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Review Article

Alzheimer's – An updated review on disease and its treatment

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of cognitive impairment in older patients and is expected to increase greatly in prevalence in the next future. An excess of senile plaques (h-amyloid protein) and neurofibrillary tangles (tau protein), ventricular enlargement, and cortical atrophy characterizes it. A cascade of pathophysiological events is triggered in AD that ultimately involves common cellular signaling pathways and leads to cellular and neural networks dysfunction, failure of neurotransmission, cell death and a common clinical outcome. A major focus of drug treatment for Alzheimer's disease is to improve *cognitive* abilities such as memory and thinking and slow the progression of these symptoms. Current treatments cannot cure or halt the disease, but can offer some people modest improvement in some symptoms. Countless new treatments are in development, so more options will be available in the near future. This article consists of a critical review of Alzheimer's disease (AD), its epidemiology, patterns of care, prognostic factors, and symptomatic strategies available for treating AD and future strategies for improving our therapeutic approach to AD.

Keywords: Alzheimer's disease, amyloid beta, epidemiology, pathophysiology, treatment strategies.

INTRODUCTION

Alzheimer's *(AHLZ-high-merz)* is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks. This incurable, degenerative, and terminal disease was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him. [1] Alzheimer's disease (AD) is rapidly becoming a major public health concern. An estimated 20% of individuals aged >80 years are believed to be affected. [2] The annual incidence of AD increases with age, from about 1% in those aged 65 to 75 years to more than 8% in those aged >85 years. [3,4] A sharp increase in the number of persons afflicted by this debilitating disease is anticipated as the proportion of the population >65 years continues to rise in Western countries. [5]

Diagnosis of AD is based on clinical features, although it should be confirmed by brain histopathological examination. There are three clinical stages of AD – mild, moderate and severe with cognitive and functional decline stretching over 5–8 years. The initial stage usually lasts 2–3 years and is characterized by short-term memory impairment often accompanied by symptoms of anxiety and depression. In the moderate stage, these symptoms appear to abate as neuropsychiatric manifestations, such as visual hallucinations, false beliefs and reversal of sleep patterns emerge. The severe and final stage is characterized by motor signs, such as motor rigidity and prominent cognitive decline. [6]

At the present there is no definitive treatment or cure for AD. Linear correlation between the stages of AD and volume of brain structures, suggest that successful therapeutic intervention might stop the progress of pathological changes at any stage of disease. [7] The aim of this paper was to review available data on etiology, pathophysiology and different aspect for the treatment of AD.

SYMPTOMS OF ALZHEIMER'S DISEASE

The onset of Alzheimer's disease is usually gradual, and it is slowly progressive. Memory problems that family members initially dismiss as "a normal part of aging" are in retrospect noted by the family to be the first stages of Alzheimer's disease. When

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memory and other problems with thinking start to consistently affect the usual level of functioning; families begin to suspect that something more than "normal aging" is going on.

Problems of memory, particularly for recent events (short-term memory) are common early in the course of Alzheimer's disease. For example, the individual may, on repeated occasions, forget to turn off an iron or fail to recall which of the morning's medicines were taken. Mild personality changes, such as less spontaneity, apathy, and a tendency to withdraw from social interactions, may occur early in the illness.

As the disease progresses, problems in abstract thinking and in other intellectual functions develop. The person may begin to have trouble with figures when working on bills, with understanding what is being read, or with organizing the day's work. Further disturbances in behavior and appearance may also be seen at this point, such as agitation, irritability, quarrelsomeness, and a diminishing ability to dress appropriately.

Later in the course of the disorder, affected individuals may become confused or disoriented about what month or year it is, be unable to describe accurately where they live, or be unable to name a place being visited. Eventually, patients may wander, be unable to engage in conversation, erratic in mood, uncooperative, and lose bladder and bowel control. In late stages of the disease, persons may become totally incapable of caring for themselves. Death can then follow, perhaps from pneumonia or some other problem that occurs in severely deteriorated states of health. Those who develop the disorder later in life more often die from other illnesses (such as heart disease) rather than as a consequence of Alzheimer's disease.

Ten warning signs of Alzheimer's disease

The Alzheimer's Association has developed the following list of warning signs that include common symptoms of Alzheimer's disease. Individuals who exhibit several of these symptoms should see a physician for a complete evaluation.

1. Memory loss
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time and place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

It is normal for certain kinds of memory, such as the ability to remember lists of words, to decline with normal aging. In fact, normal individuals 50 years of age will recall only about 60% as many items on some kinds of memory tests as individuals 20 years of age. Furthermore, everyone forgets, and every 20 year old is well aware of multiple times he or she couldn't think of an answer on a test that he or she once knew. Almost no 20 year old worries when he/she forgets something, that he/she has the 'early stages of Alzheimer's disease,' whereas an individual 50 or 60 years of age with a few memory lapses may worry that they have the 'early stages of Alzheimer's disease. [8]

ETIOLOGY AND PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Three major competing hypotheses exist to explain the cause of the disease. The oldest, on which most currently available drug therapies are based, is the *cholinergic hypothesis*, 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. Other cholinergic effects have also been proposed, for example, initiation of large-scale aggregation of amyloid leading to generalised neuroinflammation. [9, 10] In 1991, the *amyloid hypothesis* postulated that amyloid beta (Aβ) deposits are the fundamental cause of the disease. [11, 12] 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. [13, 14] Also APOE4, the major genetic risk factor for AD, leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, Aβ deposition precedes clinical AD. [15] Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits. [16] Researchers have been led to suspect non-plaque Aβ oligomers (aggregates of many monomers) as the primary pathogenic form of Aβ. A 2004 study found that deposition of amyloid plaques does not correlate well with neuron loss. This observation supports the *tau hypothesis*, the idea that tau protein abnormalities initiate the disease cascade. [14] In 2009, it was found that oligomeric Aβ exerts a deleterious effect on brain physiology by binding to a specific receptor on neurons. The identity of this receptor is the prion protein that has been linked to mad cow disease and the related human condition, Creutzfeldt-Jakob disease, thus potentially linking the underlying mechanism of these neurodegenerative disorders with that of

Alzheimer's disease. [17] This theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by aging-related processes in later life to cause the neuronal withering of Alzheimer's disease.

AD is characterized pathologically by the presence of cerebral beta-amyloid (Aβ) plaques (with Aβ42 as the major peptide constituent), NFT of paired helical filaments made of hyperphosphorylated microtubule-associated protein t (MAPt), and neuronal loss [Fig. 1]. NFT are made up partly of a protein called t, which links together to form filaments. The density of these filaments within neurons in the brain is directly related to the severity of dementia. It is unclear why tangles are formed. Different alleles of a gene are known to create forms of t that likely become tangles. [18]

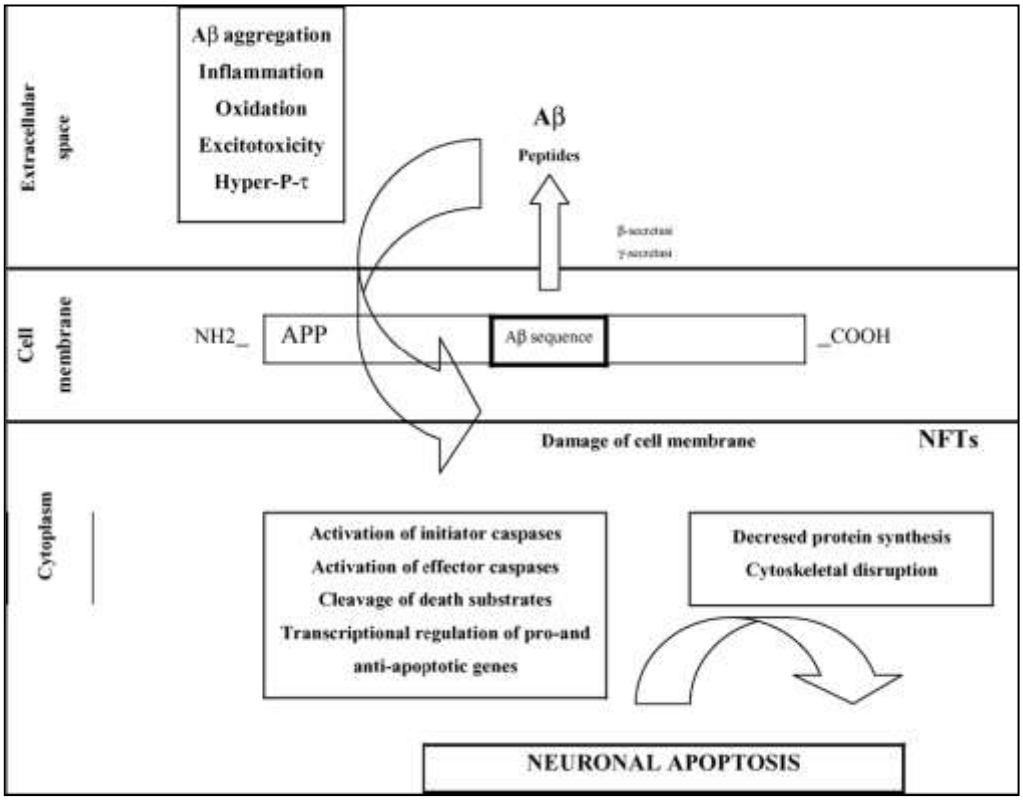

Fig.1. Pathophysiological events in neurodegenerative AD. Abbreviations: APP: amyloid precursor protein; Ab: β amyloid; NFT: neurofibrillary tangles.

PREVALENCE OF ALZHEIMER'S DISEASE

It is estimated that there are currently about 18 million people worldwide with Alzheimer's disease. This figure is projected to nearly double by 2025 to 34 million. Much of this increase will be in the developing countries, and will be due to the ageing population. Currently, more than 50% of people with Alzheimer's disease live in developing countries and by 2025, this will be over 70%.

Alzheimer's disease can occur at any age, even as young as 40 years, but its occurrence is much more common as the years go by. In fact, the rate of occurrence of the disease increases exponentially with age, which means that it occurs very rarely among those 40-50 years old, increases between 60 and 65 years, and is very common over 80 years. In November 2000, the National Institute on Aging (USA) estimated that up to 50% of Americans aged 85 years or more may have Alzheimer's disease. Combining the results of several studies, the following rates of occurrence of Alzheimer's disease are estimated in the general population in the West:

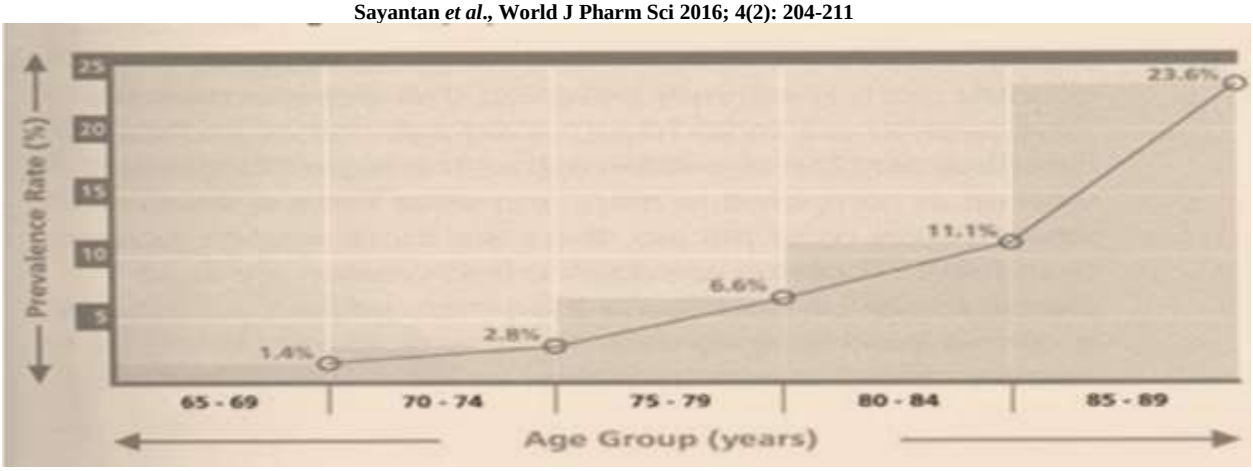

Fig.2. rate of occurrence of Alzheimer's disease in the general population in the West

Since the risk of getting the disease increases with age, the number of patients with the illness to be found in any community will depend on the proportion of older people in the group. Traditionally, the developed countries had large proportions of elderly people, and so they had very many cases of Alzheimer's disease in the community at one time. However, the developing countries are now undergoing a demographic transition so that more and more persons are surviving to an old age. For example in India, the 1991 census revealed that 70 million people were over 60 years. This number increased in 2001 to about 77 million, or 7.6% of the population. Studies done in South India, Mumbai and the northern state of Haryana in India have reported very low rates of occurrence of Alzheimer's disease in those at 65 years of age or older, ranging from about 1% in rural north-India (the lowest reported from anywhere in the world where Alzheimer's disease has been studied systematically) to 2.7 in urban Chennai. Similar demographic changes are occurring in other Member Countries of the SEA Region. In Sri Lanka, the life expectancy is 74.1 (with 9.6% of the population being over 60 years), which is the highest in the Region, followed by Thailand (life expectancy 70, with 8.7% of the population over 60 years). With this increased number of elderly people, there will be many cases of Alzheimer's disease. Thus, the time has come to discuss issues related to Alzheimer's disease in the Member Countries of the Region. [19]

DIAGNOSIS

Diagnosis of AD is problematic for there is no specific biological marker for the disease. The only sure way to diagnose AD is by a histological examination of the brain tissue, which can only be done after death, or through a brain biopsy. In practice, patients are screened and are then diagnosed for AD based on a physical exam, patient history, and a systematic determination of their mental state using specific cognitive and psychological tests. The screening tool most often encountered and used in epidemiological and clinical studies to assess overall mental status is the mini-mental state examination (MMSE), or the modified mini-mental state examination (3MS). [20, 21] Another instrument, mostly encountered in prevalence studies, is the Cambridge mental disorders of the elderly examination (CAMDEX), which includes the MMSE, as well as the Blessed dementia rating Scales. [22, 23] The Blessed dementia rating scale and the mattis dementia rating scale have also been used alone for screening purposes. [24] Finally, since depression may impact cognitive performance, scales such as the Hamilton rating scale for depression may also be administered as part of the screening phase. [25] The Diagnosis and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-III-R), and the current DSM-IV, contain criteria for diagnosing AD-type dementia. [26] An additional set of criteria, classifying AD as definite, probable, and possible, has been developed by the working group established by the National Institutes of Neurological and Communicative Disorders and Stroke (NINCDS), and the Alzheimer's disease and Related Disorders Association (ADRDA). [27] The International Classification of Disease (ICD) 9th and 10th eds., also offer diagnostic criteria for AD; but are most often used for administrative purposes. Diagnosis of AD is often confirmed by excluding differential diagnoses. The Hachinski ischemia scale is used to differentiate between vascular dementia, mixed dementia and AD. But there is, in fact, a growing body of evidence which points to the fact that AD itself has an intrinsic vascular component. [28] Furthermore, the spectrum of heterogeneity in both AD and VaD is such that it may be difficult for the clinician to exclude the vascular contributions to AD. When assessing the diagnosis, the relative importance of AD and VaD symptoms in individual patients will generally determine in which type of dementia patients will be classified.

[29] Diagnostic criteria were mainly developed to attain uniformity of classification for research purposes. [30] However, these criteria are difficult to put into operation. Aside from the NINCDS-ADRDA, they fail to specify which neuropsychological tests and diagnostic tools should be used. Consequently, this introduces a high variability among studies. Even if similar diagnostic criteria were used, the instruments to evaluate them may differ. Moreover, classification errors may result from a lack of specificity of the criteria or the instruments used. [31] On the other hand, a lack of sensitivity in the diagnostic criteria may result in some AD cases remaining undiagnosed.

Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia. [32]

A new brain scan, called diffusion tensor imaging (DTI), has been found to be better at detecting earliest signs of Alzheimer's disease in healthy people, according to a new study. The study found that DTI can easily detect if a person with memory loss might have brain changes of Alzheimer's disease. [33]

According to UK scientists a simple eye test might be able to detect Alzheimer's diseases before symptoms develop. The technique uses fluorescent markers which attach to dying cells which can be seen in the retina and give an early indication of brain cell death. It exploits the fact that the light-sensitive cells in the retina at the back of the eye are a direct extension of the brain. Using eye drops which highlight diseased cells, the researchers showed for the first time in a living eye that the amount of damage to cells in the retina directly corresponds with brain cell death. [34]

TREATMENT AND MANAGEMENT AVAILABLE FOR ALZHEIMER'S DISEASE

The management of Alzheimer's disease consists of medication based and non-medication based treatments organized to care for the patient and family. Treatments aimed at changing the underlying course of the disease (delaying or reversing the progression) has so far been largely unsuccessful. Medicines that restore the defect, or malfunctioning, in the chemical messengers of the nerve cells have been shown to improve symptoms. Finally, medications are available that deal with the psychiatric manifestations of Alzheimer's disease. In this segment three mostly accepted medicine system namely allopathic, homeopathic and traditional Indian ayurvedic are discussed.

Allopathic treatment of AD: AD is regarded as a brain amyloidosis. Prevention/deletion of Aβ deposition is one of the most promising targets of the treatment. [35] Therapeutic options for treatment of AD have so far focused on modifying neurotransmitter systems, in particular the cholinergic system, to maximize the remaining activity in affected neuronal circuits.

Cholinesterase inhibitors: Symptomatic treatment of AD is based on cholinergic neurotransmission enhancement obtained by pharmacological means. Among the different compounds that can modify cholinergic neurotransmission, the only class of drugs that have been obtained form regulatory authorities the indication for the symptomatic treatment of AD are the ChEIs. These drugs act by slowing the biochemical breakdown of acetylcholine and thereby, at least theoretically, prolonging cholinergic neurotransmission. [36] Three ChEIs are commonly used to treat patients with mild to moderate AD: donepezil, rivastigmine and galantamine. Donepezil and galantamine are selective AChE inhibitors. Rivastigmine inhibits both AChE and BuChE from degrading ACh. ChEIs are indicated in patients with mild to moderate AD, although some studies suggested a small benefit also in patients suffering from advanced stages of AD. [36, 37]

Memantine: Overstimulation of the NMDA receptor by glutamate is implicated in neurodegenerative disorders. Glutamate is the principal excitatory neurotransmitter in the brain. Glutamatergic overstimulation may result in neuronal damage, a phenomenon that has been termed excitotoxicity. Such excitotoxicity ultimately leads to neuronal calcium overload and has been implicated in neurodegenerative disorders. Glutamate stimulates a number of postsynaptic receptors, including the NMDA receptor, which has been particularly implicated in memory processes, dementia, and the pathogenesis of AD. [36]

Homeopathic treatment of AD: Homeopathy is based on the principle that a substance which in relatively large amounts will cause a disease will, when given in infinitesimally small (homeopathic) amounts, cure that same disease. It is ironic that homeopaths knew over 150 years ago that homeopathic concentrations of aluminum oxide would cure symptoms of dementia while we are just now realizing that much larger amounts of aluminum may actually cause these symptoms. Homeopathic treatment of AD is an important

option. The remedy *alumina* was discovered by the founder of homeopathy, Dr. Samuel Hahnemann, in 1829. Dr. Hahnemann found it highly effective in treating "Great weakness or loss of memory" and in cases where "Consciousness of personal identity is confused". [38, 39]

Ayurvedic treatment of AD: Ayurvedic treatment for Alzheimer's disease is very much on its developmental stage. Ayurveda scientists in India, US and Germany are on the lookout of an effective cure for Alzheimer's disease using Ayurvedic herbs like Brahmi. According to Ayurveda, all the diseases are caused due to imbalances in body. Tridosha concept is the basis of Ayurvedic knowledge. The food, the daily actions, the thought etc should be in tune with tridoshas. Alzheimer's disease is due to imbalance of vata, which is common in old age. According to Ayurvedic principles, vata in the tissues of nervous system, especially brain gets imbalanced. This directly leads to problems like lower levels of co-ordination, clear thinking, lack of inhibitions and retarded words and actions. Mano vaha srotas or the mind-channel that carries thoughts is affected due to vitiation of vata. This is the reason for delusions and mental disturbances. According to Ayurveda, the tensions and stress a person experience during his or her life cause disturbances to vata, the accumulation of which causes severe nervous problems. Vata imbalances are common in old age. Ayurveda Alzheimer's treatment mainly aims at restoring vata balance. Therapy for Alzheimer's starts with choice of a vata balanced diet. Ashwagandha (Withania somnifera) powder with milk, ghee or skimmed milk according to the digestive capacity of the person is the first re-arrangement in daily diet. This soothes and empowers vata. Daily oil massage before bath is another important part of Alzheimer's treatment in Ayurveda. Ayurvedic cleansing processes like panchakarma are not indicated for aged people. Other mild cleansing techniques like fumigation and enema are directed to purify body tissues. Nervine tonics like brahmi, aswagandha etc are main herbs for Alzheimer's treatment. [40]

Current trends in Alzheimer's treatment: Various antioxidants, free radical scavengers, calcium channel blockers, metal chelators, or modulators of certain signal transduction pathways might protect neurons from the downstream effects of accumulation of Aβ protein. A chelator of copper and zinc ions that may decrease cerebral b-amyloid protein levels is being tested in patients with AD[41]. Some studies suggest that high intake of vitamins C, E, B6, and B12, and folate, unsaturated fatty acids, and fish are related to a low risk of AD, but the results of different reports are inconsistent. Modest to moderate alcohol intake, particularly wine, may be related to a low risk of AD. [41, 42]

Another approach to treating AD is to administer anti-inflammatory drugs that could interfere with aspects of the microglial, astrocytic, and cytokine responses found in the brain of a patient with AD. The epidemiologic evidence that prolonged use of certain NSAIDs (specifically inhibitors of cyclooxygenase-1) is associated with a lower risk for AD could be explained on this basis. [43]

Descriptive studies have shown that postmenopausal women who take estrogen have a lower incidence of AD. [36]

Sufficient progress in delineating the AD cascade has been achieved to envision several discrete types of potentially disease-modifying treatments. Inhibitors of Aβ protein production, consisting in small compounds crossing the blood–brain barrier and decreasing (but not eliminating) either β- or γ-secretase activity, could be therapeutic in the early clinical phases of the disease, particularly in patients with the subtle syndrome of minimal cognitive impairment (mild cognitive impairment). [44]

Cholesterol lowering compounds decrease the risk of developing AD via a mechanism which may be independent of cholesterol (induction of nitric oxide synthase; decrease of endothelin-1). These compounds may inhibit the formation of Aβ by giving priority to a-secretase activity and by decreasing the activities of β- and γ -secretases, with the latter enzymes co-localized in cholesterol-rich membrane rafts. [45, 46]

An alternative approach to secretase inhibition would be to use small molecules to bind Aβ protein monomers and prevent their aggregation into potentially neurotoxic oligomers. Knowledge gained from studies on Aβ peptide immunotherapy will allow optimization of new-generation vaccines, targeting highly specific epitopes while reducing undesired side effects. In harnessing and steering the immune system, an effective response can be generated against Ab. [47] A new study suggests that commonly used high blood pressure medicines may help protect older adults from risk of dementia, a condition commonly associated with memory loss and Alzheimer’s disease. The scientists, reporting in the British Medical Journal (BMJ) on Jan. 12, 2010, say a class of hypertension medications, Angiotensin receptor blockers (ARB) may have an important part in slashing down the risk of dementia and Alzheimer’s disease in older people. [48]

Philip Scheltens, M.D., of VU University Medical Center in Amsterdam in the issue of *Alzheimer's & Dementia* reported that Patients with very mild Alzheimer's disease show improvements in memory after taking a multi-nutrient drink. Supplementation with a medical food including phosphatide precursors and cofactors for 12 weeks improved memory (delayed verbal recall) in mild Alzheimer's disease patients. [49]

CONCLUSION

Thirty years ago, we knew very little about AD. Since then, scientists have made many important advances. Research supported by many organizations has expanded knowledge of brain function in healthy older people, identified ways we might lessen normal age-related declines in mental function, and deepened our understanding of AD. Many scientific and clinical fields are now working together to untangle the genetic, biological, and environmental factors that, over many years, ultimately result in AD. This effort is bringing us closer to the day when we will be able to manage successfully or even prevent this devastating disease.

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