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RESEARCH ARTICLE

ALZHEIMER'S DISEASE: FACTS AND FINDINGS.

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Abstract

Alzheimer's disease is the most common form of dementia, which is set to rise significantly. With a rapidly aging population, the burden of the disease will be profound affecting not just the person afflicted, but also the caregiver and family. Among Asian population including India and China, the prevalence of the disease is lower compared to the Latino and non-Latino Americans, increased with age and was not associated with gender or literacy. Possible explanations include low overall life expectancy, short survival with the disease and low age-specific incidence potentially due to differences in the underlying distribution of risk and protective factors compared with populations with higher prevalence. While the exact cause of Alzheimer's disease remains unknown, one of its pathological hallmarks is clear – the clumping of APP product in brain when the protein is abnormally processed. Finding out more about APP can help researchers gain a better understanding of the disease and potentially identify biomarkers and therapeutic targets for it. However, up till this point, little was known about the APP's primary function in brain. Advanced research has identified the major causes -- amyloid deposition, tangle of hyperphosphorylated tau protein. As our knowledge increases the treatment and their application also developed to cope with the debilitating and devastating disease. The three major hypotheses regarding Alzheimer's gives this information that the main causes are the generation of clumps of amyloid, the neurofibrillary tangles of tau protein and the reduced synthesis of neurotransmitter acetylcholine; the proteins damage the neurons although the cause for most Alzheimer's cases is still unknown. Although the two hypotheses amyloid and tau has been widely accepted, current research on Alzheimer's disease has revealed some other genetic, dietary and also some environmental factors involved in the pathogenesis of this disease. In this review paper I have tried to shed a little light on the epidemiology, molecular pathogenesis, genetic basis, some possible risk factors and effect of several dietary factors, diagnosis and treatment regarding Alzheimer's disease. Recent developments and findings in genetics and treatment of this disease are highlighted here.

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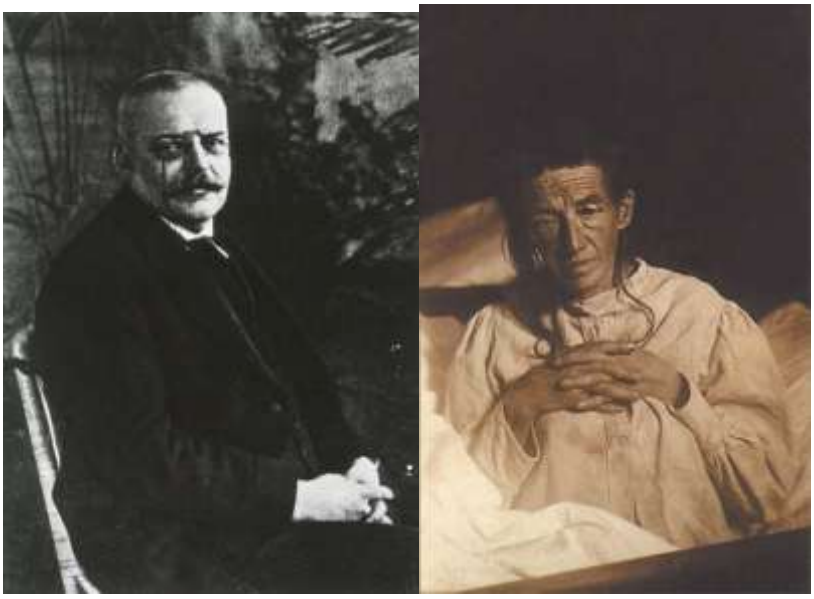
Introduction:-

Alzheimer's, the irreversible progressive brain disease, currently has no cure and remains under worldwide research. This neurological brain disorder is characterized by cognitive deficits, synaptic loss and neuronal death. It is the most common and severe form of dementia, a group of disorders that impairs normal mental functioning. The disease was first described in 1906 by German psychiatrist and neuropathologist Alois Alzheimer and was named after him. He identified the first case of what became known as Alzheimer's disease in a 50 years old woman, Auguste Deter. The disease was first described as a distinctive disease by Emil Kraepelin[66].Alzheimer's disease is generally diagnosed in people over 65 years of age. Most cases of this disease are sporadic, 5-10% are familial. Memory loss is one of the earliest symptoms of the disease, along with a gradual decline of other intellectual and thinking abilities, called cognitive functions and changes in personality and behavior. This is a form of dementia that affects person's cognitive behavior i.e., power of thinking, concentration, memory and judgment and ultimately impedes the person's ability to perform normal daily activities. The disease also causes disturbances in circadian rhythms and the sundowning is related to a phase delay of body temperature. Sundowning is the occurrence or exacerbation of behavioral symptoms of AD in the afternoon and evening [59]. A transitional state was identified between the cognitive changes of normal aging and AD, known as mild cognitive impairment (MCI). MCI patients experience memory loss to a greater extent than one would expect for age, yet they do not meet currently accepted criteria for clinically probable AD [3]. Amyloid deposition is the central event in the aetiology of the disease [22]. The amyloid hypothesis proposed that the fundamental cause of AD is the accumulation of the peptide Aβ in the brain. This hypothesis has been supported by observations that genetic defects in APP and presenilin increase Aβ production and cause familial AD [5]. The paired helical filament is the major fibrous component of neurofibrillary pathology in AD [18]. The hyperphosphorylation of tau results both from an imbalance between the activities of tau kinases and tau phosphatases as well as changes in tau's conformation which affects its interaction with these enzymes. A decrease in the activity of protein phosphatase-2A (PP-2A) in AD brain and certain missense mutations seen in frontotemporal dementia promotes the abnormal hyperphosphorylation of tau [26]. Abnormal interactions and misfolding of synaptic proteins in nervous system are being extensively explored as important pathogenic events resulting in neurodegeneration in Alzheimer's. In Alzheimer's, misfolded amyloid-beta peptide (Aβ), a proteolytic product of APP metabolism, accumulates in neuronal ER and extracellularly as plaques. It has been proposed that translocation of misfolded proteins to mitochondrial membrane plays an important role in either triggering or perpetuating neurodegeneration. The insights obtained from the characterization of this process may be applied to the role of mitochondrial dysfunction in the disease. New evidence may also provide a rationale for the mitochondrial membrane as a target for therapy in a variety of neurodegenerative diseases [39]. Certain shared features exist in the pathogenesis of vascular disease and AD in the general population. In Down syndrome all adults over the age of 40 years develop sufficient neuropathology for a diagnosis of AD [36]. Oxidative stress is an early event in AD, occurring prior to cytopathology and therefore may play a key pathogenic role in AD [9]. Synapse formation and function is modulated by amyloid precursor protein (APP). Lack of APP increases the number of functional synapses [49]. Most often, AD is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier. Everyone experiences slight cognitive changes during aging but the symptoms of Alzheimer's are quite different from those.

Lewy bodies (LB), the characteristic pathological lesion of substantianiagra neurons in Parkinson's disease, are frequently observed to accompany the amyloid plaque and neurofibrillary tangle pathology of Alzheimer's disease. However, the typical anatomic distribution of Lewy bodies in Alzheimer's disease is distinct from Parkinson's disease. The most common site of occurrence is the amygdale, where LBs are observed in approximately 60% of both sporadic and familial Alzheimer's disease. Other common sites of occurrence include the periamygdaloid and entorhinal cortex, while neocortical and brainstem areas develop LBs in a lower percentage of cases. The observation of LBs in FAD cases suggests that like neurofibrillary tangles, the formation of LBs can be induced by pathological state caused by Aβ overproduction. The role of LB formation in the dysfunction and degeneration of neurons remains unclear. The protein alpha-synuclein appears to be an important structural component of LBs, an observation spurred by the discovery of point mutations in the alpha-synuclein gene linked to rare cases of autosomal dominant PD. Further investigation of alpha-synuclein and its relationship to pathological conditions promoting LB formation in Alzheimer's disease, PD and dementia with lewy bodies (DLB) may yield further insight into pathogenesis of these diseases [32].



Dr. Alois Alzheimer

Alois Alzheimer's patient Auguste Deter in 1906

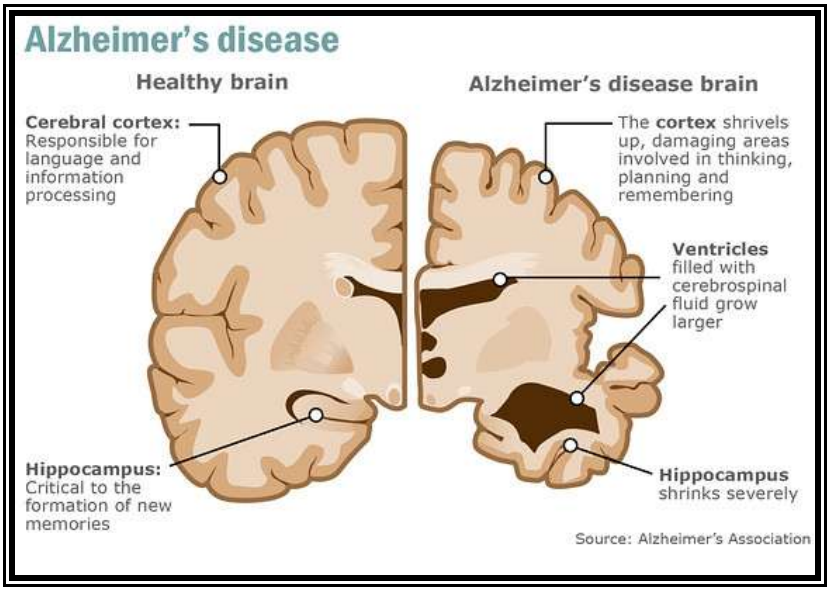


Fig 1:- Comparison of Alzheimer's Affected Brain and Normal Brain.

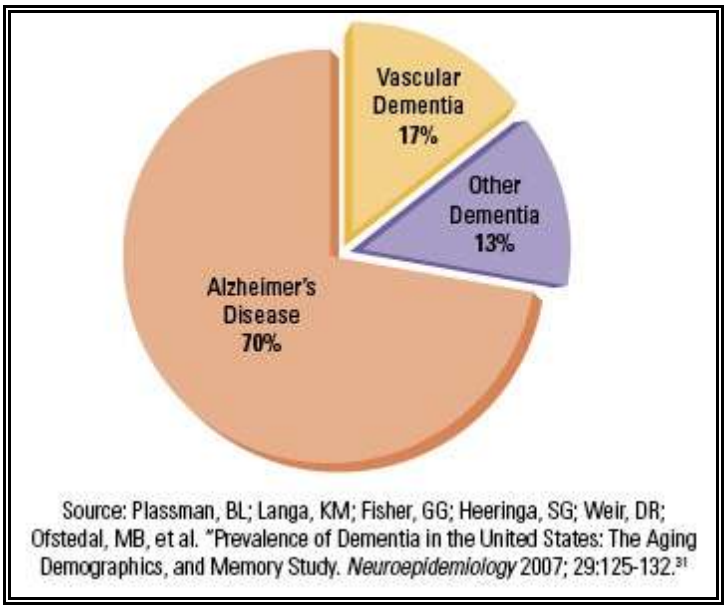


Fig 2:- Prevalence of Dementia.

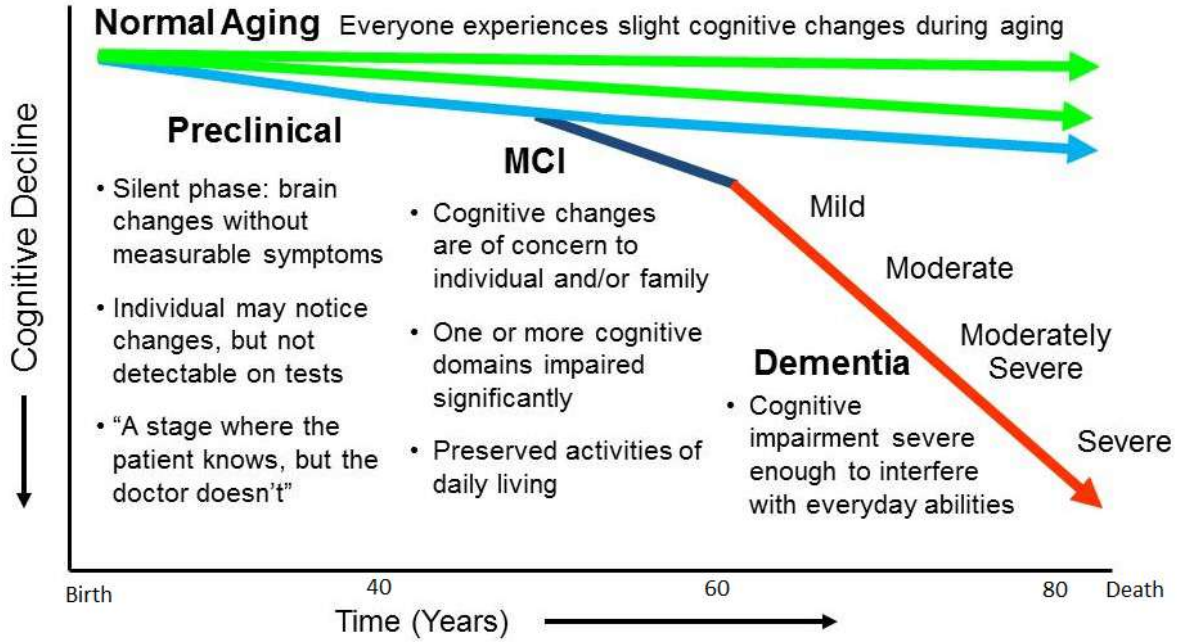


Fig 3:- Stages of Alzheimer's Disease.

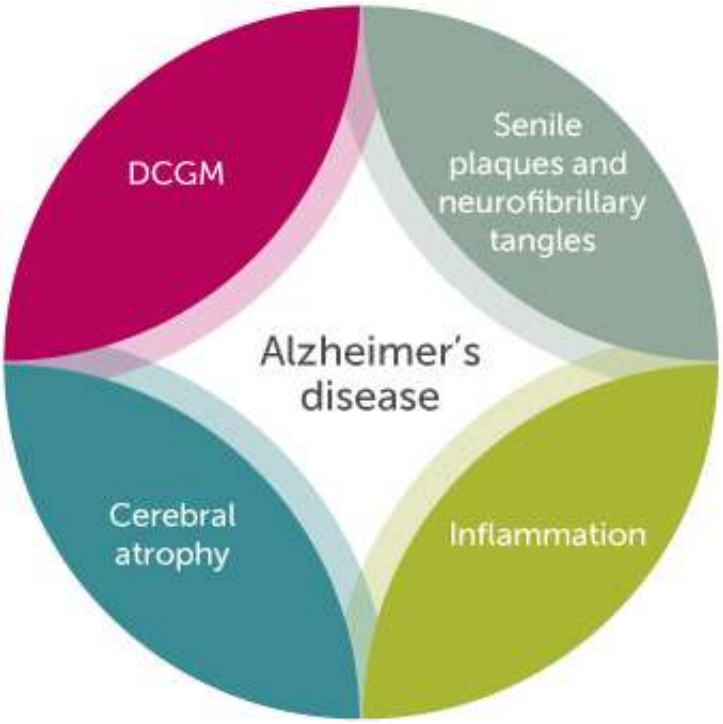
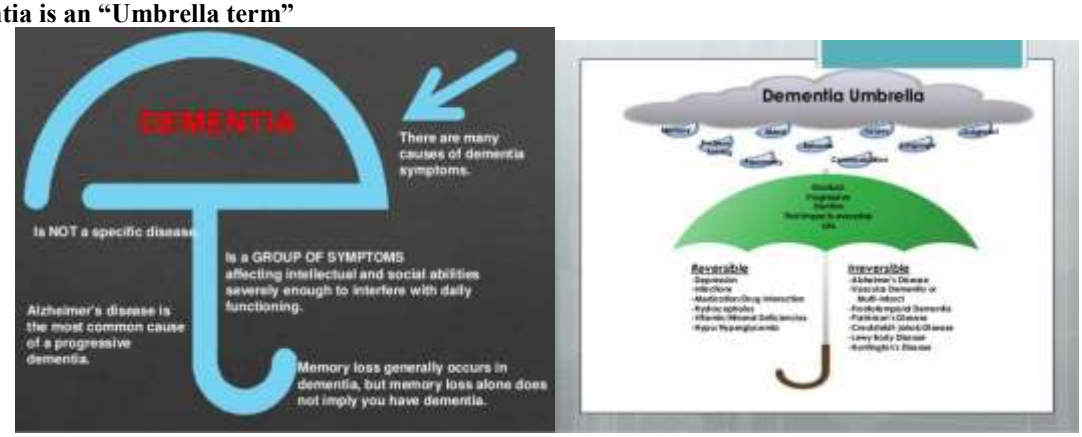
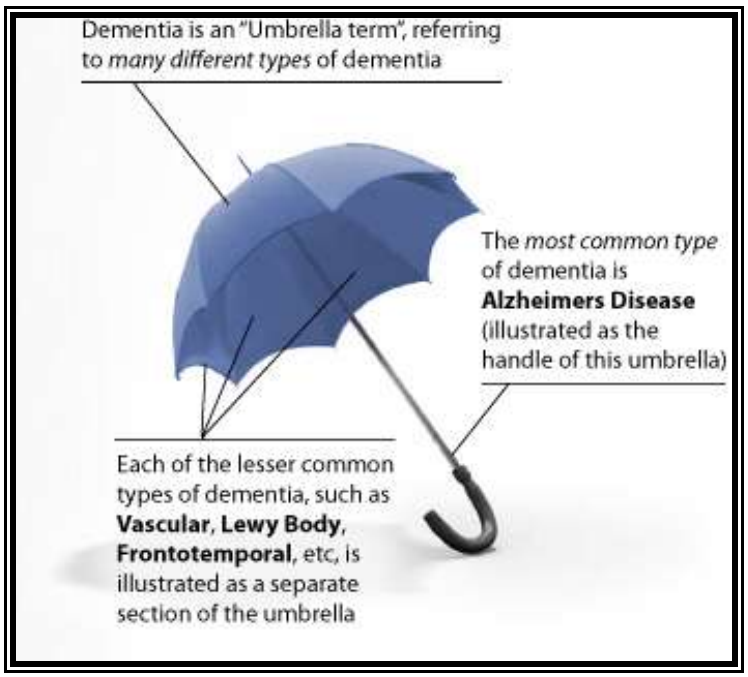


Fig 4:- Four characteristic pathological features in the Alzheimer's brain and they are not directly addressed by current drug treatments.
Note: DCGM = Decreased Cerebral Glucose Metabolism

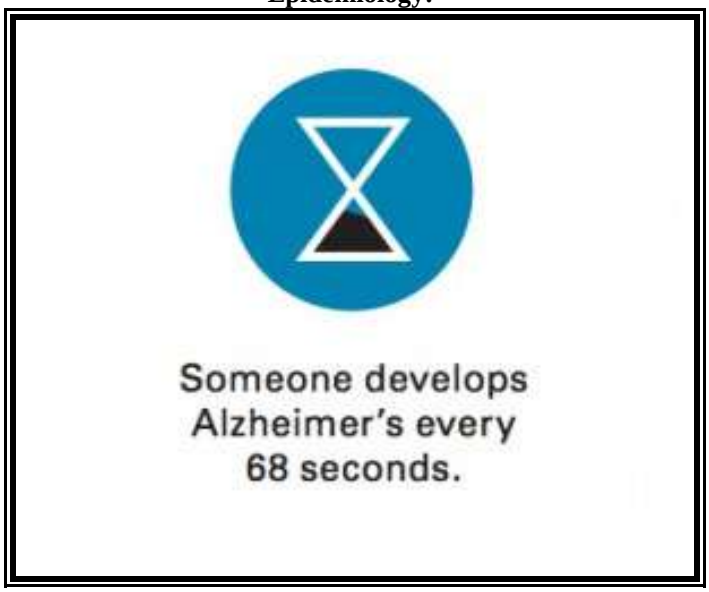
Dementia is an "Umbrella term"





- ✓ **There are 750,000 people with dementia in the UK with numbers set to rise to over 1 million by 2021! This will soar to 1.7 million by 2050!**

Epidemiology:-



Most often, AD is diagnosed in people over **65 years** of age, although the less prevalent early-onset Alzheimer's can occur much earlier.

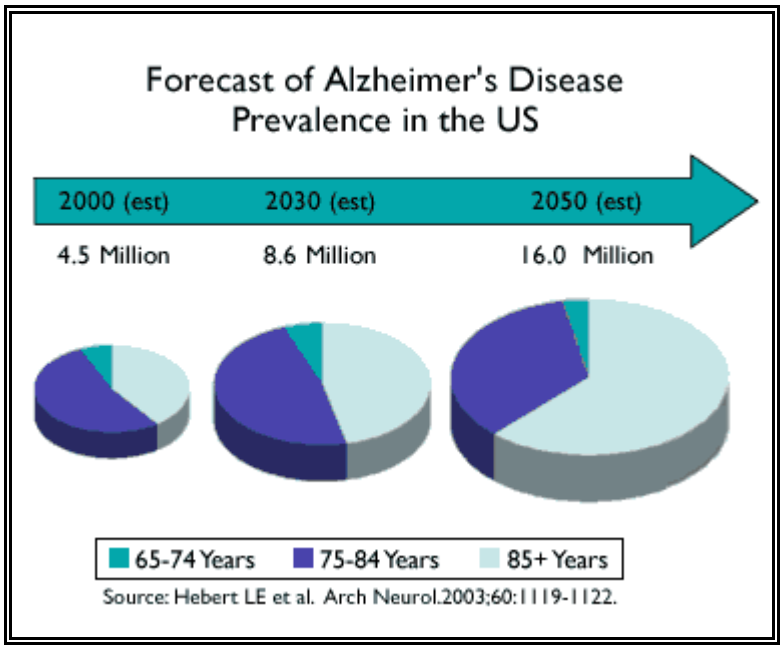


Fig 5:- Forecast of Alzheimer's Disease Prevalence in the U.S.

Table 1:- Prevalence of Dementia.

The Prevalence of Dementia	
Age Group	International Prevalence Rate
60 – 64	1.3 %
65 – 69	2.2 %
70 – 74	3.8 %
75 – 79	6.5 %
80 – 84	11.6 %
85 – 89	20.1%
90 +	41.5%

In **2006**, the worldwide prevalence of Alzheimer's disease was **26.6** million. By **2050**, the prevalence will **quadruple**, by which time **1** in **85** persons worldwide will be living with the disease. It has been estimated that about **43%** of prevalent cases need a high level of care, equivalent to that of a nursing home [11]. If interventions could delay both disease onset and progression by a modest one year, there would be nearly **9.2** million fewer cases of the disease in **2050**, with nearly the entire decline attributable to decreases in persons needing a high level of care.

We face a looming global epidemic of AD as the world's population ages. Modest advances in therapeutic and preventive strategies that lead to even small delays in the onset and progression of AD can significantly reduce the global burden of this disease.

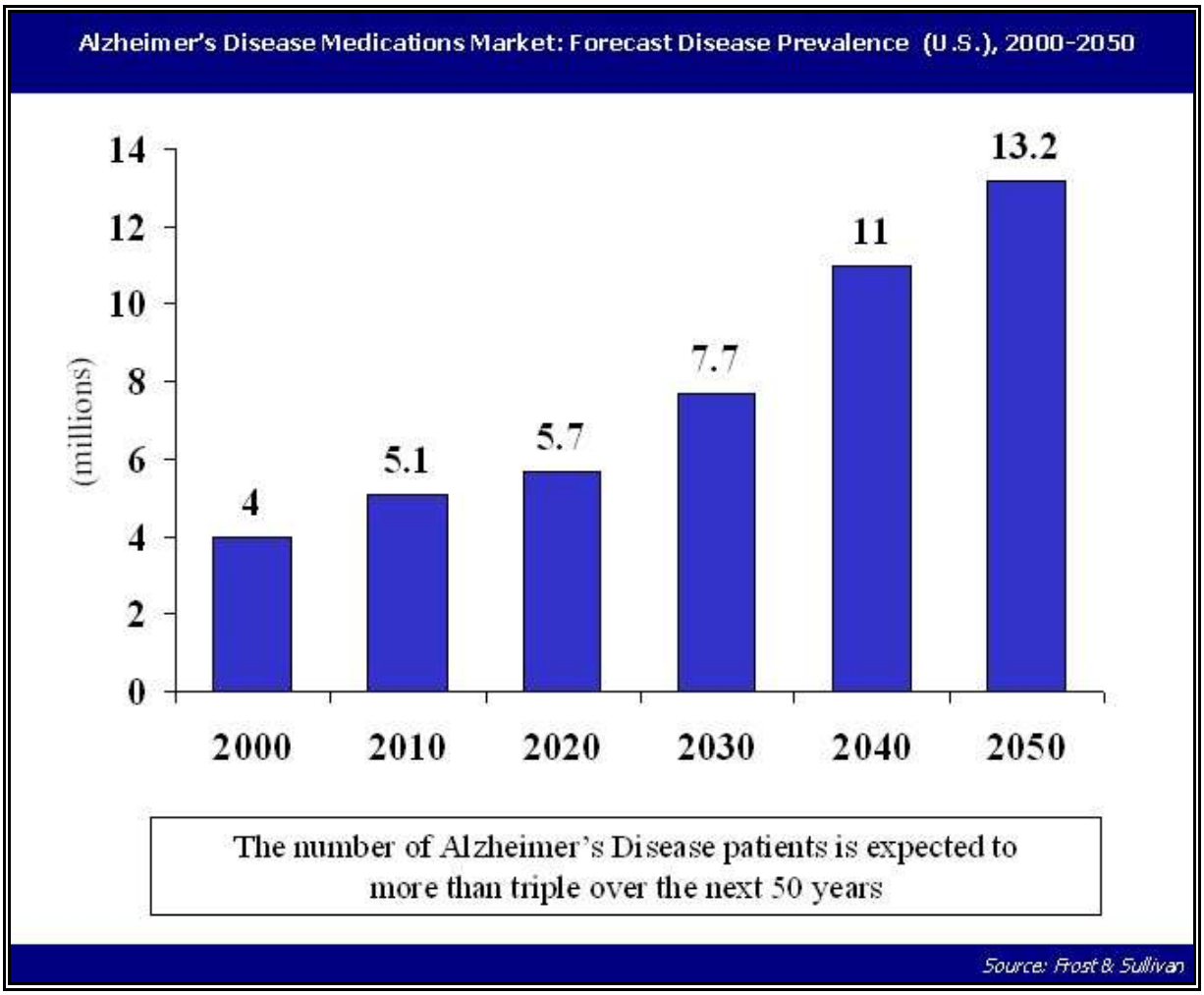


Fig 6:- Forecast of Alzheimer's Disease Prevalence (U.S.), 2000-2050

The number of **Latinos** suffering from Alzheimer's is predicted to increase **600%** by the year **2050**. At that moment, the life expectancy for Latinos will exceed all the other ethnic groups', reaching 87 years. Latin community develops Alzheimer's and other memory problems nearly **10 years** before the rest of Americans. They have a greater vulnerability to the disease than non-Latino white Americans. The risk for developing AD is **1.5times** greater for Latinos than for non-Latino white Americans. Existing evidence indicates that conditions like diabetes, obesity, high pressure and high cholesterol can be risk factors for AD. Specifically, the scientists are finding new evidence that could connect type II diabetes to AD. Latinos present each one of these risk factors. Although there is a greater rate of Latinos versus non-Latinos suffering from AD in the U.S., there is greater probability for Latinos to get a non-specific or incorrect diagnosis. The lack of sufficient healthcare coverage for the population leads to fewer confirmed cases and lack of critical care. Latinos face greater risk of developing the disease and other types of dementia because they live longer but, at the same time, they have higher rates of cardiovascular problems which is also a risk factor of AD [69].

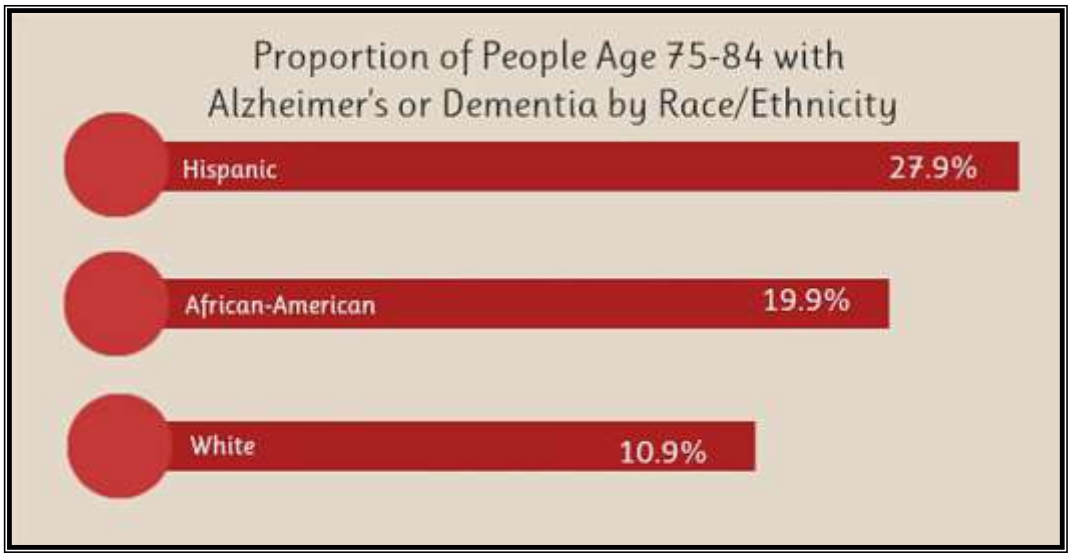
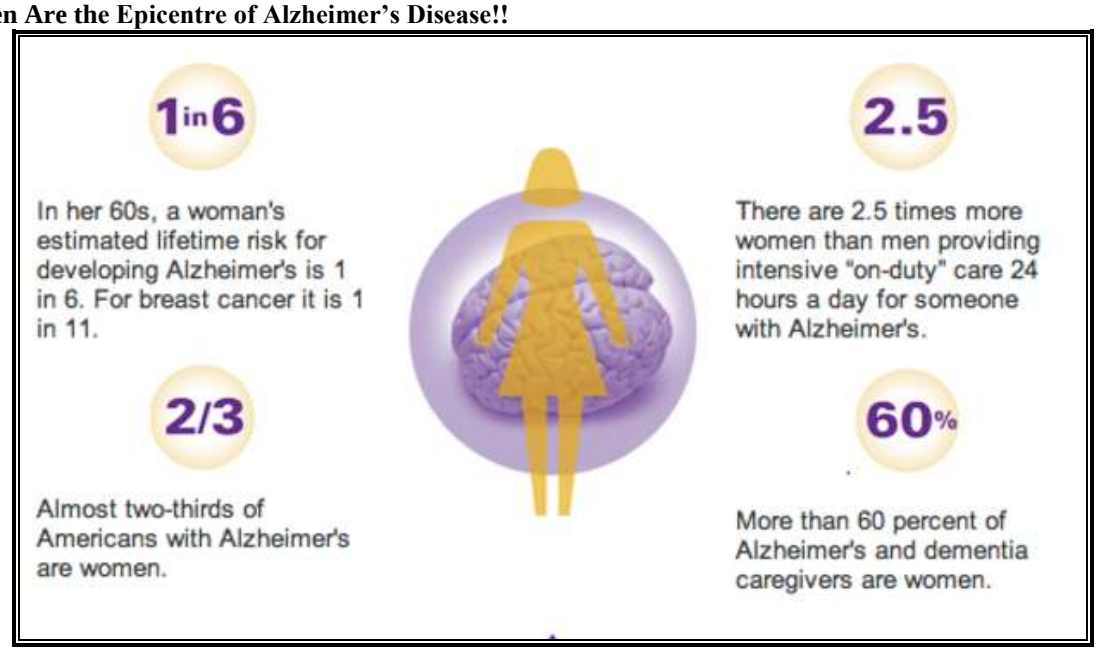


Fig 7:- Proportion of People Age 75-84 with Alzheimer's or Dementia by Race/Ethnicity.

Women are more prone to this disease than men [58]. Almost **two-thirds** of **Americans** with Alzheimer's are **women**. A woman's estimated lifetime risk of developing AD at age **65** is **1** in **6**, compared with nearly **1** in **11** for a man. As real a concern as breast cancer is to women's health, women in their **60s** are about **twice** as likely to develop **AD** over the rest of their lives as they are to develop **breast cancer** [71].

Women Are the Epicentre of Alzheimer's Disease!!



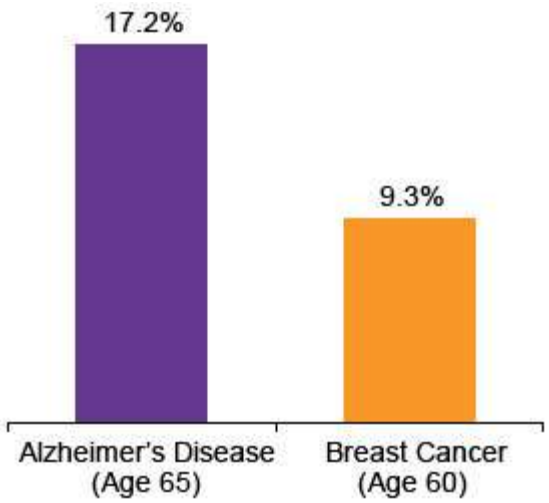


Fig 8:- Comparative Analysis of Alzheimer's Disease and Breast Cancer.

Several studies have suggested a link between high formal education levels and a lower risk of dementia and AD. Furthermore, research has shown a tendency for those in highly skilled occupations to be less likely to develop the disease than those in lower skilled, "blue-collar" jobs. People working in **low-skilled occupations** were at a greater risk of developing AD. People with combination of a low-skilled job and low education levels were at almost **three times** the risk of developing AD. While educated people tend to develop AD and other forms of dementia much later in life, it has been found that highly educated individuals appear to deteriorate much quicker upon diagnosis of AD. It is thought that those with higher levels of education may be better able to tolerate a small degree of deterioration in brain meaning early stage AD might go unnoticed for a long period of time. Because of this, AD may be well advanced at the time of diagnosis which might explain the faster rates of mental decline observed in highly educated people following the diagnosis of AD [72].

People who were living with a **spouse** or a **partner** in midlife ran a **50%** lower risk of developing dementia during their older years than people living alone. How long a person had been single and the reason they were single also affected risk. Living alone for entire adult life **doubled** risk, but those who had been married and then divorced and remained single in midlife showed **three times** the risk. The people were at greater risk of developing dementia who had lost their partner before middle age and then continued to live as a widow or widower. These individuals had a **six times** greater chance of developing AD than those who were married [121].

Status of Alzheimer's Disease in Asian Countries including India and China:-

Among Asian population including **India** and **China**, the prevalence of the disease is low compared to the **Latino** and **non-Latino Americans**, increased with age and was not associated with gender or literacy. Possible explanations include low overall life expectancy, short survival with the disease and low age-specific incidence potentially due to differences in the underlying distribution of risk and protective factors compared with populations with higher prevalence [12].

First AD incidence rates were reported from **Southern India**. The incidence rates appear to be much higher than that reported from **rural north India**, comparable with that reported from **China** and marginally lower than that reported from the **western world** [41].

As of **2013**, there were an estimated **44.4** million people with dementia worldwide. The number will increase to an estimated **75.6** million in **2030** and **135.5** million in **2050**. Much of the increase will be in developing countries. Already **62%** of people with dementia live in developing countries, but by **2050** this will rise to **71%**. The fastest growth in the elderly population is taking place in **China**, **India** and their **South Asian** and **Western Pacific neighbours** [70].

The occurrence of the disease will set to rise significantly from the current 28,000 cases to 80,000 cases in 2030 among Singaporeans aged 60 and above [122].

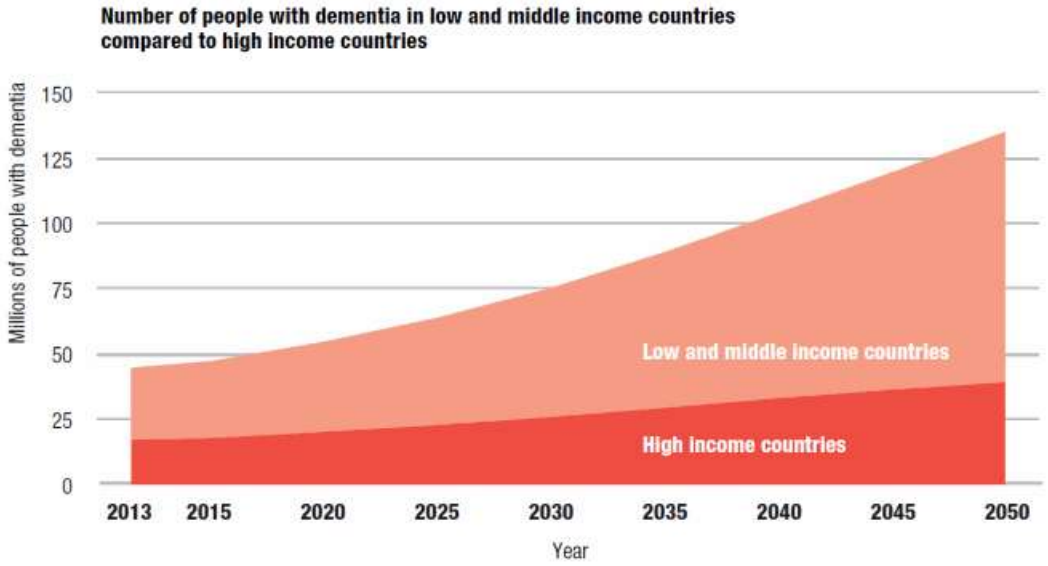
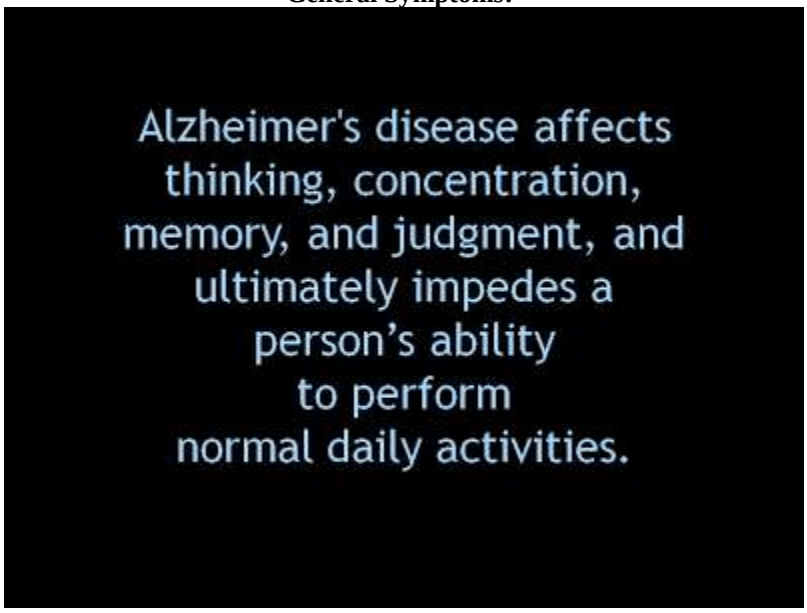


Fig 9:- Number of People with Dementia in Low and Middle Income Countries Compared to High Income Countries

General Symptoms:-



The disease causes memory loss, changes in thinking and behavior. Usually, the symptoms develop slowly and get worse over time becoming severe enough to interfere with daily tasks [67].

Patients with Alzhiemer's

- ✓ **As the population ages, finding a cure for AD is increasingly imperative – but there will be a number of hurdles to overcome along the ways!!**

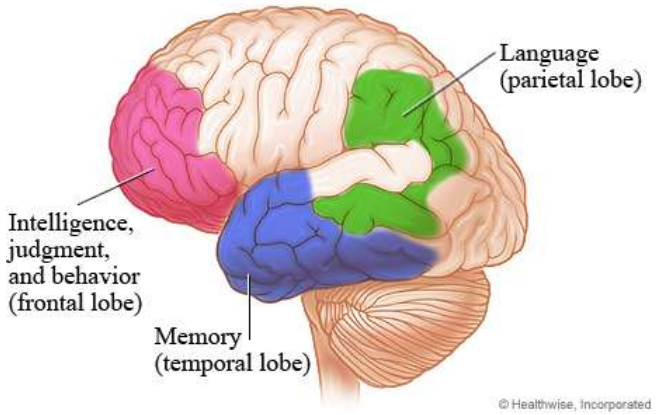


Fig 10:- Areas of Brain Affected by Alzheimer's and other Dementias.

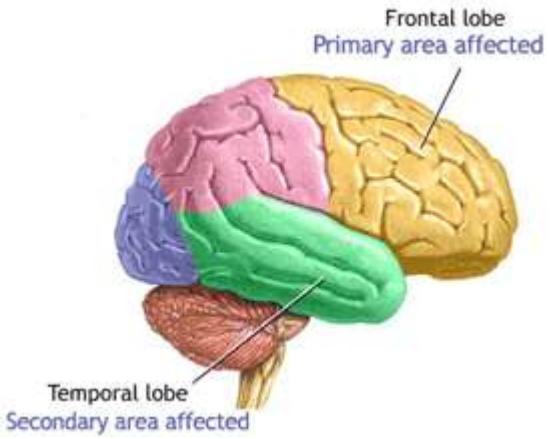


Fig 11:- Primary and Secondary Area of Brain Affected in Alzheimer's Disease.

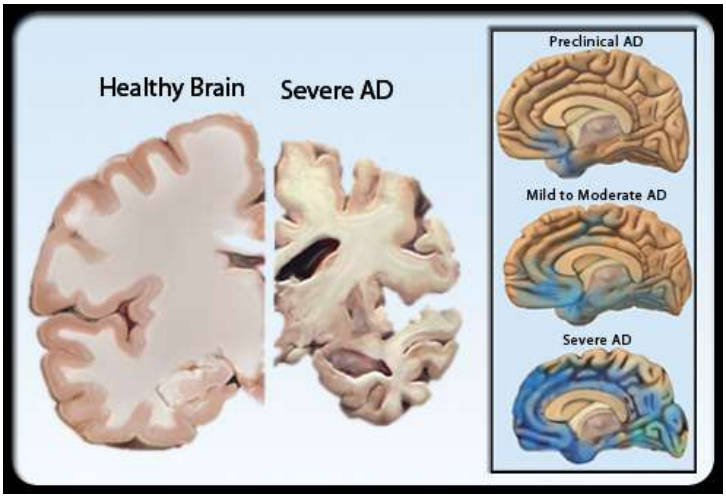
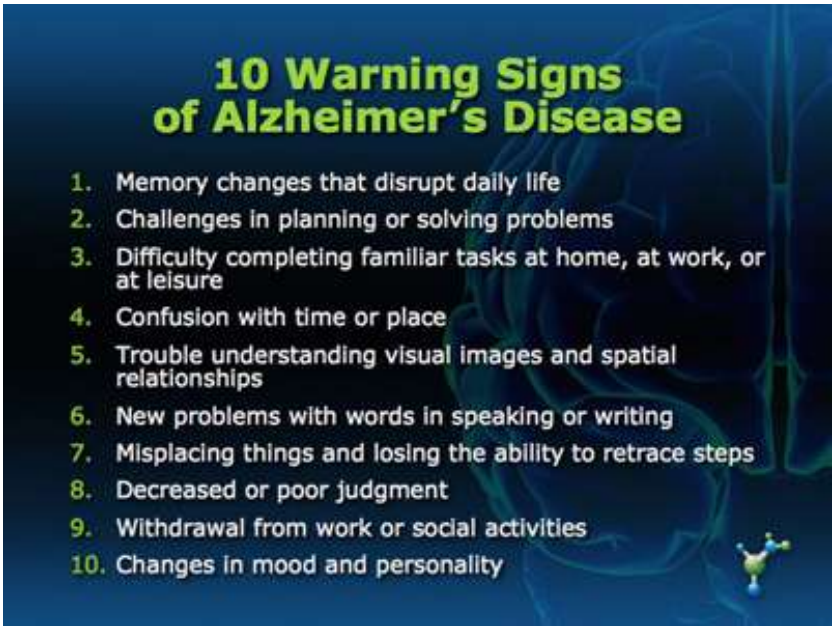


Fig 12:- Difference between Healthy Brain and Brain Affected with Severe Alzheimer's Disease.

Understanding the significance of these age-related changes begins with knowing the difference between what is normal and what is an early symptom of Alzheimer's [68].

Table 2:-

Signs Of Normal Change vs. Early Alzheimer's Symptoms	
Normal	**Early Alzheimer's Disease**
Can't find your keys	Routinely place important items in odd places, such as keys in the freeze, wallet in the dishwasher
Search for casual names & words	Forget names of family members and common objects, or substitute words with inappropriate ones
Briefly forget conversation details	Frequently forget entire conversations
Feel the cold more	Dress regardless of the weather, wear several skirts on a warm day, or shorts in a snow storm
Can't find a recipe	Can't follow recipe directions
Forget to record a cheque	Can no longer manage chequebook, balance figures, solve problems, or think abstractly
Cancel a date with friends	Withdraw from usual interests and activities, sit in front of the TV for hours, sleep far more than usual
Make an occasional wrong turn	Get lost in familiar places, don't remember how you got there or how to get home
Feel occasionally sad	Experience rapid mood swings, from tears to rage, for no discernible reason



Famous People with Alzheimer's.

Charlton Heston

Ronald Reagon

Rita Hayworth

Glen Campbell

How does it happen?

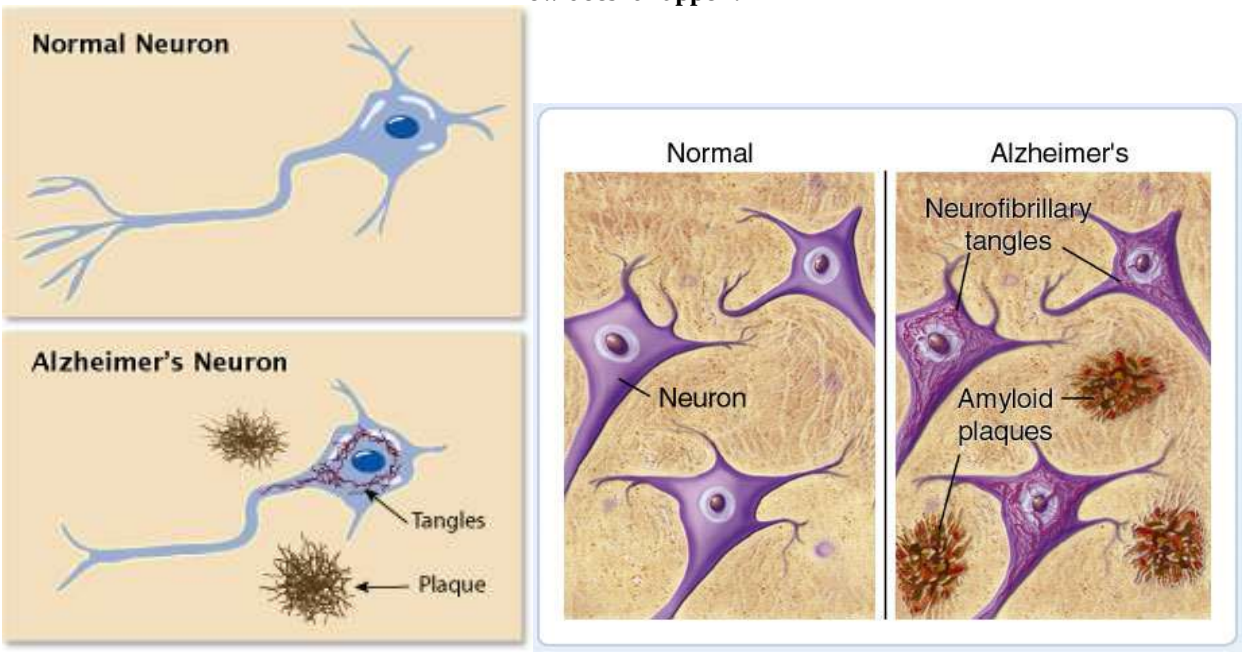


Fig 13:- Tangles and Plaques of Alzheimer's Disease.

1. Clumps of protein *(amyloid plaques and tau tangles)* grow in brain.
2. Protein strands twist, damaging brain cells *(neurons).*
3. Brain cells die, certain areas of brain shrink.

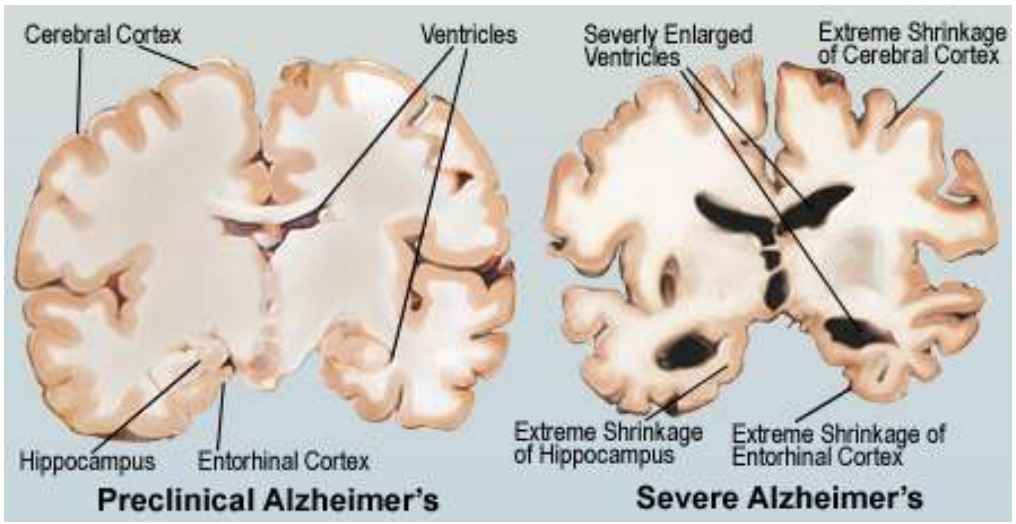


Fig 14:- Effect of Preclinical and Severe Alzheimer's Disease on Brain.

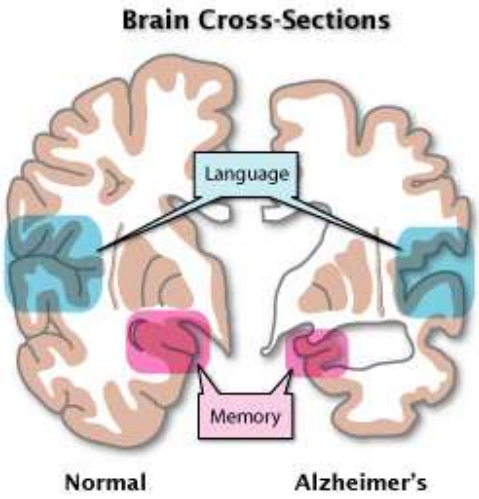
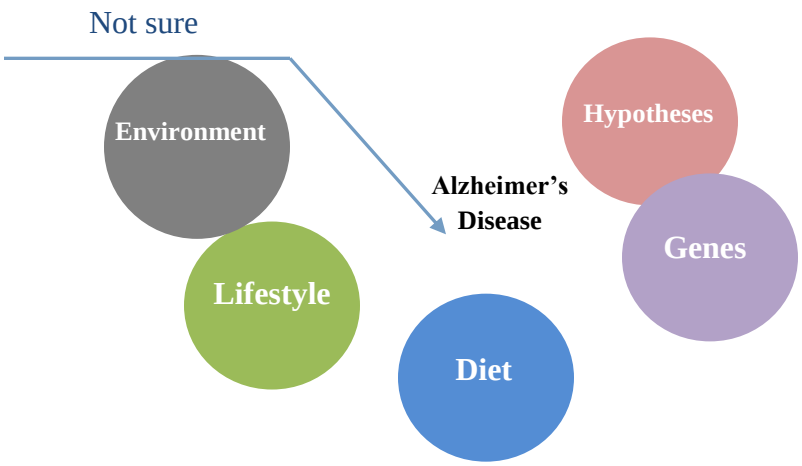


Fig 15:- Difference between Normal Brain and Alzheimer's affected Brain

Cause.



The cause for most Alzheimer's cases is still mostly unknown. It may be a combination of various genetic and environmental factors that trigger the process in which neurons are destroyed. Several competing hypotheses exist trying to explain the cause of the disease:

Cholinergic Hypothesis:-

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 generalized neuroinflammation [66].

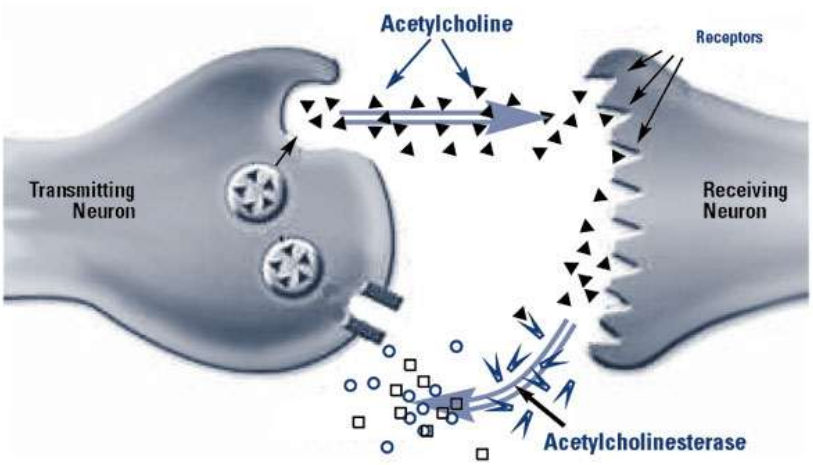


Fig 16:- After signalling, acetylcholine is released from receptors and broken down by acetylcholinesterase to be recycled in a continuous process.

Amyloid Cascade Hypothesis.

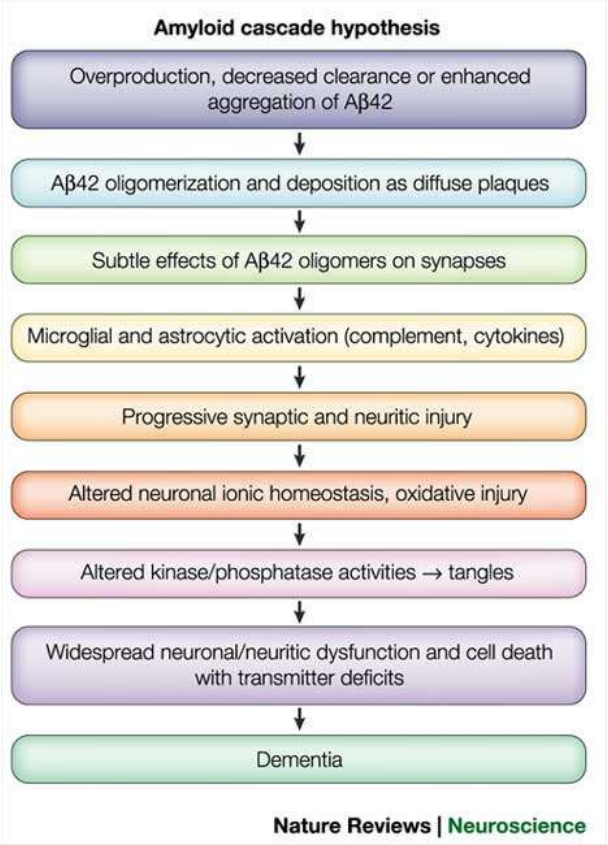


Fig 17:- Amyloid Cascade Hypothesis.

The sequence of pathogenic events that are thought to lead to Alzheimer's disease is shown. The cascade is initiated by the generation of **amyloid-β 42** (**Aβ42**). In familial early-onset AD, **Aβ42** is overproduced owing to pathogenic mutations. In sporadic AD, various factors can contribute to an increased load of **Aβ42 oligomers** and **aggregates**. Amyloid-β oligomers might directly injure the synapses and neurites in brain neurons, in addition to activating microglia and astrocytes. Tau pathology, which contributes substantially to the disease process through hyperphosphorylated tau and tangles, is triggered by **Aβ42**.

Tau Hypothesis:-

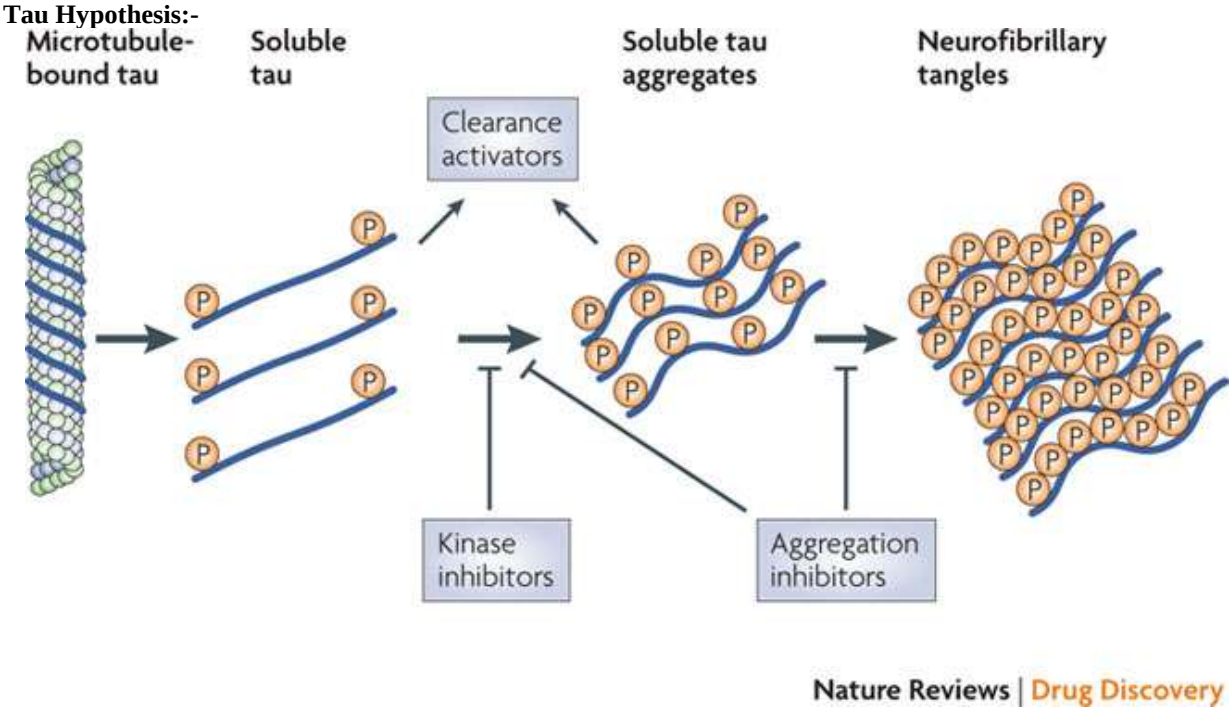


Fig 18:- Tau Hypothesis.

Microtubule-bound soluble tau supports axonal transport. Tau is hyperphosphorylated in Alzheimer's disease, which could lead to the detachment of tau from microtubules, which could then lead to the formation of soluble tau aggregates and insoluble paired helical filaments that ultimately form neurofibrillary tangles. Destabilization of microtubules (impairing axonal transport) and direct toxic effects of soluble hyperphosphorylated tau and fibrillar tau may all contribute to tau-mediated neurodegeneration. Anti-phosphorylated strategies (kinase inhibitors) aim to inhibit these processes. Aggregation inhibitors could block the formation of soluble tau aggregates and the formation of tangles. Tau toxicity could also be prevented by enhancing the clearance of tau and the degradation of tau aggregates.

Genetic Basis of Alzheimer's Disease:-

Epistasis in case of Alzheimer's Disease:-

Understanding **epistatic interactions** may be the key to understand complex diseases, such as Alzheimer's disease, diabetes, cardiovascular diseases and cancer. Alzheimer's disease, is a progressive neurodegenerative disorder that causes memory loss and dementia. In the early 1990s, a number of scientists found that a gene called **apolipoprotein E4** was associated with a higher risk of developing Alzheimer's disease. However, the researchers also noted that while having one or two copies of **apolipoprotein E4** increases one's risk of Alzheimer's, not all carriers of **apolipoprotein E4** develop this disease. This suggested that other genes and/or gene-gene interactions were involved in the development of this disease. Eventually, it was confirmed that 27 different significant epistatic interactions are involved which were grouped into 5 categories: cholesterol metabolism, beta-amyloid production, inflammation, oxidative stress and other networks. Some interactions were synergistic, while others were antagonistic. The synergistic interactions indicate that the pair of genes involved together increases the risk of Alzheimer's disease. Meanwhile, the antagonistic relationships indicate a protective relationship between two genes. Many of the other predictions of **epistasis** between genes could also prove to be significant if a larger population of Alzheimer's patients were studied. Indeed, now that there is a foundation for understanding epistatic interactions between pairs of genes in sporadic Alzheimer's disease, future studies can focus on epistatic interactions between combinations of three or more genes and between additional pairs of genes.

Alzheimer's disease is characterized by the development of amyloid plaques and neurofibrillary tangles, the loss of connections between neurons in brain and death of these nerve cells. There are two types of Alzheimer's – **early-onset** and **late-onset**. Both types have genetic components [73].

Early-onset Alzheimer's disease occurs in people **age** of year **30** to **60**. Some cases of early-onset Alzheimer's have no known cause, but most cases are inherited, a type known as **Familial Alzheimer's Disease** (**FAD**).

Genetic factors Associated with Alzheimer's Disease.

Table 3:-

Chromosome	Defective Gene	Onset	Putative Mechanisms
21	APP	Early	Increased production of Aβ42
19	APOE ε4	Late	Tau hyperphosphorylation Impaired production/ polymerization/ clearance of Aβ
14	PS-1	Early	Increased production of Aβ42
1	PS-2	Early	Altered Aβ metabolism

Note: APP = amyloid precursor protein; Aβ = beta-amyloid protein; APOE = apolipoprotein; PS = presenilin.

Familial Alzheimer's Disease is caused by any one of a number of different single-gene mutations on chromosomes 21, 14 and 1. Each of these mutations causes abnormal proteins to be formed. Mutations on chromosome 21 cause the formation of abnormal amyloid precursor protein (APP). A mutation on chromosome 14 causes abnormal presenilin-1 to be produced, and a mutation on chromosome 1 leads to abnormal presenilin-2. Most mutations in the APP and presenilin genes increase the production of a small protein called $A\beta_{42}$, which is the main component of senile plaques. Each of these mutations plays a role in the breakdown of APP, a protein whose precise function is not yet known. This breakdown is part of a process that generates harmful forms of amyloid plaques, a hallmark of the disease. A child whose mother or father carries a genetic mutation for FAD has a 50/50 chance of inheriting that mutation. If the mutation is in fact inherited, the child almost surely will develop FAD.

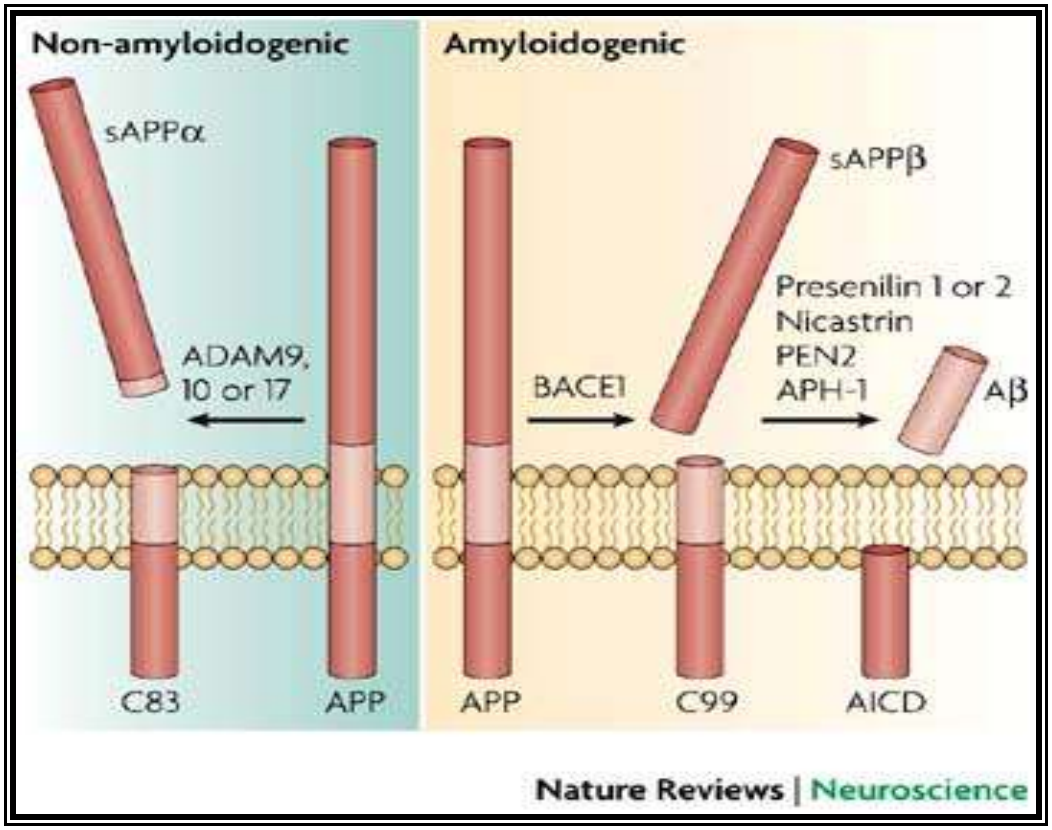


Fig 19:-APP Proteolysis.

The amyloid-β (Aβ) peptide is derived via proteolysis from a larger precursor molecule called the amyloid precursor protein (APP), a type 1 transmembrane protein consisting of 695-770 amino acids. APP can undergo proteolytic processing by one of two pathways. Most is processed through the non-amyloidogenic pathway, which precludes Aβ formation. The first enzymatic cleavage is mediated by α-secretase, of which three putative candidates belonging to the family of a disintegrin and metalloprotease (ADAM) have been identified: ADAM9, ADAM10 and ADAM17. Cleavage by α-secretase occurs within the Aβ domain, thereby preventing the generation and release of the Aβ peptide. Two fragments are released, the larger ectodomain (sAPPα) and the smaller carboxy-terminal freagment (C83). Furthermore, C83 can also undergo an additional cleavage mediated by γ-secretase to generate P3 (not shown). APP molecules that are not cleaved by the non-amyloidogenic pathway become a substrate for β-secretase (β-site APP-cleaving enzyme 1; BACE1), releasing an ectodomain (sAPPβ) and retaining the last 99 amino acids of APP (known as C99) within the membrane. The first amino acid of C99 is the first amino acid of Aβ. C99 is subsequently cleaved 38-43 amino acids from the amino terminus to release Aβ, by the γ-secretase complex, which is made up of presenilin 1 or 2, nicastrin, anterior pharynx defective and presenilin enhancer 2. This cleavage predominantly produces $A\beta_{1-40}$ and the more amyloidogenic $A\beta_{1-42}$ at a ratio of 10:1. AICD, APP intracellular domain; APH-1, anterior pharynx defective; PEN2, presenilin enhancer 2.

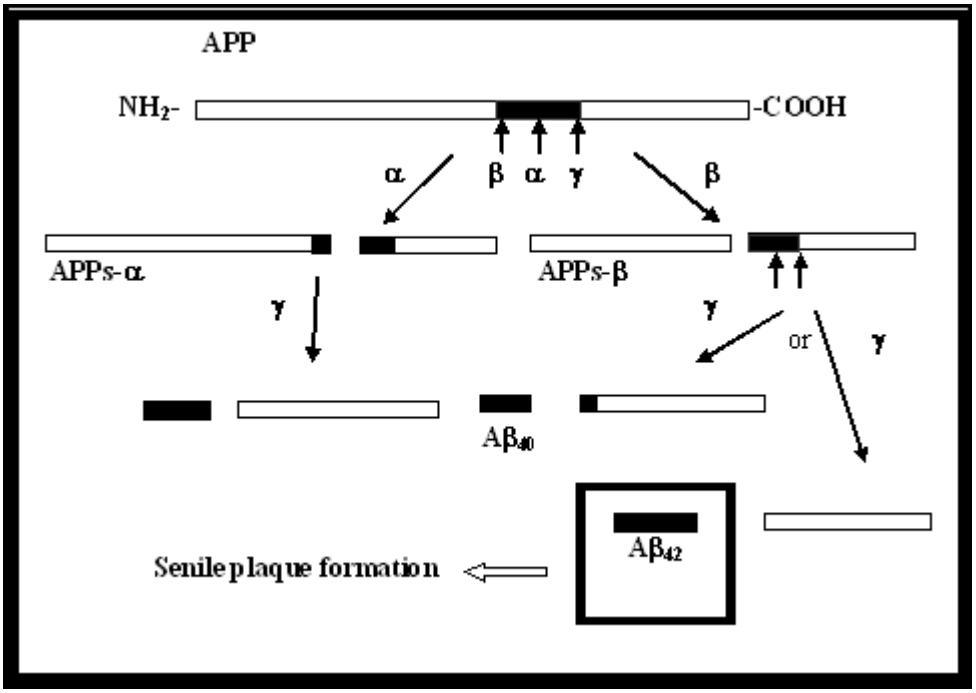


Fig 20:- Action of Secretases.

Late-onset Alzheimer's disease- Most cases of Alzheimer's are late-onset form, which develops after age of **60 years**. The causes of late-onset Alzheimer's are not yet completely understood, but they likely include a combination of genetic, environmental and lifestyle factors that influence a person's risk for developing the disease.

One genetic risk factor appears to increase a person's risk of developing the disease. This increased risk is related to the **apolipoprotein E (APOE)** gene found on **chromosome 19**. APOE contains the instructions for making a protein that helps to carry cholesterol and other types of fat in the bloodstream. **APOE** comes in several different forms, or alleles. Three forms – APOE ε2, APOE ε3 and APOE ε4 occur most frequently.

APOE ε2 is relatively rare and may provide some protection against the disease. If the disease occurs in a person with this allele, it develops later in life than it would in someone with APOE ε4 gene.

APOE ε3, the most common allele, is believed to play a neutral role in the disease – neither decreasing nor increasing risk.

APOE ε4 is present in about 25-30% of the population and in about 40% of all people with late-onset Alzheimer's [73]. The ε4 allele of APOE is significantly associated with an increased risk of late-onset AD [48]. **APOE ε4** is the therapeutic target in Alzheimer's disease [38]. The people who develop the disease more likely to have an APOE ε4 allele than those people who do not develop the disease.

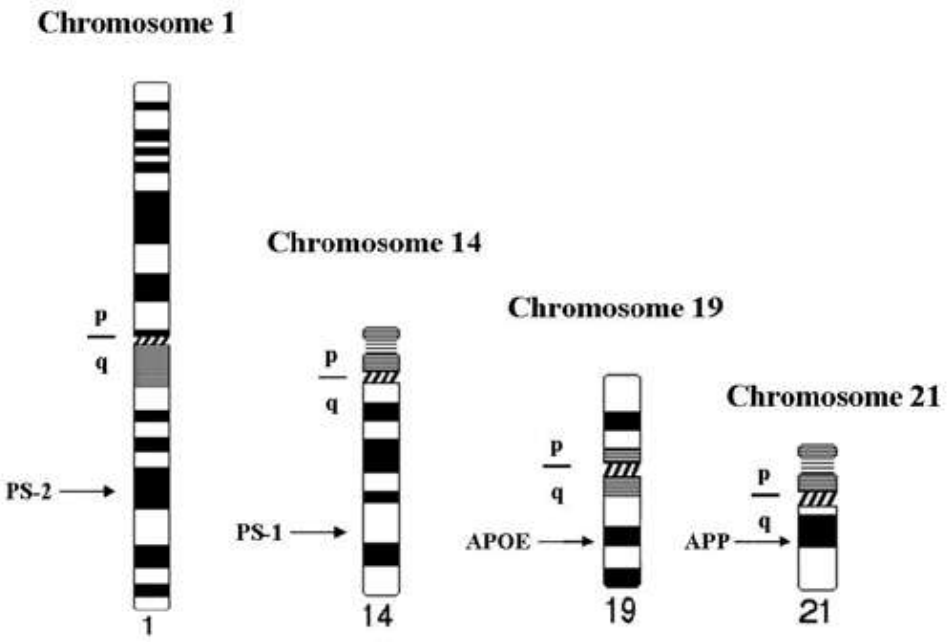


Fig 21:- Ideograms of Human Chromosomes 1, 14, 19 and 21 showing cytogenetic locations of genes presenilin-1, presenilin-2, apolipoprotein E and amyloid-precursor protein.

There was a significant interaction between **cholesterol**, **APOE-ε4** and the risk of AD in Yoruba in Nigeria, a population that has lower cholesterol levels and lower incidence rates of AD compared to African American. APOE status needs to be considered when assessing the relationship between lipid levels and AD risk in population studies [20]. The possible reason may be that APOE contains the instructions for making a protein that helps to carry cholesterol and other types of fat in bloodstream.

Dozens of studies have confirmed that the APOE ε4 allele increases the risk of developing the disease so it is called a risk-factor gene, but how that happens is not yet understood. These studies also help to explain some of the variation in the age at which Alzheimer's disease develops, as people who inherit one or two APOE ε4 alleles tend to develop the disease at an earlier age than those who do not have any APOE ε4 alleles.

However, inheriting an APOE ε4 allele does not mean that a person will definitely develop the disease. Some people with one or two APOE ε4 alleles never get the disease, and others who do not have any APOE ε4 alleles develop Alzheimer's disease.

In addition to APOE ε4, 19 areas of genes have been identified by using a relatively new approach called **Genome-Wide Association Study** (**GWAS**), which may increase a person's risk of developing the disease. These genes include: CASS4, CELF1, FERMT2, HLA-DRB5, INPP5D, MEF2C, NME8, PTK2B, SORL1, ZCWPW1, S1C24A4, CLU, PICALM, CR1, BIN1, MS4A, ABCA7, EPHA1, CD2AP.

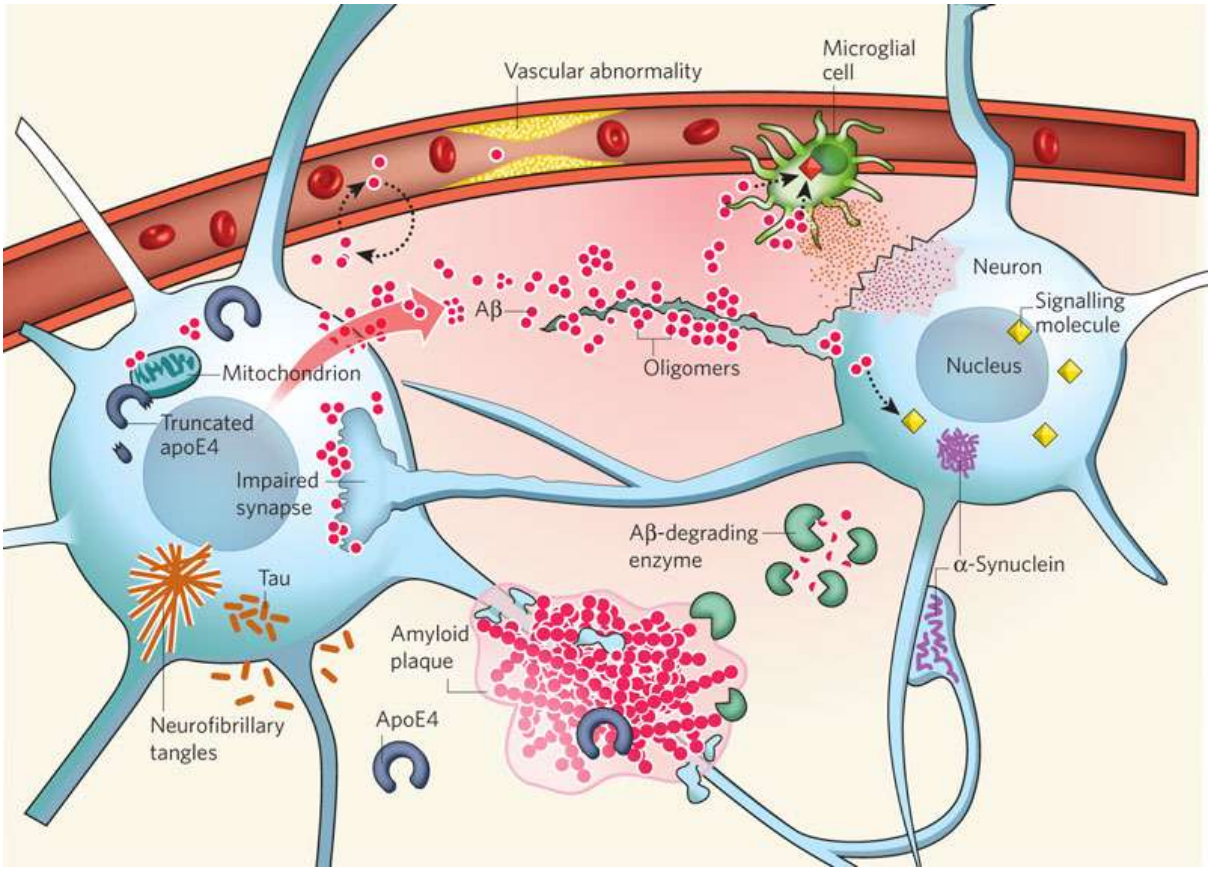


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Fig 22:- Some Key Players in the Pathogenesis of Alzheimer's Disease

Aggregation and accumulation of amyloid-β (Aβ) in the brain may result from increased neuronal production of Aβ, decreased activity of Aβ-degrading enzymes, or alterations in transport processes that shuttle Aβ across the blood-brain barrier. Aβ oligomers impair synaptic functions, whereas fibrillar amyloid plaques displace and distort neuronal processes. Aβ oligomers interact with cell-surface membranes and receptors, altering signal-transduction cascades, changing neuronal activities and triggering the release of neurotoxic mediators by microglia (resident immune cells). Vascular abnormalities impair the supply of nutrients and removal of metabolic by-products, cause microinfarcts and promote the activation of astrocytes (not shown) and microglia. The lipid-carrier protein apoE4 increases Aβ production and impairs Aβ clearance. When produced within stressed neurons, apoE4 is cleaved into neurotoxic fragments that destabilize the cytoskeleton and, like intracellular Aβ, impair mitochondrial functions. The proteins tau and α-synuclein can also self-assemble into pathogenic oligomers and can form larger intra-neuronal aggregates, displacing vital intracellular organelles.

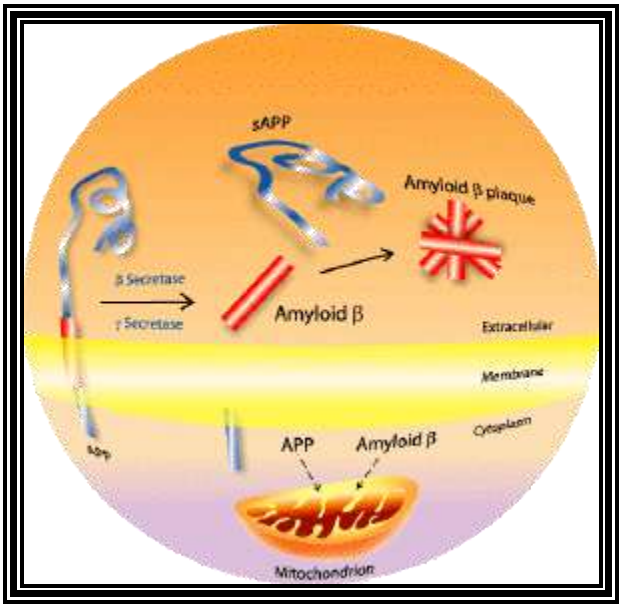


Fig 23:- Role of Mitochondria in Pathogenesos of Alzheimer's Disease.

The involvement of mitochondria in AD has been known for many years with reduced **Cytochrome C oxidase** (**Complex IV**) assembly and activity considered as an early event in the disease and reduced Cytochrome C oxidase activity has been reported in platelets from patients with AD. Recent studies begin to explain mitochondrial involvement. The Alzheimer's APP has now been localized to mitochondria as has the toxic Aβ peptide. The binding site for Aβ has been identified as **alcohol dehydrogenase** in the matrix space of the organelle. This enzyme can metabolize aldehydes and if the function is impaired could be involved in generation of oxidative radicals and a consequent cell death. Another mitochondrial protein implicated in AD is **pyruvate dehydrogenase** [74].

The most common form of Alzheimer's disease i.e., late-onset is thought to be caused by inability of to clear Aβ protein from brain. The production and turnover of **cerebrospinal fluid** (**CSF**) helps to clear toxic molecules like Aβ from the interstitial fluid space of brain to the bloodstream [75].

Presenilin-1 is most commonly associated with the early-onset familial form of Alzheimer's disease. The gene performs a crucial biological function that enables cells to digest unwanted proteins and is essential for brain cell survival. The mutations in the **presenilin-1gene** causes early-onset Alzheimer's disease disrupt this cellular protein recycling process, killing neurons [76].

Mutations in the **TREM2gene** have been associated with a **three** to **five times** risk of developing the disease. A suggested mechanism of action is that when TREM2 is mutated, WBCs in the brain are no longer being able to control the amount of Aβ present [66].

A rare missense mutation (rs75932628-T) in the gene encoding **the triggering receptor expressed on myeloid cells** (**TREM2**), which was predicted to result in an R47H substitution, was found to confer a significant risk of Alzheimer's disease in Iceland. These findings strongly implicate **variant TREM2** is involved in the pathogenesis of Alzheimer's disease [28].

Amyloid Precursor Protein (**APP**) and **Death Receptor 6** (**DR6**) activate a widespread caspase-dependent self-destruction programme. N-APP binds DR6 to cause axon pruning and neuron death via distinct caspases [1].

A novel function of **APP**, one of the main pathogenic culprits of this disease, has been discovered recently. This discovery may help to understand how the protein goes awry in brains of Alzheimer's patients and potentially pave the way for the development of innovative therapeutics to improve brain function in dementia patients. **APP** can control growth and maturation of newborn brain cells, which are critical for the maintenance of a healthy brain function. **APP** does this by regulating a target known as **microRNA-574-5-p**, which normally promotes the

production of newborn neurons in brain. In turn, **APP** antagonizes it to ensure the timely birth of new neurons to support normal brain function. In other words, **APP** controls the growth and maturation of brain cells, without which neuron expression can go unregulated and cause brain activities to go out of control. The mechanisms of how **APP** regulates **microRNA-574-5-p** in association with the impairment of newborn neurons as seen in this disease have not yet been investigated. This **microRNA-574-5-p** may be a potentially useful new target for drug development against Alzheimer's disease. This important finding suggests a link between a key neurodegenerative disease gene and regulation of microRNAs in brain [60, 122].

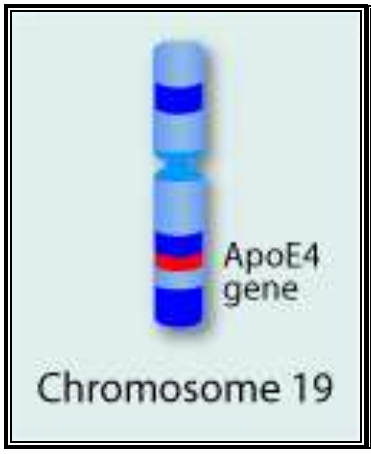
A mutation in **APP** protects against AD and age-related cognitive decline. A coding mutation has been found (A673T) in the APP gene that protects against AD and cognitive decline in the elderly without AD. This substitution is adjacent to the **aspartyl protease β-site** in **APP**, and results in approximately 40% reduction in the formation of amyloidogenic peptides in vitro [29].

Locus cereleus (LC)–supplied **norepinephrine** (**NE**) suppresses neuroinflammation in the brain. Decrease of NE in LC projection areas facilitates the inflammatory reaction of microglial cells in AD and impairs microglial migration and phagocytosis, thereby contributing to reduced Aβ clearance. Consequently, therapies targeting microglial phagocytosis should be tested under NE depletion [24].

A protein (gene) called **Regulator ofCalcineurin 1 (RCNA1)** whose excess production starts a "chain reaction" that destroys neurons in the hippocampus and cortex parts of the brain in people suffering from Alzheimer's disease and Down syndrome. This discovery could one day lead to the development of a therapy or drug to prevent dementia in people suffering from these two conditions [77].

A new gene called **BCHE (Butyrylcholinesterase protein-coding gene)** has been identified to be associated with amyloid plaque deposits found in patients with Alzheimer's disease. This gene is responsible for an enzyme that breaks down acetylcholine in brain [78].

In late-onset familial form of Alzheimer's disease, high-avidity binding of Apolipoprotein E to beta-amyloid and increased frequency of type 4 allele was found. Apolipoprotein E is immunochemically localized to the senile plaques, vascular amyloid and neurofibrillary tangles of the disease. In vitro, apolipoprotein E in CSF binds to synthetic beta A4 peptide (the primary constituent of the senile plaque) with high avidity. Amino acids 12-28 of the beta A4 peptide are required. The gene for APOE is located on **chromosome 19q13.2**, within the region previously associated with linkage of late-onset FAD. Analysis of APOE alleles in Alzheimer's disease and controls demonstrated that there was a highly significant association of APOE type 4 allele (APOE-ε4) and late-onset FAD. It was suggested that APOEε4 isoform has a functional role in the pathogenesis of late-onset FAD [56].



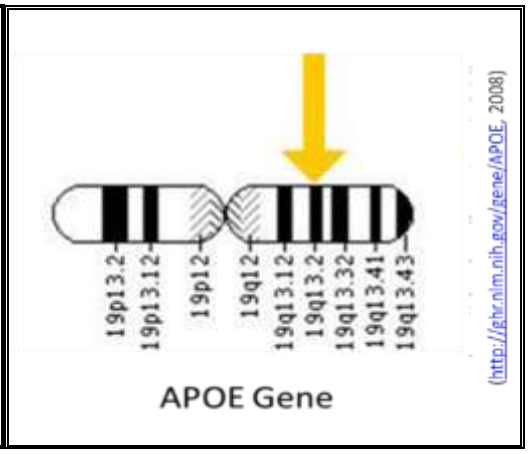


Fig 24:- APOE ε4 Allele**Fig 25:-** APOE Gene.

A brain protein, **Caspase-2** has been identified that may have a role in causing dementia and Alzheimer's. This protein usually maintains the synapses. Disruption of normal synapse function is one of the early effects of this disease, which can lead to neuronal death. It has been thought that Caspase-2 might play a role in the degeneration of synapses. The Aβ plaques in Alzheimer's patients make Caspase-2 and a few other proteins more active, damaging the way electrical signals travel through the brain. This new knowledge about the activities of Caspase-2 protein may help to develop new medical therapies to treat the disease [81].

A new brain protein called **TDP-43** (**TDP-43**, **transactive response DNA binding protein 43 kDa**), has been found linked to Alzheimer's, different from the amyloid and tau that make up the sticky brain plaques and tangles long known to be its hallmarks. The invention could give a new target for developing drugs and other treatments for Alzheimer's, the most common form of dementia. It also might help to explain why many people have plaques and tangles in the brain yet show no symptoms of the disease. Everyone has this protein, TDP-43, but the abnormal form is found in different parts of the cell and in ball-like deposits in certain areas in the brain [80].

Reelin, a crucial protein for adult brain plasticity, recovers cognitive functions in mice with Alzheimer's disease. A new preclinical study demonstrates that an increase in reelin brain levels avoids cognitive deterioration in mouse models of AD. Moreover, reelin delays Aβ fibril formation in vitro and reduces amyloid deposits in mice with Alzheimer's disease [120].

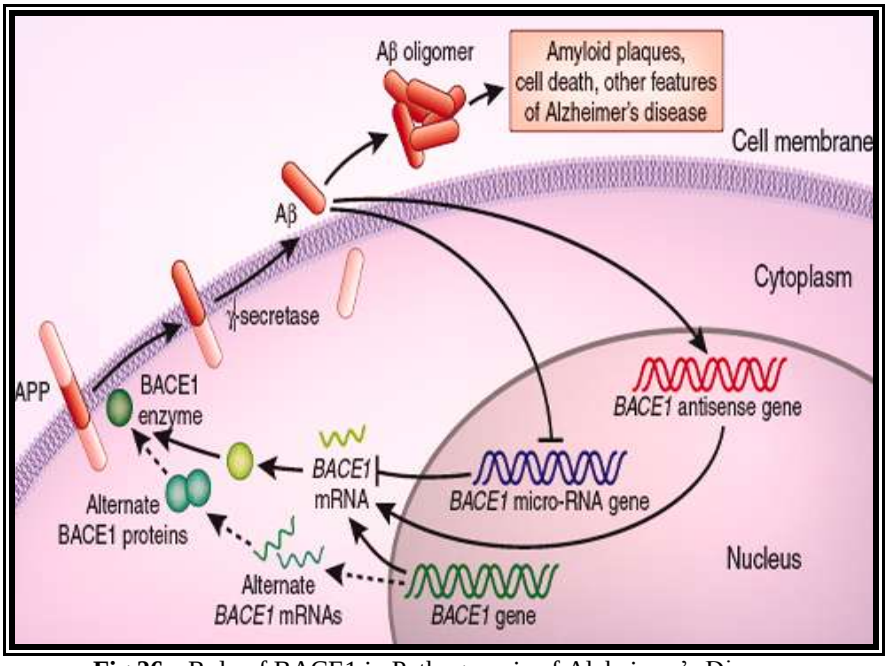


Fig 26:- Role of BACE1 in Pathogenesis of Alzheimer's Disease.

A noncoding antisense RNA against β-secretase, also known as **BACE1** [**β-site amyloid precursor protein** (**APP**) **cleaving enzyme**], may contribute to pathogenesis of the disease. **BACE1** is a vertebrate-specific enzyme, which, together with presenilin-dependent γ-secretase, cleaves APP to generate the neurotoxic Aβ [17].

Brain-derived neurotrophic factor (BDNF) is needed to support neuronal survival and differentiation. It also promotes synaptic remodeling and modulates the function of many other neurotransmitters. Potential association between single nucleotide polymorphism (SNPs) of the BDNF gene (G11757C, C270T, G196A, G-712A) and Alzheimer's related depression was examined. Participants included 336 patients with the disease; 128 of these patients had Alzheimer's-related depression (AD-D). Response to 8-weeks paroxetine treatment was also assessed. The frequency of 11757C allele was significantly higher in Alzheimer's-related depression than in the Alzheimer's without depression (AD-nD) patients. The 196A allele occurred with significantly higher frequency in AD-D patients. Carriers of the A allele of G196A responded better to paroxetine treatment. These findings support an important role of BDNF polymorphism in AD-D [65].

Repressor element 1-silencing transcription factor (**REST**, also known as **neuron-restrictive silencer-factor**, **NRSF**) protects neurons in healthy older people from aging-related changes which was previously thought to act mostly in brains of developing fetuses. But in people with Alzheimer's and other dementias, the protein is sharply depleted in key brain regions. REST appears to switch off genes that promote cell death, protecting neurons from normal aging processes like energy decrease, inflammation and oxidative stress. Chromatin immunoprecipitation with deep sequencing and expression analysis show that REST repress genes that promote cell death and AD pathology and induces the expression of stress response genes. Moreover, REST potently protects neurons from oxidative stress and Aβ toxicity and conditional deletion of REST in the mouse brain leads to age-related neurodegeneration. A functional orthologue of REST, Caenorhabditiselegans SPR-4, also protects against OS and Aβ toxicity. REST appears to work by travelling to a neuron's nucleus when the brain is stressed. In dementia, though, REST somehow gets diverted, travelling with toxic dementia-related proteins to another part of the neuron where it is eventually destroyed. During normal aging, REST is induced in part by cell non-autonomous Wnt signaling. However, in Alzheimer's, frontotemporal dementia and DLB, REST is lost from the nucleus and appears in autophagosomes together with pathological misfolded proteins. Finally, REST levels during aging are closely correlated with cognitive preservation and longevity. Thus, the activation state of REST may distinguish neuroprotection from neurodegeneration in the aging brain. This finding may solve one of the big mysteries of Alzheimer's- why do some people whose brains accumulate the plaques and tangles so strongly associated with Alzheimer's not develop the disease? While investigating how different genes in the brain change as people age, it was found that the REST was the most active gene regulator in older brain, although it is not yet possible to analyze REST levels in brain of living people [79].

People who remained cognitive healthy, but whose brains had the same accumulation of amyloid plaques and tau tangles as people with AD, had three times more REST than those suffering from AD symptoms. About a third people who have such plaques will not develop Alzheimer's symptoms. REST levels dropped as symptoms worsened, so people with MCI had more REST than Alzheimer's patients and only key brain regions are affected. In Alzheimer's, REST steeply declined in prefrontal cortex and hippocampus, areas critical to learning, memory and planning. Other areas of the brain are not involved in Alzheimer's showed no REST drop-off. The role of this protein could spur development of new drugs for dementia, which has so far been virtually impossible to treat [57].

Dietary Factors:-

Table 4:-

POSSIBLE HELPFUL AGENTS TO PREVENT ALZHEIMER'S DISEASE
Antioxidant vitamins
NSAID therapy
Fish & omega-3 fatty acids
Mediterranean diet
Fruit & vegetables
Homocysteine, vitamin B_6& B_{12}, folate
Alcohol
Caffeine
Hormone therapy
NSAID= non-steroid anti-inflammatory drug.
Source: Bassil N, Grossberg GT. *Primary Psychiatry*. Vol 16, No 6. 2009

Dietary factors play an important role in the occurrence and prevention of this devastating disease. At present, in older persons, healthy diet, antioxidant supplements, the prevention of nutritional deficiencies, and moderate physical activity could be considered as the first line of defense against the development and progression of predementia and dementia syndromes [53]. Current research indicates several dietary risk factors associated with Alzheimer's.

Elevated **saturated fatty acids** could have negative effects on age-related cognitive decline and MCI. Furthermore, at present, epidemiological evidence suggests that there is a possible association between fish consumption, **MUFA** and **PUFA** (in particular, **n-3 PUFA**) and a reduced risk of cognitive decline and dementia. Poorer cognitive function and increased risk of vascular dementia (VaD) were found to be associated with lower consumption of milk and dairy products. However, the consumption of whole-fat dairy products may be associated with cognitive decline

in elder people. The limited epidemiological evidence available on fruit and vegetable consumption and cognition generally supports a protective role of these macronutrients against cognitive decline, dementia and AD [52].

Recently, higher adherence to **Mediterranean-type diet (MeDi)** was associated with decreased cognitive decline, although the Mediterranean diet combines several fruits, micro- and macro-nutrients already separately proposed as potential protective factors against dementia and predementia syndromes. Recent prospective studies provided evidence that higher adherence to MeDi could be associated with slower cognitive decline, reduced risk of progression from MCI to AD and decreased all-cause mortality in patients with AD. There are evidences that people who follow this diet have a lower risk of the disease, and it may improve outcomes with those with the disease. The Mediterranean diet's cardiovascular effect has been proposed as the mechanism of action. Studies in support of this as an optimal diet for prevention of cardiovascular diseases have rapidly evolved. There is significant association between a greater adherence to this diet and a reduced risk of major chronic degenerative diseases, including Alzheimer's. Moreover, this diet has been extensively reported to be associated with a favorable health outcome and a better quality of life [51]. These findings have suggested that adherence to the MeDi may affect not only the risk of AD, but also of predementia syndromes and their progression to overt dementia. Based on the current evidence concerning these factors, no definitive dietary recommendations are possible.

Oleocanthal, a natural compound found in **extra-virgin olive oil** associated with the consumption of MeDi, has antioxidant and anti-inflammatory action has the potential to reduce the risk of Alzheimer's or related neurodegenerative dementias. The protective effect of oleocanthal on the abnormal protein is that this olive oil phenol promotes the production of two other proteins that are believed to play an important role in removing Aβ from the brain [82].

Vitamin B6, **B12**, and **folic acid** may help to slow the progress of the disease. B-family vitamins may play a significant role in dementia. High-dose B-vitamin treatment in people at risk for the disease slowed the shrinkage of whole brain volume, and especially reduced shrinkage in areas known to be affected in Alzheimer's. B-vitamins lower **homocysteine**, which directly leads to a decrease in gray matter atrophy, thereby slowing cognitive decline. B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the Alzheimer's process and that are associated with cognitive decline. Few large epidemiological studies have explored the associations between nutrients and Alzheimer's disease, and there has been only one trial of Vitamin E in the prevention of Alzheimer's disease [37, 86].

An Australian fruit, the **Kakadu plum** (*Terminaliaferdinandiana*) may hold future potential as an Alzheimer's therapy. The fruit grows wild in the Northern Territory and Western Australia where it is used as a traditional medicine and food by indigenous people. Compared to curcumin-the compound in turmeric currently undergoing in clinical trials as an Alzheimer's therapy-- the Kakadu plum is now recognized to have pronounced antioxidant capacities. This fruit is an abundant source of **tannins** and **ellagic acid** [83].

The onset of the disease can be slowed and some of its symptoms curbed by a natural compound found in pomegranate. **Punicalagin**, which is a **polyphenol** – a form of chemical compound, found in pomegranate, can inhibit inflammation in specialized brain cells known as **microglia**. This inflammation leads to destruction of more and more brain cells, making the condition of Alzheimer's sufferers progressively worse. There is still no cure for

the disease, but the punicalagin in pomegranate could prevent it or slow down its development. Most of the antioxidant compounds are found in the outer skin of the pomegranate, not in the soft part of the fruit [87].

Caffeine may slow the development of Alzheimer's disease. Retrospective studies have evaluated caffeine intake in the 20 years before AD was diagnosed and it was noted that regular caffeine consumption decreased the probability of developing AD. It may work against AD by improving the production of CSF which is known for its ability to clear away toxic molecules like Aβ proteins which cause brain tissue damage. Indeed, caffeine treatment shows higher levels of CSF production compared to the control group. Higher levels of CSF were associated with the increased expression of Na^+-K^+ ATPase and increased cerebral blood flow. This Na^+-K^+ ATPase is an essential driving force of CSF production by exchanging 3Na+ ions for 2K+ ions across the cell membrane. CSF production falls with acute caffeine treatment and suggests that caffeine is effective up to a certain point. This complicates matters, since the exact mechanism for caffeine's action via adenosine receptors to increase CSF production is not well understood [75].

Cinnamaldehyde and **epicatechin**, two compounds found in **cinnamon**, have an inhibitory effect on the aggregation of tau protein which plays a large role in structure and function of neurons. But when tau is hyperphosphorylated, it forms "neurofibrillary tangles", which are a hallmark of AD. Both compounds were found to protect tau from oxidative damage that can lead to dysfunction. **Cinnamaldehyde** is like a cap. While it can protect tau protein by binding to its vulnerable cysteine residues, it can also come off, which can ensure the proper functioning of the protein. It's interesting to note that there is a high correlation between **type II diabetes** and Alzheimer's. Some even believe Alzheimer's may be a form of brain diabetes. Insulin and insulin receptors in brain are crucial for learning and memory, and it's known that these components are lower in people with Alzheimer's. In addition to the above findings, cinnamon has also been found to have beneficial effects on blood glucose management in type II diabetes [86].

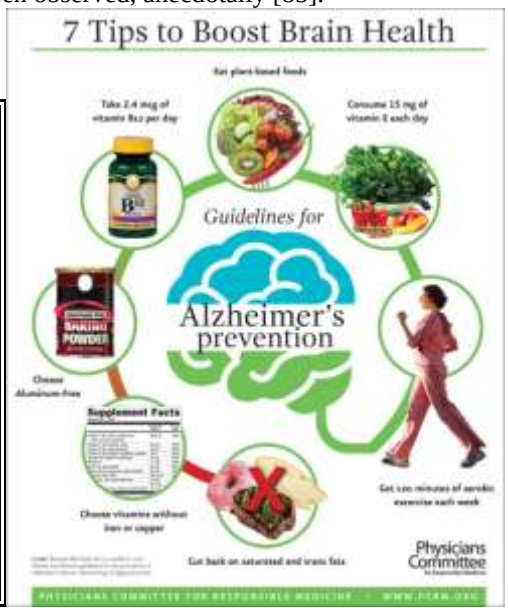
Cocoa powder and **chocolate** contain numerous substances among which there is a quite large percentage of antioxidant molecules, mainly **flavonoids**, abundantly found in the form of **epicatechin**--these substances have some beneficial effects on the brain. They enter the brain and induce widespread stimulation of brain perfusion. They also provoke angiogenesis, neurogenesis and changes in neuron morphology, mainly in regions involved in learning and memory. **Epicatechin** improves various aspects of cognition in animals and humans. **Chocolate** also induces positive effects on mood under emotional stress. In addition, **flavonoids** preserve cognitive abilities during aging in rats, lower the risk for developing Alzheimer's and decrease the risk of stroke in humans. In addition to their beneficial effects on the vascular system and on cerebral blood flow, **flavonoids** interact with signalization cascades involving protein and lipid kinases that lead to the inhibition of neuronal death by apoptosis induced by neurotoxicants such as oxygen radicals, and promote neuronal survival and synaptic plasticity [45].

Dietary **flavonoids** are supposed to protect against deleterious effects of environmental oxidants, due to antioxidant properties linked to their polyphenolic structure. Inverse correlations exist between consumption of some foods or beverages with high flavonoid content, (especially **flavonols** and **anthocyanins**), and coronary stroke mortality or prevalence of AD and PD. **Red wine**, **some grape juices**, **red fruits**, **tea** and **cocoa** are rich in flavonoid content. The hypothesis of cause effect relationship between dietary flavonoid intake and observed protection is further supported. However, composition of ingested food or beverage is complex and poorly defined, especially their content in different flavonoids. In addition, knowledge on bioavailability of these compounds and their fate in the organism is still limited. The best documented effect is protection or restoration of the vascular endothelium function, principally involving nitric oxide (*NO). It is not established that ingested flavonoids produce a direct antioxidant effect in vivo. By contrast, at the cell level, some flavonoids can modify protein kinases mediated signal transmission, thereby inducing antioxidant and anti-inflammatory genes, and, vice versa, inhibiting oxidant and inflammatory gene expression [55].




- ✓ **Fruits like cranberries, blueberries, blackberries and red beans (kidney beans) contain high amount of flavonoid!**

Coconut oil may attenuate cognitive deficits associated with aging and Alzheimer's. Ketone bodies formed as a by-product of coconut oil metabolism may counterbalance Aβ-induced impairment of mitochondrial function and thus energy metabolism. The medium chain triglyceride found in coconut known as **caprylic acid** crosses the blood-brain barrier, and has recently been found to have anti-convulsant, in addition to, ketogenic effect; coconut oil likely has a neuroprotective effect. It prevents Aβ-induced changes in mitochondrial size and circularity. These findings have great significance, as mitochondrial function is often compromised in brain of Alzheimer's patients. Clearly, one of the ways that it can rescue brain of Alzheimer's patient is by addressing the metabolic derangement in brain associated with the condition, or what is known as "**Type III diabetes**". As the brain ages, it becomes increasingly resistant to insulin, and therefore, incapable of using glucose efficiently to meet its sufficient energy -- hence, the metaphor "**Type III diabetes**". Thankfully, nature has devised an alternative fuel source for the brain that is dependent of glucose utilization and the insulin signaling system, namely, the use of ketone bodies. Coconut oil provides the substrate for immediate production of ketone bodies, enabling significant quantities to be produced within a matter of only minutes following ingestion. This metabolic restoration of function may explain why remarkable recoveries in cognitive function and memory have been observed, anecdotally [85].



Possible Risk Factors:-

Table 5:-

PROBABLE MODIFIABLE RISK FACTORS FOR ALZHEIMER'S DISEASE
Hypertension
Diabetes mellitus
Hyperlipidemia
Smoking
Alcohol
Depression
Metabolic syndrome
Trace mineral, chemical and environmental exposure
Head trauma
Elevated homocysteine; Vitamin B_6, Vitamin B_{12} and folate deficiency
Chronic kidney disease
***Source*: Bassil N, Grossberg GT. *Primary Psychiatry*. Vol 16, No 6. 2009**

The main risk factors for developing Alzheimer's disease are **age** and **gender**. The incidence of the disease is higher in women than in men and this cannot simply be attributed to the higher longevity of women versus men. Thus, there must be a specific pathogenic mechanism to explain the higher incidence of Alzheimer's disease cases in women. In this regard, it is notable that mitochondria from young females are protected against Aβ toxicity, generate less ROS and release less apoptogenic signals than those from males. However, all these advantages are lost in mitochondria from old females. Since estrogenic compounds protect against mitochondrial toxicity of Aβ, estrogenic action may be important in protecting cells from Aβ toxicity and suggests a possible treatment or prevention strategy for the disease. Unfortunately, to date, clinical trials with *Ginkgo biloba* and other estrogenic therapies have not proved successful in treating the disease [58]. Although the major causes are accumulation of abnormal Aβ and neurofibrillary tangles of tau, recent understanding has helped us to know about some of the probable risk factors associated with this disease like Western diet, smoking, depression, deficiency of vitamin D, chronic kidney disease, hypertension, trace mineral, chemical and environmental exposure. Statistically significant correlations were found between the prevalence of AD and diabetes, hypercholesterolemia, hypertension, hyperhomocysteinemia, dietary saturated fats, cholesterol, antioxidants, alcohol consumption, smoking, physical activity, the presence of atrial fibrillation, artherosclerotic disease and the plasma concentration of some haemostatic factors in epidemiologic studies, both cross-sectional and longitudinal [50]. Most of the **cardiovascular risk factors** found to be associated with are age-dependent and the prevalence of the disease increases with age. Therefore, the association could simply be attributed to aging. On the other hand, the common pathogenetic mechanisms for the generation of both artherosclerotic disease and Alzhemer's disease, such as inflammation and the generation of toxic radicals, suggest a causal link [50].

Western diet intake is associated with cognitive impairment, with a specific emphasis on learning and memory functions that are dependent on the integrity of hippocampus. Intake of **saturated fat** and **simple carbohydrate**, two of the primary components of a modern Western diet, is linked with the development of obesity and AD. Intake of saturated fat and simple carbohydrate is correlated with neurobiological changes in the hippocampus that may be related to the ability of these dietary components to impair cognitive function [30].

Diabetes mellitus may be associated with an elevated risk of developing AD and may affect cognitive systems differentially [4].

People who are **heavy smokers** in their midlife years are more than **doubling** their risk of developing Alzheimer's and other forms of dementia two decades later. Strong reason has been found to believe that smoking more than two packs of cigarettes daily from age of **50** to **60 years** increases risk of dementia later in life, compared with non-smokers. On the other hand, former smokers or people who smoked less than half a pack per day did not appear to be at increased risk of developing dementia. Association between dementia and smoking did not vary by race or sex. Smoking contributes to oxidative stress and inflammation, which are believed to have an important role in development of AD. Although smoking's ill effect on public health has been well-established, there are some evidences showed that its impact is likely to become even greater as the population ages and dementia prevalence increases. Heavy smoking was found to be associated with a greater than **100%** increase in risk of dementia and its forms **20 years** after midlife and that the brain is thus "not immune to long-term consequences of heavy smoking" [92].

Chronic Kidney Disease is strongly associated with the incidence of dementia independent of age, sex, education and other vascular risk factors [63].

Vitamin D may help prevent AD. Older people face higher risk of dementia and AD if they have Vitamin D deficiency. People who were severely vitamin D deficient were more than twice as likely develop dementia and AD. It was found that those who were moderately deficient in vitamin D had a 53% increased risk of developing dementia of any kind and the risk increased to 125% in those who were severely deficient. Similar results were recorded for AD, with the moderately deficient group 69% more likely to develop this type of dementia, jumping to a 122% increased risk for those severely deficient [89].

High levels of unhealthy cholesterol may contribute towards one of the key signs of AD developing in brain. High levels of **LDL**, or bad cholesterol and low levels of **HDL** were both associated with more amyloid in the brain while

high levels of **HDL** seemed to be linked to lower number of plaques. **HDL** was found to have a potential protective effect that lowered Aβ plaques. Patients with high levels of **LDL** in their blood tended to have more harmful tangles inside their brain cells. The exact causes are still to be understood, this may be due to the cholesterol causing cells to divide incorrectly. This may lead to a build-up of the harmful amyloid protein in brain cells and so impair the way they work [91].

Hypercholesterolemia is an established risk factor for AD and there is a clear link between cholesterol turnover and neurodegenerative diseases. The failure to demonstrate transfer of cholesterol from the circulation into the brain in humans and experimental animals makes it difficult to explain the link between hypercholesterolemia and AD. In contrast to cholesterol itself, side-chain oxidized cholesterol metabolites such as **24S-hydroxycholesterol** and **27-hydroxycholesterol** are able to pass the **blood-brain barrier** (**BBB**). So any cholesterol-related process that occurs will affect the brain and nervous system heavily, most likely more than any other bodily system. Formation of 24S-hydroxycholesterol is the quantitatively most important mechanism for elimination of cholesterol from the brain and a significant net uptake of 27-hydroxycholesterol by the brain from the circulation has recently been demonstrated. Patients with AD have increased brain levels of 27-hydroxycholesterol, which may affect the production of Aβ in the brain. The levels of 27-hydroxycholesterol in the circulation are correlated with the levels of cholesterol and the possibility must be considered that the flux of 27-hydroxycholesterol into the brain is the missing link between hypercholesterolemia and AD. Discovery of the correlations between **oxysterols** and AD may lead to a cure for this disease, or some types of treatment that halt the progression. This finding will also help to find who is at the highest risk to develop AD [8, 93].

A common food-flavoring ingredient **Diacetyl**, used to produce the distinctive buttery flavor and aroma of microwave popcorn, margarines, snack foods, candy, baked goods, pet foods and other products, intensifies the damaging effects of the abnormal brain protein Aβ, which is the marker protein of AD. Diacetyl has been the focus of much research recently because it is linked to respiratory and other problems in workers at microwave popcorn and food-flavouring factories. It also forms naturally in fermented beverages such as beer, and gives some chardonnay wines a buttery taste. Exposure to Diacetyl in the long run leads to neuronal toxicity. It can easily penetrate the so-called "blood-brain barrier", which keeps many harmful substances from entering the brain. It favours aggregation of Aβ plaques in brain. Diactyl has architecture similar to a substance that makes Aβ proteins clump together in the brain. Moreover, it can also stop a protective protein called **glyoxalase I** from safeguarding nerve cells. **Glyoxylase I**is involved in detoxification of harmful products and prevent clumping of Aβ [84, 96].

Human engineered **nanoparticles**, present in chemicals found in sunscreen and an additive in some diesel fuels – **titanium dioxide** and **cerium oxide** can induce neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The brain had built up protective mechanisms but a major worry was that nanoparticles seemed to be able to bypass them. Nanoparticles can have highly significant impacts on the rate of misfolding of key proteins associated with Alzheimer's disease and Parkinson's disease. More research is needed to find their connection to AD and PD [94].

Two **biofactots** are involved in cognitive impairment: one is **excess inorganiccopper**, leached from copper plumbing, causing neuronal toxicity. The other is **zincdeficiency**, causing neuronal damage. Zinc has critical functions in brain and lack of zinc can cause neuronal death. Zinc may act by lowering copper toxicity or by direct benefit on neuronal health, or both [10].

A history of **concussions** involving momentary loss of consciousness might be linked to accumulation of plaque associated with AD. Research on brain scans of elderly participants in Minnesota area has showed that the individuals with thinking impairments and a history of concussions had **18%** higher levels of accumulation of Alzheimer's-associated plaque than those without a history of brain trauma [98].

It has been found that **commonsleeping tablets** and **anxiety drugs** taken by millions of patients has been linked to Alzheimer's disease. Taking the drugs known as **benzodiazepines**, which include **diazepam** and **lorazepam**, for three months or more was linked with a greater chance of being diagnosed with the disease **five years** later. Although it cannot be definitively proven that the drugs are causing the disease there is a strong suspicion of possible direct causation. The results may reflect that people who are already in the early stages of Alzheimer's are often treated for sleep problems and anxiety and this is confusing the findings. The drugs should not be taken for more than three months in light of these findings. It is especially important considering the prevalence and chronicity of benzodiazepine use in elderly populations and the high and increasing incidence of dementia in developed countries. This finding has major importance for public health [54].

Factors Related to Lifestyle:-

A possible role of lifestyle-related factors was recently proposed for age-related changes of cognitive function, predementia syndromes and the cognitive decline of degenerative (Alzheimer's disease) or vascular origin [53]. **Low fitness** raises AD risk. Mounting evidence has suggested a preventive value for physical activity in the preservation of cognitive functions with age. Among people in their **50s**, those who self-rate their level of fitness as poor were **four times** more likely to develop dementia **within30 years** than those who say that they have a good level of fitness. The link between poor self-assessment of physical fitness and dementia was strongest among people with chronic illnesses and those who did not carry the **APOE4 gene** perceived poor physical fitness reflects a combination of biological and lifestyle-related factors that can increase dementia risk [99]. Maintaining **hippocampus** volume is key in delaying cognitive decline and onset of dementia symptoms in those with genetic risk for Alzheimer's. **Moderate physical activity** may protect brain health and keep away shrinkage of hippocampus--brain region responsible for memory and spatial orientation that is attacked first in Alzheimer's. **Physical activity** has potential to preserve the volume of hippocampus in those who have increased risk of the disease [117].

Late-life depression could become a major risk factor for developing AD faster than others. Depression in elderly people would be responsible for a build-up of Aβ protein in brain. Mild cognitively impaired persons with depressive symptoms suffer from elevated amyloid levels when compared with non-depressive individuals. The combination of elevated amyloid levels and coexisting depressive symptoms constitute a patient population with a high risk for faster progression to AD [90].

In several longitudinal studies **low-to-moderate alcohol intake**, particularly **red wine**, has been suggested as a protective factor against the development of age-related changes in cognitive function, predementia syndromes and cognitive decline of degenerative (AD) or vascular origin (VaD) [47].

Breastfeeding may have a decreased risk of AD in later life. Certain biological effects of breastfeeding, such as its action in restoring women's glucose tolerance after pregnancy and rebalancing the levels of important hormones in

the body, may well play a part in protecting the brain against the onset of the disease. The link may be down to breastfeeding's action in restoring insulin sensitivity and glucose tolerance, which is significantly reduced during pregnancy. AD is characterized by a resistance in the brain--and therefore glucose intolerance. Breastfeeding also reduces level of progesterone, the production of which increases during pregnancy. Progesterone desensitizes the proteins in the brain that react to estrogen – which may play a role in protecting brain against AD [88].

It has been suggested that women who start **hormone therapy** earlier in life- before they turn **65**, could reduce the risk of developing AD or other dementias. Hormone therapy in older women seems to increase the risk for different dementias. But, in younger postmenopausal women, the relationship between hormone therapy and the disease is less clear. Women who reported using any form of estrogen therapy before they turned **65** were nearly **50%** less likely to develop this disease or another dementia than women who did not use such therapy by that age. But women who started estrogen-only therapy after the age of **65 years** had about a **50%increased risk** of developing dementia. The risk was nearly **double** among women using combined (estrogen plus progesterone) therapy [95].

The immediate effects of a **head injury** can include dementia symptoms, such as confusion, memory loss and changes in speech, vision and personality. Depending on the severity of the injury, these symptoms may clear up quickly, last a long time or never go away completely. However, such symptoms that begin soon after the injury generally don't get worse over time as happens with AD. Certain types of head injuries may increase the risk of developing AD and other dementias later in life. The greatest increase in future dementia risk seems to occur after a severe head injury that knocks out for more than 24 hours. A moderately serious head injury that causes unconsciousness for more than 30 minutes, but less than 24 hours, also seems to increase risk to a smaller extent. There is no evidence that a single mild head injury that doesn't knock out, or that knocks out for less than 30 minutes, increase the risk of dementia. Repeated mild injuries may increase risk of future problems with thinking and reasoning. A person is at greatest risk of developing dementia and AD later in life, post-head injury, if he/she has also other risk factors. For example, carrying one form of the APOE gene increases the risk of AD in any individual. It's important to note that many people who sustain a severe head injury never develop AD or later dementia [97].

The metabolic syndrome is a risk factor for cardiovascular diseases, which have been linked to AD. The prevalence of the metabolic syndrome, characterized by the clustering of abdominal obesity, hypertension, hyperglycemia and dyslipidemia (high plasma concentration of triglycerides and low concentration of HDL, is now reaching epidemic proportions. Metabolic syndrome is associated with an increased risk of type II diabetes mellitus and cardiovascular disease, which are linked to AD. This could have implications for the prevention and treatment of AD. However, a link between AD and the metabolic syndrome has not yet been established [100].

Factors Related to Environment:-

A common virus **Herpes Simplex Virus type 1** (**HSV1**) has a major causative role in Alzheimer's, acting in combination with a genetic factor – the type 4 allele of the apolipoprotein gene, a known susceptibility factor [27]. **HSV-1** has been suggested as an environmental risk factor for AD which infects **limbic system** structure in the **CNS** [40]. **HSV-1** has been located within Alzheimer's amyloid plaques. In situ PCR was used to detect **HSV type 1 DNA** and immunohistochemistry or thioflavin S staining to detect amyloid plaques. In Alzheimer's disease brain, 90% of the plaques contained viral DNA and 72% of the DNA was associated with plaques. In aged, normal brains, which contain amyloid plaques at a lower frequency, 80% of plaques contained **HSV type 1 DNA** but only 24% of the viral DNA was plaque-associated. It has been suggested that this is because in aged normal individuals, there is a lesser production and/or greater removal of Aβ, so that less of the viral DNA is seen to be associated with Aβ in brain. In HSV type 1-infected cells and mouse brain, Aβ accumulation has suggested that this virus is a major cause of amyloid plaques and hence, probably a significant aetiological factor in Alzheimer's disease [62].

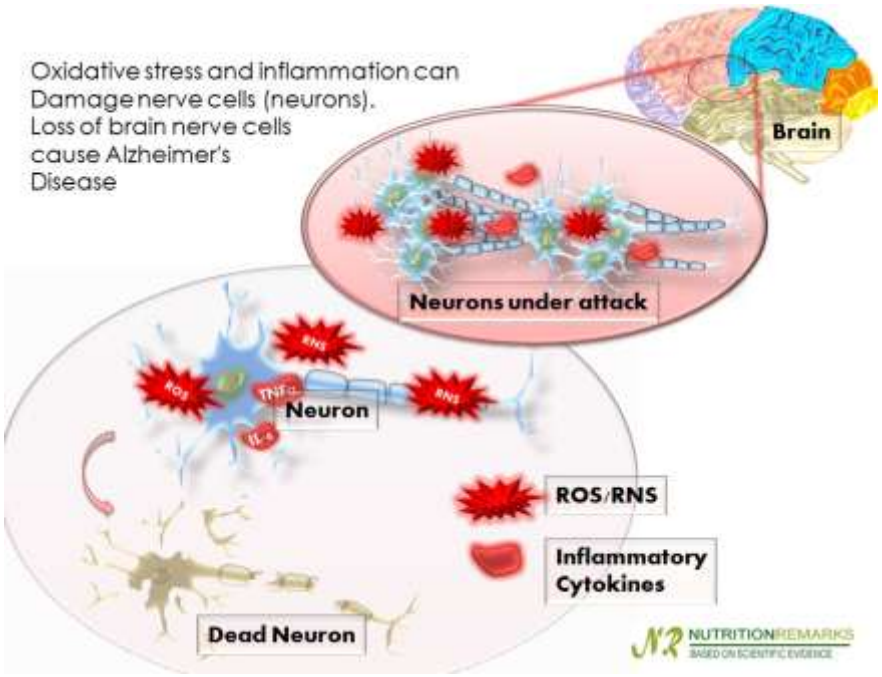


Fig 27:- Role of Oxidative Stress in Alzheimer's Disease.

Oxidative stress is an early event in Alzheimer's disease, occurring prior to cytopathology and therefore may play a key pathogenic role in AD. Oxidative stress not only temporarily precedes the pathological lesions of the disease but also activates cell signaling pathways, which, in turn, contribute to lesion formation and, at the same time, provoke cellular responses such as complementary upregulation of antioxidant enzymes found in vulnerable neurons in AD [9].

Environmental toxins such as air pollution have also been implicated in Alzheimer's disease causation. Exposure to air pollution can lead to chronic oxidative stress, which is involved in the pathogenesis of the disease. Whereas air pollution plays a role in the disease pathology, the epidemiological evidence for this association is limited [43].

Diagnosing Alzheimer's Disease:-

Alzheimer's disease is diagnosed by a thorough history of symptoms, physical and neurological exam, neuropsychological tests like MMSE, brain-imaging scans i.e., MRI and CT scan and some laboratory tests, although there is no single definitive medical test for identifying Alzheimer's disease, arriving at the correct diagnosis can take time and patience.

Diagnosing this disease requires a detailed evaluation, including: knowing a thorough history from the patient, spouse and other family members and also about past and present functioning can help in diagnosis. Determining classic pattern can help to eliminate other causes of Alzheimer's symptoms and also distinguish Alzheimer's from other forms of dementia [101]**. Physical** and **neurological tests** like cognitive tests are used to assess some factors such as orientation (ability to recall details about self, place and time), attention span, speed of information processing, working memory, mood and personality [101]. The disease is usually diagnosed clinically based upon patient history, collateral history of relatives and clinical observations based upon the presence of neurological and neuropsychological features.

A number of **neuropsychological tests** are used to assess difficulties in attention, perception, memory, language and problem-solving, social and language skills. These tests can also be used to evaluate mood problems such as depression [102].

One commonly used test is **Mini-Mental State Exam (MMSE)**, in which a series of questions and tasks are used to evaluate cognitive function. For example, the patient is given a series of words and asked to recall and repeat them a

few minutes later. In the **clock-drawing test**, the patient is given a piece of paper with a circle on it and is asked to write the numbers in the face of a clock and then to show a specific time on the clock [102].

Laboratory testing of blood, urine, and spinal fluid sample can help to evaluate other possible causes of dementia, such as thyroid imbalances or vitamin deficiencies [102].

Brain-imaging scans are useful for ruling out blood clots, tumours or other structural abnormalities in brain that may be causing signs of dementia. These tests include **magnetic resonance imaging (MRI)** or **computed tomography (CT)**. Functional and volumetric MRIs as well as **positron-emission testing (PET)** scans have some ability to predict the future course of early Alzheimer's disease. However, they are often not as good as or not better than clinical exam and history in predicting the course of this disease. The disease can only be definitely diagnosed after death when an autopsy of brain is done. But current research has described some novel techniques to identify the disease [102].

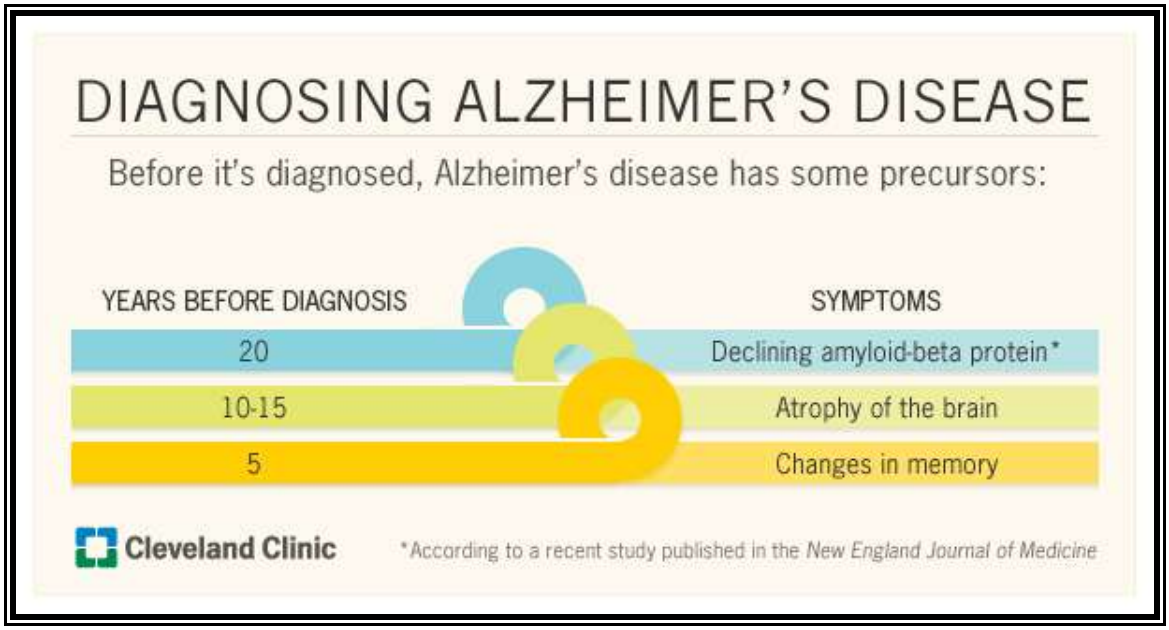


Fig 28:-Diagnosing Alzheimer's Disease.

Diagnosis by Genetic Testing:-

Although a blood test can identify which **APOE alleles** a person has, it cannot predict who will or will not develop AD. It is unlikely that genetic testing will ever be able to predict the disease with **10%accuracy** because too many other factors may influence its development and progression.

At present, **APOE testing** is used in research settings to identify study participants who may have an increased risk of developing AD. This knowledge helps to look for early brain changes in participants and compare the effectiveness of treatments for people with different APOE profiles. It is commonly believed that **APOE testing** is useful for studying AD risk in large groups of people but not for determining only one person's specific risk.

Genetic testing is used for people with a family history of early-onset AD. However, it is not generally recommended for people at risk of late-onset AD [73].

A **novel blood test** has been developed that can predict with **90% accuracy** if a healthy person will develop MCI or AD **3 years before** the first signs of cognitive decline. The test is based on identification of a set of **ten lipid blood-based biomarkers** that predict both conditions. Changes in the breakdown of neural cell membranes are resulting ten identifiable lipids, or metabolites, circulating in blood. In particular, two of the ten metabolites have strong links to the neuropathology of AD. This indicates the possible development of earlier treatment options for AD, when therapy could be more effective at slowing or even preventing onset of the disease [103].

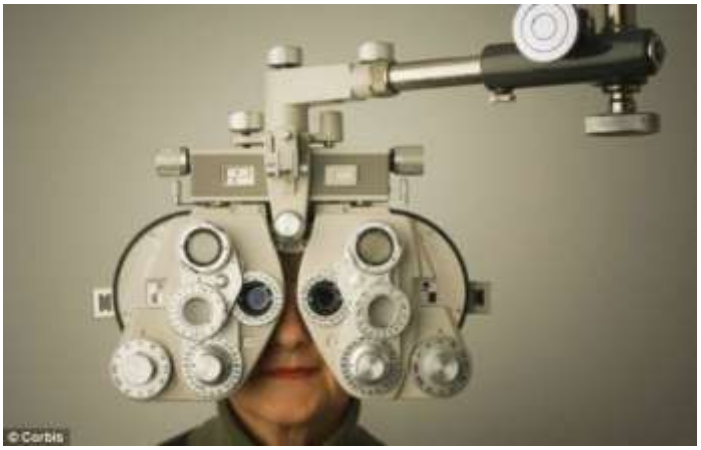
10proteins have been discovered in the blood that could indicate the onset of AD. It is predicted that someday, a simple blood test could tell a patient if he or she will develop AD even before symptoms have appeared. It was claimed that the test will be able to predicate AD with **87% accuracy**. It was found that **26 proteins** are linked with AD of which **10 proteins** can actually predict the disease. If those proteins levels were analyzed, it can be accurately predicted if a patient will develop AD in almost 9 out of 10 cases [104].

Mitochondrial DNA is typically found inside tiny structures that act like the power stations of cells and are inherited through the maternal line only. Decreased levels of this mitochondrial DNA in CSF may reflect the diminished ability of these power stations to provide energy for brain cells, and, therefore, may indicate the earliest stages of Alzheimer's disease, but more work is needed to confirm this in larger groups of people. Reductions in mitochondrial DNA may be one of the earliest signs of Alzheimer's and suggests the pathology of the disease begins far earlier than had been previously thought [105].

Sapphire Test Might Diagnose Alzheimer's Years Before Onset!!

Fig 29:-Cognoptix SAPPHIRE II System.

A technique has been developed which detects damage in nerve cell in the eye's retina which associates to nerve cell damage in the brain. It has been believed for long that there is a correlation between the amount of amyloid in the eye and amyloid in the brain. The argument for this is strong because the retina is formed from the same tissue as the brain when a fetus is developing in the womb. **Retinal Amyloid Index** and the **Sapphire II** have been developed to confirm this theory and trials are underway. **Sapphire II**, the technology is a laser-based reading device and a consumable ophthalmic ointment, may be able to diagnose Alzheimer's before significant neurological damage and irreversible memory loss occurs.



Retinal Amyloid Index utilizes a device that looks and functions similarly to a conventional retinal imaging scanner and a curcumin compound, administered orally to patients, to detect Aβ plaques in the retina. Curcumin, the active ingredient in turmeric, crosses the blood-brain and blood-retina barrier and binds with high affinity to Aβ plaques – particularly Aβ42, which is the most toxic. Curcumin is also a fluorochrome and naturally generates a fluorescent signal, so once bound to the Aβ plaques, the fluorescing curcumin signals are then captured by the retinal imaging device. An increase in fluorescence that can be detected with the retinal imager is directly proportional to the amount of Aβ protein in the back of the eye, which correlates with the amount of Aβ protein in the brain. Through digital processing of the increased fluorescence and the application of quantitative algorithms, a way has been developed to heat-map the data and refine it into a quantitative value, a Retinal Amyloid Index number [106, 107, 108].

Treatment:-

Current treatments of Alzheimer's disease can be divided into **pharmaceutical**, **psychosocial** and **caregiving**. Four acetylcholinesterase inhibitors – **tacrine**, **rivastigmine**, **galantamine**, **donopezil** and an NMDA receptor antagonist **memantine** are conventional medicines currently used to treat the cognitive problems of AD but no medication has been clearly shown to delay or halt the progression of the disease [66]. The benefit from their use is small. One of the aims of therapy is to inhibit the breakdown of a chemical neurotransmitter, acetylcholine, by blocking the relevant enzyme. This can be done by a group of chemicals known as **cholinesterase inhibitors** [66]. The crucial role of **cholinesterases** in neural transmission makes them a primary target of a large number of cholinesterase-inhibiting drugs and toxins. In pharmacology, this has relevance to the treatment of neurodegenerative disorders [42]. Reduction in the activity of cholinergic neurons is a well-known feature of Alzheimer's disease. Acetylcholinesterase inhibitors are employed to reduce the rate at which acetylcholine is broken down, thereby increasing the concentration of acetylcholine in brain and combating the loss of acetylcholine caused by the death of cholinergic neurons [66].

Recent research has revealed various novel therapeutic approaches. The three cholinesterase inhibitors **donopezil**, **galantamine** and **rivastigmine** are efficacious for mild to moderate Alzheimer's disease. Less adverse effects are associated with donopezil compared with rivastigmine [6].

People with mild, moderate or severe dementia due to Alzheimer's, were treated for periods of 12. 24 or 52 weeks with **donopezil** experienced benefits in cognitive function, activities of daily living and behaviour [7].

Memantine20 mg/day caused a clinically noticeable reduction in deterioration over 28 weeks in patients with moderate to severe Alzheimer's disease. There is evidence that the excitatory activity of **L-glutamate** plays a key role in the pathogenesis of the disease and in the damage from an ischaemic stroke. A low affinity antagonist to **N-Methyl-D-aspartate (NMDA) type receptors**, such as **memantine**, may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning [2].

Huperzine A is a linearly competitive, reversible inhibitor of acetylcholinesterase that is said to have both central and peripheral activity with the ability to protect cells against H_2O_2, Aβ protein (or peptide), glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis. There properties might qualify Huperzine A as a promising agent for treating dementia (including Alzheimer's). There is evidence that it seems to have some beneficial effects on improvement of general cognitive function, global clinical status, behavioural disturbances and functional performance, with no obvious serious adverse events for patients with Alzheimer's disease [35].

The diabetic drug, **pramlintide**, reduces Aβ peptide in brain and improves learning and memory in two experimental models. AD patients have a lower level of amylin in blood compared to those without this disease. These results may provide a new avenue for both treatment and diagnosis of Alzheimer's disease [110].

Curcumin has therapeutic potential in the pathophysiology of Alzheimer's disease. In in vitro studies, curcumin has been reported to inhibit Aβ aggregation and Aβ-induced inflammation as well as the activities of β-secretase and acetylcholinesterase. In in vivo studies, oral administration of curcumin has resulted in the inhibition of Aβ deposition, Aβ oligomerization and tau phosphorylation in the brains of AD animal models. These findings suggest that curcumin might be one of the most promising compounds for the development of AD therapies. Further evidences are required to determine the clinical usefulness of curcumin in the prevention and treatment of Alzheimer's disease [21].

A new class of small molecules, which is based on the chemical structure of **apomorphine**, can inhibit Aβ aggregation. These molecules were found to interfere with Aβ fibrillization as determined by transmission electron microscopy, Thioflavin T fluorescence and velocity sedimentation analytical ultracentrifugation studies [33].

Among the antioxidants, **vitamin C** has been regarded as the most important one in neural tissue. The relevance of vitamin C in the cellular and molecular pathogenesis of AD and its therapeutic potential against this neurodegenerative disorder has been explored. It also decreases Aβ generation and acetylcholinesterase activity and prevents endothelial dysfunction by regulating nitric oxide, a newly discovered factor in the pathogenesis and progression of AD [25].

D-Serine has been found in brain tissue at high levels, which could improve treatment of AD in future, leading to further investigations of its function in brain. Communication between cells in the brain depends on the triggering of receptors in a specialized way in order to strengthen connections or synapses between brain cells. Neurons communicate by releasing glutamate at a synapse that binds to an N-Methyl-D-Aspartate (NMDA) receptor on the surface of another neuron, which triggers the flow of calcium ions. The flow of calcium ions is central for creating memories within the brain. D-Serine works with glutamate to activate the NMDA receptors. Treatment with low-dose D-Serine in mice resulted in improvement of working memory and recognition learning [111].

A new type of drug, called **J147**, was designed using the chemical structure of the curry spice curcumin, to promote activity of brain cells and strengthen communication between them, not designed to target amyloid [112].

Regular use of **aspirin** may lower the risk of the disease. Aspirin can prevent the disease stems from the notion that Alzheimer's is caused by inflammation that disrupts proteins in the brain. It is believed that aspirin, and possibly other non-steroidal anti-inflammatory drugs (NSAIDs), may reduce or block the progress or completion of that the process. People who took a low dose of aspirin everyday for several years have reduced risk of developing the disease by **13%**. A similarly beneficial effect for aspirin and other NSAIDs has been found [109].

Retinoids may also influence Aβ processing upregulation of alpha-secretase via **ADAM10**. Vitamin A and other retinoids are relevant to theories of Alzheimer's disease pathogenesis [34].

Methylthioninium chloride (**MTC**) serves as a Tau Aggregation Inhibitor (TAI) in vivo both in a cellular assay, suitable for screening further TAIs and in two distinct transgenic mouse models of the disease. In the mice, brief

treatment with MTC produced a reversal of Tau pathology, the extent of which is dependent upon the amount of pathology in brain [13].

New therapeutic strategies and drug candidates for neurodegenerative diseases are **p53** and **TNF-alpha inhibitors** and **GLP-1 receptor agonists**. They have chosen specific targets to inhibit that are at pivotal rate-limiting steps within the pathological cascade, to forestall the neurodegenerative process. Such targets include TNF-alpha, p53 and GLP-1 receptor. The cytokine TNF-alpha is elevated in Alzheimer's disease. Its synthesis can be reduced via posttranscriptional mechanisms with novel analogues of the classic drug, thalidomide. The intracellular protein and transcriptional factor, p53, is activated by the AD toxic peptide, Aβ as well as by excess glutamate and hypoxia to trigger neural cell death. It is inactivated by novel tetrahydrobenzothiazole and-oxazole analogues to rescue cells from lethal effects. Stimulation of the glucagon-like peptide-1 receptor (GLP-1R) in brain is associated with neurotrophic functions that, additionally, can protect cells against excess glutamate and other toxic effects [19].

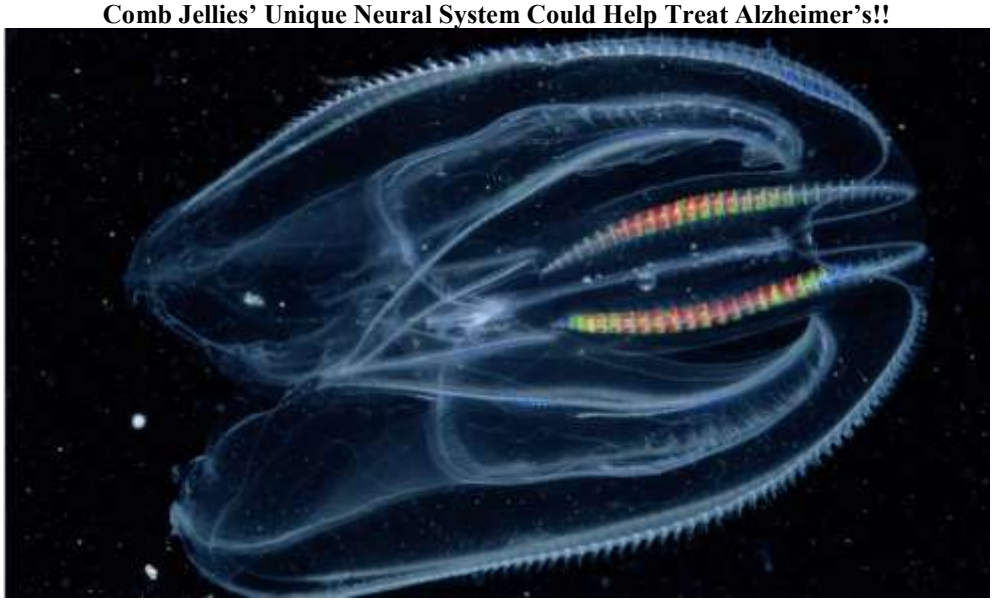
Dys-homeostasis of copper metabolism and oxidative stress are major hallmarks in the brains of Alzheimer's disease patients. Therefore, metal bioavailability and mechanisms of copper ion homeostasis throughout the body are crucial and potential targets for therapeutic agents. Many of the medications used or suggested, respectively, at present time, may either be toxic, reveal a lack of specificity or have unknown mechanisms of action in vivo. **Metal chaperones** from **medicinal plants** are proposed as medications that are relatively free from these disadvantages. Furthermore, these agents are a promising class of molecules for studies aimed at developing innovative and etiological treatments for this protein-misfolding disease [31].

Chronic cannabidiol treatment may have therapeutic potential in treating specific cognitive impairments linked with this disease. Non-psychoactive phytocannabinoidcannabidiol exerts neuroprotective, anti-oxidant and anti-inflammatory effects and promotes neurogenesis. It also reverses Aβ-induced spatial memory deficits in rodents. This is the first study to investigate the effect of chronic cannabidiol treatment on cognition in an Alzheimer's disease transgenic mouse model [14].

A peptide structure, named "**alpha sheet**", has been designed by computer simulations, that complements the toxic structure of amyloid proteins, can stop the harmful changes of the body's normal proteins into a state that is linked to Alzheimer's disease. The synthetic molecule blocks these proteins as they shift from their normal state into an abnormally folded form by targeting a toxic intermediate phase. The "**alpha sheet**" effectively attacks the toxic middle state the protein goes through as it shifts from normal to abnormal. The structures could be tailored even further to bind specifically with the proteins in certain diseases, which could be useful for specific therapies. The designed compounds can be used as diagnostics and also as drugs to treat or at least slow the progression of Alzheimer's disease [114].

A newly invented dual-purpose molecular tool has shown promise in 'clearing' Aβ plaques from the brain. The tool both grabs metal ions and interacts with Aβ and not only disrupted copper-induced plaque formation, but also broke up existing clumps. Building upon the first generation of compounds, a second generation of compounds has been reported that are more stable in biological environment. The compound is capable of disassembling the misfolded amyloid clumps to form smaller amyloid pieces, which might be 'cleansed' from the brain more easily, demonstrating a therapeutic application of the compound [113].

Comb Jellies' Unique Neural System Could Help Treat Alzheimer's!!



Comb jellyfish has a unique neural system that could inspire innovations in synthetic and regenerative medicine. Most of the animal kingdom developed along one pathway the comb jelly took its own route to evolution. Some ctenophores can regenerate an elementary brain – also known as the aboral organ or gravity sensor, in days (three and half!). One lobate ctenophore, *Bolinopsis*, can regenerate its brain **four times**. Brain of very small sea animal Comb-jelly is comprised in a different way from any other animals in the world. This invention gives a new hope in opening a novel way in curing Alzheimer's and Parkinson's disease. The brain and nervous system of this animal works in a way that does not related to others. The damaged organ is reformed in many organisms, but in this case brain also, which does not happen in case of others organisms with complicated nervous system. Many genes present in almost every neural system is absent in comb jelly. They don't use **serotonin**, **dopamine** or **acetylcholine** to control brain function, but instead employ a system of **peptides and glutamate neural signalling**, genetic editing and a diverse array of electrical synapses. So, there is more than one design for complex nervous and muscular organization. There are several genes in comb-jelly which are different from all others – the nervous system is regulated by several types of peptide and glutamate neural signalling, while in human and any other animals by certain chemicals such as serotonin, dopamine and acetylcholine. The dopamine producing cells are once damaged do not reform in other animals. Even it has been observed that the brain can be reformed in them even four times in laboratory. If the way of reformation can be found the devastating disease Alzheimer's and Parkinson's disease can be cured [123].

Immunotherapeutic Approaches:-

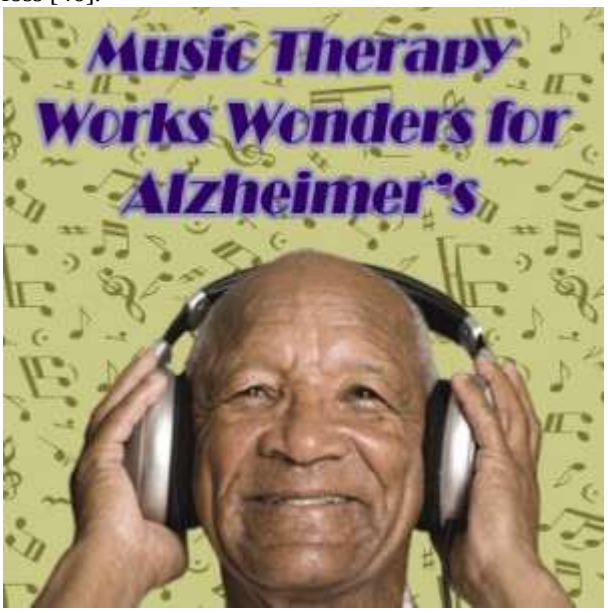
Recently, commercially available intravenous immunoglobulins (IVIG) have been used in small pilot trials for the treatment of patients with AD, based on the hypothesis that IVIG contains naturally occurring autoantibodies (nAbs-Abeta) that specifically recognize and block the toxic effects of Aβ. Active and passive immunotherapies have both been shown to be effective in clearing plaques, removing Aβ and improving behaviour in animal models of AD. Although the first active immunization trial in human was discontinued because of severe adverse effects, several new approaches are currently being investigated in clinical trials [16].

The success of active and passive anti-Aβ immunotherapies in both preventing and clearing parenchymal amyloid in transgenic mouse models led to the initiation of an active anti-Aβ vaccination (AN1792) trial in human patients with mild-to-moderate AD, but was prematurely halted when 6% of inoculated patients developed aseptic meningoencephalitis as well as T-lymphocytes in three of the patients. Furthermore, antibody responders showed some improvement in memory task measures. Anti-Aβ therapies might still be a viable option for the treatment of AD, if potentially harmful proinflammatory processes can be avoided [23].

A vaccine has been created targeting damaged tau proteins inside the neurons of the brain which cause neurodegenerative degeneration. It was tested in mice with AD, the results have shown preventing the formation of tangles and therefore of the disease. Human trials require 5 years [115].

Pharmocological as well as nonpharmacological interventions may help these patients and can be classified within behaviour-, emotion-, cognition- or stimulation-oriented approaches. Some psychotherapies like reminiscence therapy, validation therapy, simulated presence therapy and sensory integration therapy called snoezelen can help patient to cope with depression and behavioural problems after initial diagnosis of the disease. **Reminiscence therapy** (**RT**) is one of the most popular psychosocial interventions in dementia care and is highly rated by stuff and participants. It involves the discussion of past activities, events and experiences with another person or group of people, usually with the aid of tangible prompts such as photographs, household and other familiar items from the past, music and archive sound recordings. Reminiscence groups typically involve group meetings in which participants are encouraged to talk about past events at least once a week. Life review typically involves individual sessions, in which the person is guided chronologically through life experiences, encouraged to evaluate them and may produce a life story book. Family caregivers are increasingly involved in reminiscence therapy. There are some evidences to suggest it is effective in improving mood in older people without dementia. Its effects on mood, cognition and well-being in dementia are less well understood [61]. **Validation therapy** is based on acceptance of the reality and personal truth of another's experience [44]. **Reminiscence therapy** and **validation therapy** are emotion-oriented interventions. **Simulated presence therapy** (**SPT**) is based on attachment theories and involves playing a recording with voices of the closest relatives of the person with Alzheimer's disease. There is partial evidence indicating that **SPT** may reduce challenging behaviours [64]. A specially designed room for **sensory integration therapy**, also called **snoezelen**, a multi-sensory stimulation, provides sensory stimuli to stimulate the primary senses of sight, hearing, touch, taste and smell, through the use of lighting effects, tactile surfaces, mediative music and the odour of relaxing essential oil [15]. **Simulated presence therapy** and **sensory integration therapy** are supportive psychotherapies.

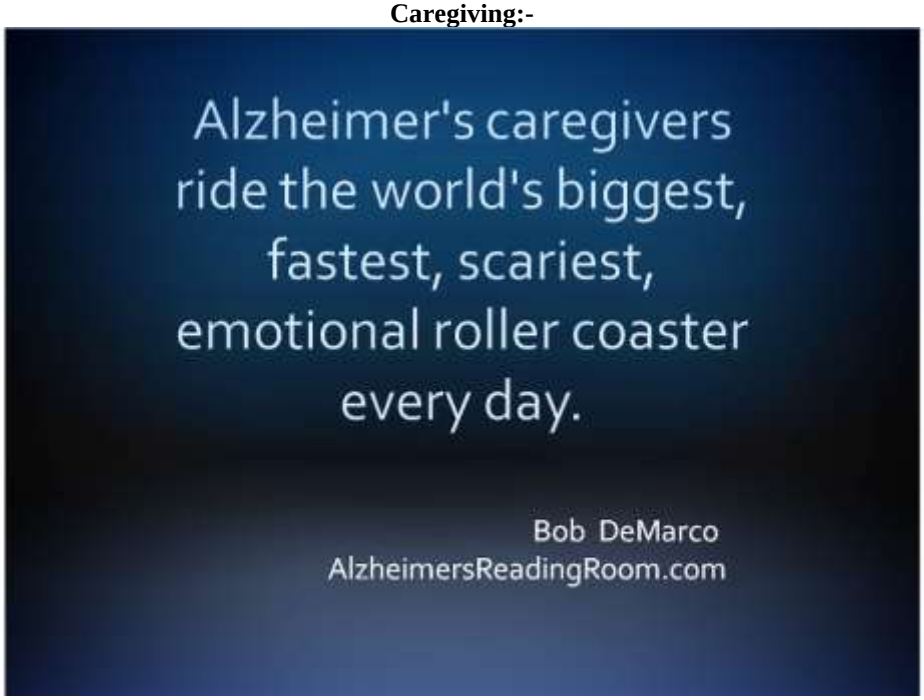
Meditation programme resulted in improvements in neuropsychological function and differences in cerebral blood flow in patients with memory loss [46].



Music therapy is one of the most common treatments for the disease. The effectiveness of music therapy can depend on the quality and length of the treatment as well as other factors. It helps in reducing agitated behaviours, decreasing wandering, increasing self-identity and mediating communication [116].

Very limited data are available regarding these psychotherapies.

Caregiving:-



Alzheimer's is a disease that affects not only those who suffer from it, but also the entire family.

Home Treatment in Early Stages:-

Telling the patient. Often doctors will not tell the patients that they have Alzheimer's. If a patient expresses a need to know the truth, it should be disclosed. Both the caregiver and the patient can then begin to address issues that can be controlled, such as access to support groups and drug research.

Mood and emotional behavior. Patients display abrupt mood swings and many become aggressive and angry. Some of this erratic behavior are caused by chemical changes in the brain. But it may also be due to the experience of losing knowledge and understanding of one's surroundings, causing fear and frustrations that patients can no longer express verbally.

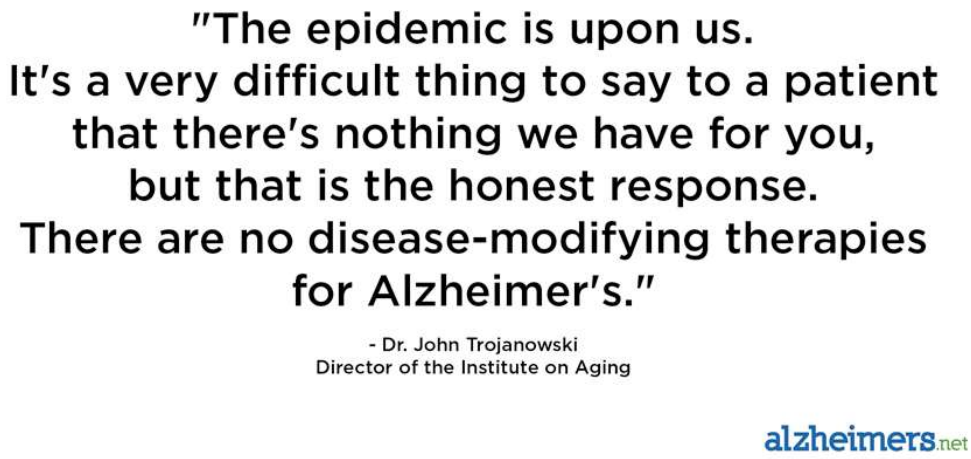
The following recommendations for caregivers may help soothe patients and avoid agitation [118]:

- Keep environmental distractions and noise at a minimum if possible. (Even normal noises, such as people talking outside a room, may seem threatening and trigger agitation or aggression.)
- Speak clearly. Most doctors recommend speaking slowly to a patient with Alzheimer's disease, but some caregivers find that patients respond better to clear, quickly spoken, short sentences that they can more easily remember.
- Use a combination of facial expressions, voice tones and words for communicating emotions.
- Limit choices (such as clothing selection).
- Offer diversions, such as a snack or car ride, if the patient starts shouting or exhibiting other disruptive behavior.
- Simply touching and talking may also help.
- Maintain as natural an attitude as possible. Patients with this disease can be highly sensitive to the caregiver's underlying emotions and react negatively to patronization or signals of anger and frustration.
- Showing movies or videos of family members and events from the patient's past may be comforting.

We will win the war!!!

May-Britt MoserEdvard Moser

This year's **Nobel LaureatesMay-Britt Moser** and **Edvard Moser** have discovered a positioning system, an "**inner GPS**" in brain that makes it possible to orient ourselves in space, demonstrating a cellular basis of higher cognitive function. Edvard Moser, May-Britt Moser and their students Torkel Hafting, Marianne Fyhn and SturlaMolden were discovered **Grid cells** at the **Centre for the Biology of Memory** (**CBM**) in **Norway**. They were awarded the **2014 Nobel Prize** in **Physiology** or **Medicine** together with **John O'Keefe** for their discoveries of cells that constitute a positioning system in the brain. In patients with Alzheimer's disease, the hippocampus and entorhinal cortex are frequently affected at an early stage and these individuals often lose their way and cannot recognize the environment. Knowledge about the brain's positioning system, therefore, help us understand the mechanism underpinning the devastating spatial memory loss that affects people with this disease.



Prevention:-
Vitamins and **omega-3 fatty acids** are effective to forestall the progression of Alzheimer's disease [119].
The disease can be prevented by a balanced diet rich in vitamins and ω-3 fatty acids -- these two components help to prevent brain shrinkage, one of the consequences associated with Alzheimer's disease.

A diet containing foods rich in vitamins (B, C, D and E) and ω-3 fatty acids, present mainly in fruits, vegetables and fish, helps to prevent the onset of a disorder that results in loss of memories. Food plays a key role in prevention and development of disease, in this case related to brain. A diet rich in vitamins and ω-3 fatty acids is a good helper to prevent shrinkage of brain, a condition related to Alzheimer's disease.

The best way to get vitamins and ω-3 fatty acids is taking foods like fish, fruits and vegetables.
Six everyday foods that can help to prevent, or erase the symptoms of Alzheimer's disease: **Oily fish, Berries, Dark green, leafy vegetables, Turmeric, Coffee** and **Coconut oil.**

Certain changes in lifestyle may help in prevention of Alzheimer's disease [118]:
Stay mentally active. Participating in intellectually engaging activity (such as doing crossword puzzles or learning a new language) may help in reducing the risk of this disease.

Stay physically active. Exercise and regular physical activity of at least moderate intensity may help to preserve cognitive function.

Stay socially active. Personal relations and connections may help protect against Alzheimer's disease.
Eat a heart-healthy & brain-healthy diet. While no specific dietary factors have been found to prevent this disease, a low-fat, low-cholesterol diet, is healthy for heart and brain. Replace saturated fat and trans-fatty acid with unsaturated fat from plant and fish oil. Docosahexanoic acid (DHA) and eicosapentanoic acid (EPA), the two main ω-3 fatty acids, present in fish oil, are an excellent source of unsaturated fat. Eat lots of dark coloured fruits and vegetables, which are the best source of antioxidant, vitamins and other nutrients. (Although extensive research has been done on vitamin B and E, but there is no evidence that vitamins are protective.) The Mediterranean diet is an example of an eating plan that includes many of these recommendations.

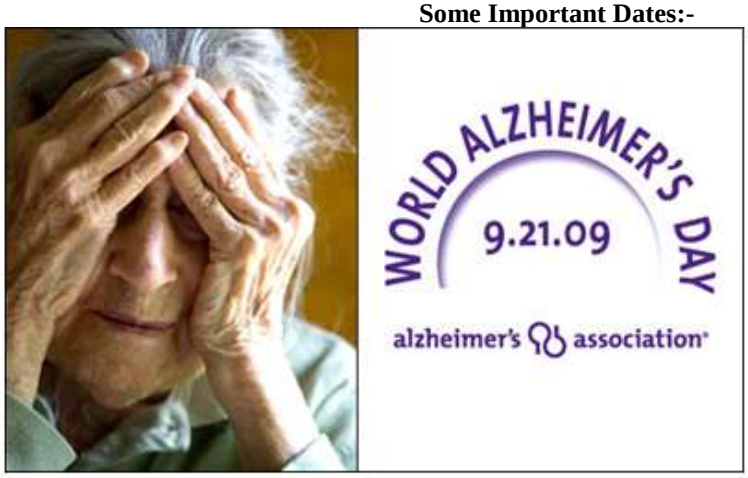
Maintain a healthy weight. Obesity leads to more sedentary lifestyle and may increase the risk of Alzheimer's disease.

Conclusion:-
Alzheimer's, the debilitating disease has no such medications which can stop the progression of the disease, the conventional treatment can only delay the progress of the disease, so more research is currently undergoing regarding the treatment and other causative factors. This is a devastating disease, in terms of both mental distress and health care cost. Epidemiological evidences indicate that occurrence of the disease is increasing in U.S. and likely in western world at an alarming rate, especially in Latinos. The conventional medications of Alzheimer's disease just delay the symptoms of the disease but no known treatment is effective in curing the disease. Researchers have found some food ingredients, spices and fruits contribute good effect on AD.

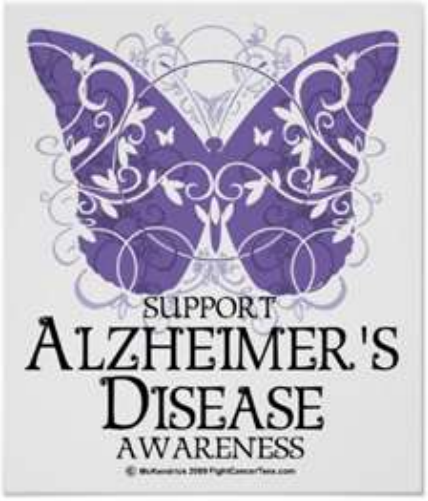
Not only the genes, several factors are Herpes simplex virus, rare missense mutation, oxidative stress, alcohol drinking, excessive consumption of alcohol, insomnia, depression, chronic kidney disease, head trauma, concussion, hypertension, diabetes, elevated deficiency of vitamin-B6, Vitamin-B12 and folate, diabetes mellitus, hyperlipidemia, higher consumption of saturated fatty acid are found to be associated with the occurrence of this disease. Inhibition of tau and amyloid abnormality is one of the most promising therapeutic approaches to AD and other taupathies, although many novel therapeutic approaches are currenly underway. Results from the passive vaccination Alzheimer's disease clinical trials that are currently underway will provide invaluable information about both the effectiveness of newly improved anti-Aβ vaccines in clinical treatment as well as the role of the Aβ peptide in the pathogenesis of the disease. The role of RCNA1 could one day lead to the development of a therapy or drug to prevent dementia in people suffering from these two conditions. However, it is better to prevent the disease by introducing some modifications in lifestyle. It has been highlighted here that following dietary advice for lowering the risk of cardiovascular and metabolic disorders, high levels of consumption of unsaturated fatty acid from fish, nonstarchy vegetables, low glycemic index fruits and a diet low in foods with added sugars and with moderate red wine intake should be encouraged. Taking a balanced diet rich in vitamins (B, C, D and E) and ω-3 fatty acids

(DHA and EPA), present mainly in fruit, vegetable and fish, can prevent the disease – these two components help to prevent brain shrinkage, one of the consequences associated with the disease. Oily fish, berries, turmeric, coffee, dark green leafy vegetables and coconut oil are rich in these food ingredients. Therefore, food plays a key role in development and prevention of this disease, in this case related to brain. Staying mentally, physically, and socially active, eating heart-healthy and brain-healthy diet and maintaining a healthy weight are required to prevent the onset of the disease. Hopefully, this will open new opportunities for the prevention and management of dementia and Alzheimer's disease.

Some Important Dates:-



☞ As there is a lack of awareness in our country so it is necessary to awake the people about the symptoms of Alzheimer's disease, which might help in the proper diagnosis of this devastating neurological disorder.



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