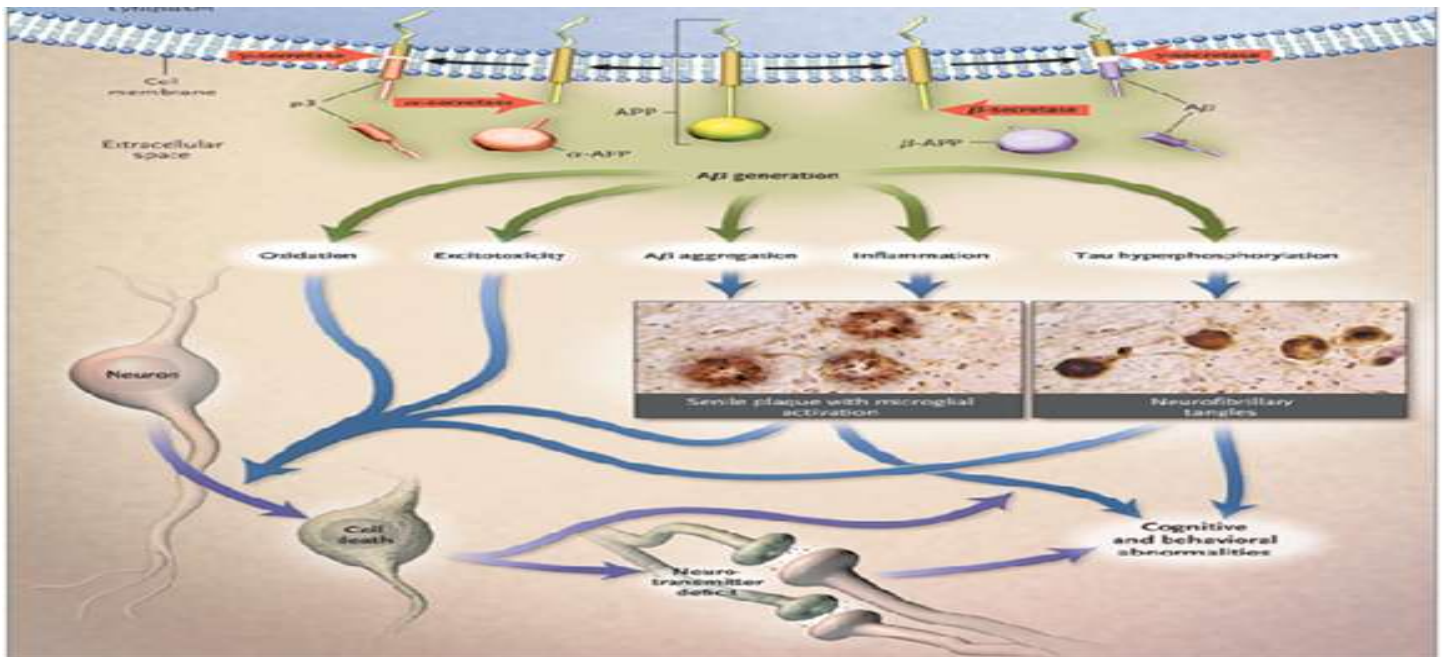


Figure 4: Putative amyloid cascade

This hypothesis of the amyloid cascade, which from the generation of beta-amyloid peptide from the amyloid precursor protein through multiple secondary steps, to cell death, forms the foundation for current and emerging options for the treatment of A.D. , APP denotes protein and amyloid beta.

**HERBAL TREATMENT:**

There are numerous natural remedies that have been shown to decrease memory loss and improve cognitive functioning. Natural medicines are able to treat a variety of conditions. A substantial benefit of a natural approach is that it offers the curative properties of conventional medicine without any of the side effects. Natural medicines can work quickly and safely to promote healing. Natural medicines have a long history of usage and there is a wealth of empirical evidence to support their effectiveness and safety. Some examples of natural herbs recommended for relieving Alzheimer's symptoms include Ginkgo Biloba, Ginseng, Licorice, Turmeric, Ginger, Maca root, Huperzine A, Salvia, Rosemary etc. Curcumin from the curry spice turmeric has shown some effectiveness in preventing brain damage due to its anti-inflammatory properties. Some of the herbal drugs used are described below:

**GINKGO BILOBA:**

Ginkgo Biloba is found growing wild around Zhejiang in Eastern China. Ginkgo biloba extract has been found in several studies to improve the symptoms and slow the progression of Alzheimer's disease. The researchers found that the use of this extract led to

significant improvements in blood and oxygen flow. Restricted blood and oxygen flow to the brain may be an important factor in the development of Alzheimer's. GBE has been shown to have the ability to normalize the acetylcholine receptors in the hippocampus area of the brain. A different study found that EGb761 prevents beta amyloid toxicity to brain cells, a key part of the development of the disease. The herb is a well-known anti-oxidant and can protect the brain from Aβ-induced oxidative damage. The herb also shifts the metabolism of amyloid precursor protein (APP) in favor of the non-amyloidogenic pathway. A study compared the effectiveness of the most common Alzheimer's drugs, such as donepezil and rivastigmine, to that of a Ginkgo extract called EGb 761. The researchers determined that EGb761 was as effective as any of these commonly-prescribed drugs in treating the symptoms of Alzheimer's patients. In general, various forms of Ginkgo have been found to be safe, but in individuals who take aspirin or other anticoagulant drugs, Ginkgo should be taken with great caution and with the advice of physician.

**GINSENG:**

Ginseng grows in North eastern Asia. It decreases senility and improve memory and behavior. Ginseng is able to enhance psychomotor and cognitive performance, and can benefit Alzheimer's disease by improving cholinergic function, reducing the level of Ab, and repairing damaged neuronal networks. Ginsenosides is the active ingredient found in ginseng which helps to protect neurons. It recruited

patients aged 50 years or older with mild to moderate dementia.<sup>[64-69]</sup>

#### ROLE OF B-SECRETASE IN ALZHEIMER'S DISEASE:

Autosomal dominant mutations in the genes for amyloid precursor protein (APP) and the presenilins (presenilin-1 and presenilin-2) cause familial Alzheimer's disease (AD) (reviewed in), and these findings together with others suggest that the amyloid-beta (A $\beta$ ) peptide plays a central role in AD pathogenesis. Consequently, therapeutic approaches to lower brain A $\beta$  levels should be efficacious for the treatment or prevention of AD. A $\beta$  is generated through the sequential endoproteolysis of APP by the  $\beta$ -secretase and  $\gamma$ -secretase enzymes.  $\beta$ -secretase cuts first at the N-terminus of A $\beta$ ;  $\gamma$ -secretase cleaves only thereafter to make the C-terminus of A $\beta$ . Then A $\beta$  is secreted from neurons to form amyloid plaques in the AD brain. Inhibition of  $\beta$ -secretase should thus decrease production of A $\beta$ , the pathogenic form of the peptide. Since the discovery of A $\beta$ , the molecular identity of the  $\beta$ -secretase has been intensely sought because of its prime status as a drug target for AD. Prior to the enzyme's

discovery, the properties of  $\beta$ -secretase activity in cells and tissues had been extensively characterized. In 1999 five groups reported the molecular cloning of the  $\beta$ -secretase variously naming the enzyme BACE [4], Asp2 or memapsin (herein,  $\beta$ -secretase will be referred to as  $\beta$ -site amyloid precursor protein cleaving enzyme 1 (BACE1)). The groups used different isolation methods (expression cloning, protein purification, genomics), yet all identified the same enzyme and agreed it possessed all the characteristics of  $\beta$ -secretase.

This dreaded disease initially manifests as a gradually progressive cognitive decline loss of memory and language skills, and inability to attend to business and activities of daily living. Contributing events are numerous and complex, involving a multitude of variables presently under intense study. The hypothesis, still under debate, is that this destructive pattern is caused by the collapse and disintegration of microtubules<sup>3</sup> within nerve cells in the brain causing "tangles" and the formation of beta amyloid (protein) plaques between nerve cells, as illustrated in fig.5. This pattern is an anti-inflammatory stimulus, which elicits an immune-inflammatory response.

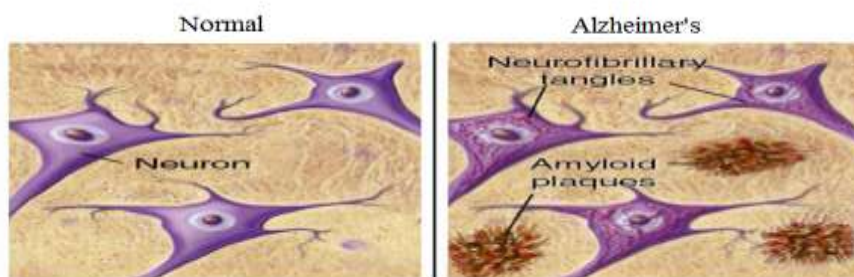


Figure 5: The formation of amyloid (protein) plaques and neurofibrillary tangles are thought to contribute to the degradation of the neurons (nerve cells) in the brain and the subsequent symptoms of Alzheimer's disease. (From Alzheimer's disease Research, a program of the American Health Association Foundation).

#### ROLE OF ACETYLCHOLINE IN ALZHEIMER DISEASE:

For a quarter of a century, the pathogenesis of Alzheimer's disease (AD) has been linked to a deficiency in the brain neurotransmitter acetylcholine. This was based on observations that correlated cholinergic system abnormalities with intellectual impairment<sup>[71]</sup>. Subsequently, the 'cholinergic hypothesis' of AD gained considerable acceptance. It stated that a serious loss of cholinergic function in the central nervous system contributed to cognitive symptoms<sup>[72]</sup>. Over the years, both evidence for and challenges to the relationship between acetylcholine dysfunction and AD have been put forward<sup>[73]</sup>. In essence, it has been argued that acetylcholine dysfunction is not a primary pathological cause for AD but rather a consequence of the disease. Hence, in addition to cholinergic dysfunction, a role for

amyloid deposition, oxidative stress and inflammation have been investigated in the etiology of AD, and currently, trials are underway to test disease-modifying agents. Nevertheless, attempts at correcting acetylcholine deficiency in the brain of affected individuals produced the first licensed medication for the symptomatic treatment of AD in the form of acetyl cholinesterase inhibitors (AChEIs). Although the benefits of these agents are modest, three (donepezil, rivastigmine and galantamine) are licensed in the UK. Current guidelines by the National Institute of Clinical Excellence support the use of these agents, although possible changes to the guidelines are presently awaited. AChEIs are widely available for the treatment of mild-to-moderate AD, and they are well tolerated in the majority of patients. Although their main use has been in the stabilization of cognitive decline, there is evidence

linking them with improvement in behavioral and psychological symptoms of dementia [74]. It has been the prevailing view that the symptomatic efficacy of AChEIs is attained through their augmentation of acetylcholine-mediated neuron-to-neuron transmission. However, there is evidence that AChEIs may slow disease progression and hippocampal atrophy and may have disease-modifying effects [75-77]. In addition, symptomatic improvement in AD patients is not restricted to agents that enhance acetylcholine function in the brain, as is the case for memantine which acts on another neurotransmitter. Interestingly, memantine, whose benefits also appear to be modest, and is licensed in Europe for moderate-to-severe AD, has been recently linked to modulation of inflammation [78]. Further research is needed to establish an anti-inflammatory role for memantine; overall however, inflammatory pathways in general are being recognized as an important contributor to cell death in AD [79]. In cell cultures and animal studies, as well as in human epidemiological surveys, agents known to dampen down inflammation such as vitamin antioxidants, herbal extracts with antioxidant properties (e.g. Ginkgo Biloba) and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) have shown some protective effect against AD pathology. There is also current interest in statins for the treatment of AD. Significantly, their suspected role in cognitive enhancement appears to be mediated through an anti-inflammatory effect, independent of their cholesterol-lowering properties [80]. To date, none of these agents have shown clear benefit to AD patients. In the case of NSAIDs, although strong evidence from epidemiological studies seems to point towards a protective role for these drugs in relation to the development of AD, randomized controlled trials have failed so far to show any benefit [81,82]. The efficacy of anti-inflammatory agents may be limited by the fact that inflammation appears to be interlinked with other pathological events in AD, including  $\beta$ -amyloid deposition and cholinergic dysfunction [83]. However, this interrelationship and the central role of inflammation along with evidence that symptomatic improvement in AD can be achieved independent of acetylcholine raise the possibility that the mechanism of action of AChEIs may not be restricted to direct neuron-to-neuron signaling. Indeed it has been speculated that these agents might offer a degree of neuroprotection in AD [84]. Hence, it may be reasonable to consider that the efficacy of AChEIs is, at least in part, because of the anti-inflammatory effects. However, for an anti-inflammatory mechanism of action to be confirmed for AChEIs, two essential requirements are to be satisfied. They are the following:

- (i) direct link between the cholinergic system and inflammation (i.e. a direct role for acetylcholine in attenuating inflammation) and
- (ii) data showing clear effect of AChEIs on inflammatory mediators of toxicity and inflammatory processes. Recent research and discoveries allow for evidence for both to be presented below.

A link between the cholinergic system and inflammation has been established through the discovery of an anti-inflammatory role for a stimulated vagus nerve [85]. In an animal model of toxemia, acetylcholine suppressed proinflammatory cytokine release from peripheral tissue-activated macrophages. This resulted from the action of acetylcholine on specific nicotinic receptors expressed on these cells [86]. Hence, this 'cholinergic anti-inflammatory pathway' provides a physiological mechanism linking acetylcholine with inhibition of inflammation. [87] have shown the presence of similar pathway in the brain linking the cholinergic system with the regulation of mouse-cultured microglial activation. Here again, acetylcholine acting on the same nicotinic receptors to those expressed on macrophages attenuated cytokine release from microglia (brain cells increasingly linked with AD pathology). These interesting results in the brain have also been confirmed in rat microglial cultures [88]. Furthermore, there is a growing body of evidence from animal and, recently, human studies directly linking AChEIs with an anti-inflammatory role. Pre-incubation of rat cells with tacrine and donepezil protected them from the effect of hydrogen peroxide, a toxic-free radical, and significantly produced an increase in catalase and glutathione peroxidase antioxidants [89]. Tacrine also prevented hydrogen peroxide-induced cell death possibly through inhibition of certain genes expression [90]. Free radicals are known to directly damage cells and appear to be involved in reciprocal induction of other mediators of toxicity in AD such as  $\beta$ -amyloid and as such contribute to inflammation [91]. Hence, blocking the action of toxic-free radicals helps in attenuating the inflammatory response. Data also show that AChEIs protected cells directly against  $\beta$ -amyloid-induced injury [92] and that donepezil was recently shown to protect rat septal neuronal cells against toxicity of  $\beta$ -amyloid [93]. Recent evidence also point to a direct role of AChEIs in the inhibition of the release of inflammatory substances from specialized cells. Galantamine, for example, attenuated release of cytokines from activated murine microglia [94]. In mice, peripheral administration of AChEIs almost completely blocked activated microglia's cytokine production in hippocampus and blood [95]. Significantly, similar results have now been shown in humans. Donepezil treatment of AD patients for

1 month led to an attenuation of the release of cytokines from peripheral monocytes<sup>[96]</sup>. Increasing evidence now points towards an anti-inflammatory role for AChEIs through action against free radicals and amyloid toxicity and through decreasing release of cytokines from activated microglia in the brain and blood. More research is now needed to clarify the anti-inflammatory role of AChEIs in AD patients and to define the mechanisms involved. This undoubtedly will shed further light on the pathogenesis of AD and the interaction between the various pathological factors involved in its aetiology. However, based on the accumulating research evidence so far, it is no longer appropriate to consider that the sole action of AChEIs in AD is through direct acetylcholine mediated enhancement of neuronal transmission.

#### **CONCLUSION:**

It is disease of the ageing population. In that short term memory loss is observed but long term memory as it is.

In AD there is marked atrophy of the cerebral cortex and subcortical neurons i.e., senile plaque which are aggregates of beta-amyloid are pathognomonic of the disease. They are most abundant in the hippocampus and associative areas of the cortex, which correlates well with impairment of memory as observed in the disease. There is evidence for marked decrease in choline acetyltransferase and other markers of cholinergic neurone activity additionally there are changes in brain glutamate, dopamine, noradrenaline, 5-HT, and somatostatin activity.

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