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Chapter 2: The science of Alzheimer's disease: Current research, therapies, and hope for the future

2.1. Introduction to Alzheimer's Disease

Alzheimer's Disease is a progressive neurodegenerative disorder that is the most common cause of cognitive impairment and dementia in older adults, with approximately 6 million people afflicted in the United States. Major risk factors include advanced age, male sex, family history, prior head trauma, and genetic factors that promote amyloid deposition. The clinical hallmarks are slow but progressive memory loss and loss of function for daily tasks, but secondary neuropsychiatric symptoms such as depression and apathy are present in the early stages and may precede memory loss. Characteristic changes in the cerebrospinal fluid that can aid in diagnosis are reduced amyloid-beta and increased total tau and phosphorylated tau.

The histopathologic signatures of Alzheimer's are neocortical and hippocampal amyloid plaque deposition and tau tangles involving the neocortex, affecting limbic regions initially in an aging-related manner, then progressing to more complete neocortical involvement. Other neurodegenerative but often overlooked pathologic changes regularly accompany Alzheimer's, including tau tangles outside of the neocortex, which often correlates with adverse behavioral symptoms; TDP-43 proteinopathy; other non-AD tauopathies; and cerebrovascular disease, particularly small vessel disease changes of the white matter and lacunar infarcts (Rajasekhar & Govindaraju, 2018; Fatima et al., 2024; Kim et al., 2024).

Understanding how these and the characteristic Alzheimer's changes relate to the cognitive decline and other clinical features of the disease is an area of continuing active research. This understanding is not only of academic interest. Research on other neurodegenerative and associated vascular pathologies is fruitful in the quest for AD biomarkers and therapies to halt or reverse its progression. As such, they are discussed

to give the reader a holistic approach to what the disease is; its current known pathophysiology; the emerging CSF, blood, and imaging biomarkers; and its current clinical therapy and research pipeline, with an eye towards hope for the future (Thangwaritorn et al., 2024; Sharma et al., 2025).

2.1.1. Background on Alzheimer's Disease

Alzheimer's disease is a dementia type that influences memory, thinking, and behavior. Symptoms will become severe enough to disrupt daily living. Alzheimer's disease is categorized into early-onset (with symptoms starting before age 65) and late-onset (with symptoms starting after age 65). The completed diagnostic tests give possible, probable, or definitive descriptions of the condition, with only the last being a person who may be referred after death to an institution performing a complete neuropathological examination of the brain tissue. Clinical assessment during the lifetime is used more commonly. Dementia symptoms tend to affect the temporal lobes of the cerebral cortex; however, in Alzheimer's disease, other anatomical areas can also be affected depending on how far the disease-affected started and progressed. Alzheimer's disease and related potential pathologies usually start in the entorhinal cortex and hippocampus regions of the brain. In this regard, other symptoms can be produced if other brain regions are also affected, such as personality changes at the frontal lobe level and problems with language at the temporal lobe. Nevertheless, other types of dementia or other pathologies can produce a similar pattern, which must be considered a possible complication.

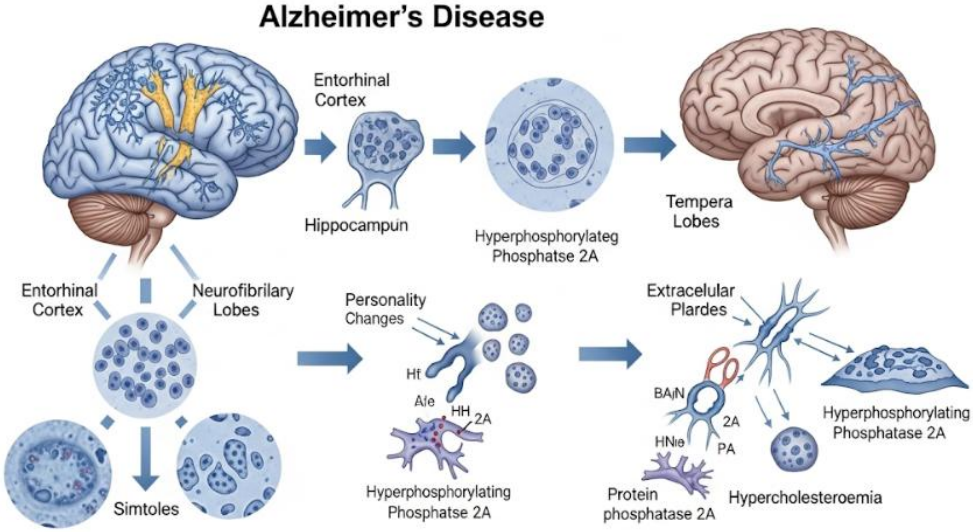

Fig 2 . 1 : Alzheimer's Disease

The characteristic histopathological hallmarks of the Alzheimer's individual are intracellular/mechanized tangles produced by the accumulation of hyperphosphorylated tau protein alongside the activity status level of the hyper phosphorylating phosphatase 2A, extracting protein phosphatase 2A, in addition, the presence of neglected insoluble Aβ from peptide 40 or peptide 42 derived from precursor amyloid protein in some brain regions that were altered. There are at least 8 other potential risk factors associated with the development of Alzheimer's disease among individuals with atypical familial hereditary patterns. Thus, the disease has been considered a highly modeled and empirical trial concerning inflammation and hypercholesterolemia. Aβ is thermodynamically soluble at physiological pH. The disease is caused not only by the natural formation of these two crucial histopathological hallmarks but also by their association with others that are explained in-depth.

2.2. Epidemiology and Risk Factors

Approximately 47 million people worldwide are living with dementia. Alzheimer's disease is the most common cause, with an estimated 27 million affected worldwide. As the population over 65 years of age increases, the growing number of older adults is predicted to contribute substantially to the resources needed to care for these individuals and to treat the associated comorbidities. By the year 2050, it is predicted that the annual costs associated with dementia will exceed $1 trillion, due to more than 115 million people worldwide being diagnosed with dementia, many with Alzheimer's disease. The increase in the burden of dementia on healthcare systems is predicted to occur at an unprecedented rate, especially in transition countries such as China, Brazil, India, and Mexico. Countries such as the United States, Europe, and Japan have already invested significant resources to help prepare for the future crisis, by investing in a range of research initiatives to discover interventions aimed at slowing cognitive decline and developing better therapies for delaying the onset of, or treating, dementia.

What makes this situation even more challenging is that, at present, there are no effective treatments to reverse or prevent cognitive decline in such patients. In the absence of promising interventions to delay the onset of or treat dementia, a greater emphasis has been placed on identifying modifiable risk factors for dementia. Because age is the primary risk factor for dementia, and also because people are living longer, the prevalence of dementia, particularly Alzheimer's disease, is increasing. Several changes in demographic factors since the 1970s have been associated with a relatively stable prevalence of dementia, particularly Alzheimer's disease. In this chapter, we will explore the epidemiology of Alzheimer's disease, highlighting key discoveries early in the understanding of this disease, and will examine risk factors that are associated with

Alzheimer's disease, including vascular, injury, environmental, psychological, genetic, medical, metabolic, socioeconomic, and lifestyle factors.

2.2.1. Prevalence and Demographic Trends

Alzheimer's disease (AD) is currently the most prevalent form of dementia, with estimates in 2020 of 39 million cases worldwide. This total is expected to increase steeply, with estimates of 120 million cases by 2050. The incidence of AD is difficult to assess, particularly considering differences in methodology and study design across different regions and countries. However, one method of estimating incidence is through patient registries, which report probable AD cases in a geographic area that can then be multiplied by the total expected population within that area. AD presents early in life, occurring in early, middle, and late adulthood. Incidence is very rare until the 40s, however, and spikes between the ages of 50 and 70. The number of expected cases in this early-onset, early-adult period is very small and poorly understood. Late-onset AD is observed as early as 60 or 65 years but increases substantially thereafter.

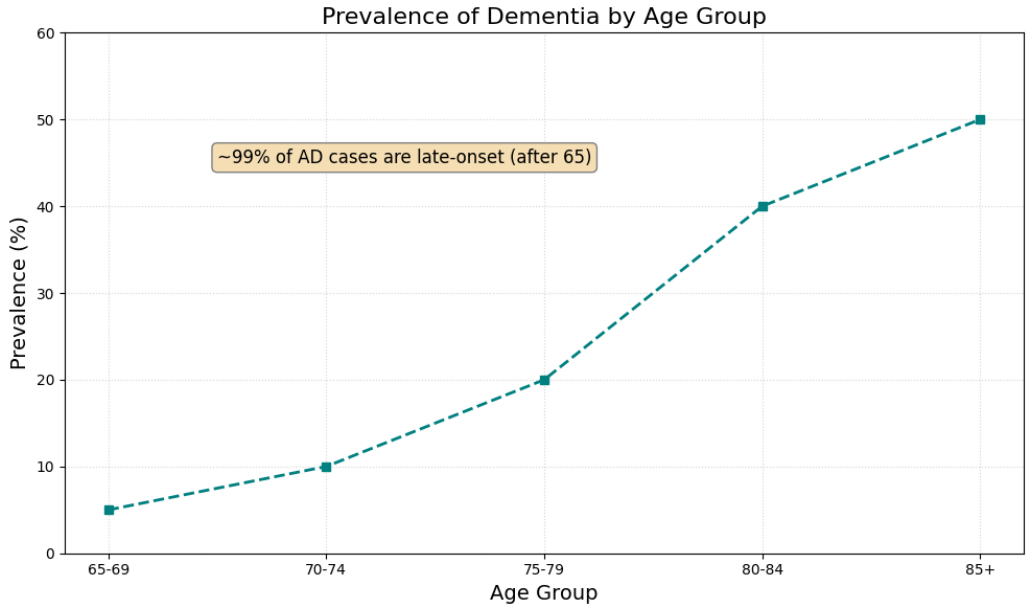

Fig 2 . 2 : Prevalence of Dementia by Age Group

The bulk of expected cases, close to 99%, are classified as late-onset AD. In this elderly population, the prevalence of dementia is approximately 5% at ages 65-69, rising to between 30% and 50% at ages 80-84. Prevalence is influenced by age, sex, and ethnic backgrounds, for example, higher rates of dementia observed in African Americans and Hispanics as compared to non-Hispanic whites, and several risk factors. AD is more common in women, particularly because women live longer than men, but is also

associated with age. The majority of AD patients are over the age of 65, an important risk factor for the disease. Risk factors such as diabetes, cardiovascular disease, or stroke, as well as higher education levels and reduced inflammation, may also contribute to the earlier or later onset of the disease.

2.3. Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is classified as the most common subtype of dementia, accounting for about 60-70% of the total cases. Consequently, an immense number of research efforts are performed to address the questions surrounding the causes and mechanisms of AD onset and propagation. Besides the clinical observation of cognitive decline symptoms, the main pathological hallmarks are the aggregation of amyloid-β (Aβ) protein into extracellular senile plaques and the formation of intracellular neurofibrillary tangles (NFTs) seen with the deposition of hyperphosphorylated tau protein. Tau pathology correlates better with clinical symptoms than Aβ pathology and affects AD patients to a higher extent. As demonstrated in autopsy studies at the end stage of AD, the limbic cortex and the temporal cortex representing memory circuits are severely affected, while the medial occipital lobe representing visual function is spared even in advanced AD. The ordered system of tau pathology has been described in what is generally referred to as the "break stage" of neurofibrillary degeneration. Stages I and II are confined to the transentorhinal region. In stage III, NFTs appear in the entorhinal and hippocampal formation. In stages IV and V, NFTs widely disseminate throughout the neocortex. In stage VI, the neocortex is heavily affected.

Despite extensive research, many questions remain to be answered, such as: how do amyloid plaques and tau tangles initiate the pathology of AD and how are they connected? To what extent are these aggregates neurotoxic and how do they lead to cell death? Do they also trigger inflammation in AD brains which is a hallmark of AD-related pathology? Neuroinflammation is the result of activated astrocytes and microglia expressing inflammatory cytokines and neurotoxic factors leading to neurodegeneration.

2.3.1. Amyloid Plaques

Alzheimer's disease (AD) is a complex and incompletely understood neurodegenerative disorder characterized clinically by progressive cognitive and functional decline. The hallmark pathologic findings in the AD brain are the presence of toxic beta-amyloid plaques and hyper-phosphorylated tau protein-containing neurofibrillary tangles in discrete cortical and subcortical regions. The precise roles of both these pathologic entities in the underlying mechanisms and clinical presentation of AD are not certain. Although the pathologic findings of beta-amyloid plaques and neurofibrillary tangles are

highly distinctive for the disease, these changes can also be found in older individuals who do not exhibit clinical behavior consistent with dementia, a condition referred to as mild cognitive impairment. The absence of behavioral impairment in these so-called "pathological controls" suggests that neither beta-amyloid plaques nor neurofibrillary tangles are deleterious for the patient when found in isolation but rather that the co-existence of both these pathologic processes is required to achieve the clinical endpoint of dementia. It is of interest to note that beta-amyloid-containing plaques can be observed in the brains of older patients with a variety of neurodegenerative disorders as well as in those with no neurodegenerative disorder, indicating that the mere presence of beta-amyloid is not sufficient to cause nerve cell degeneration.

Although tau is redistributed in the neuritic swellings around plaques, these beta-amyloid plaques developed years before the tangles in the shipping and transport task of cellular metabolism. Furthermore, immunohistostaining indicates that oligomeric forms of beta-amyloid, likely from the plaque core but not the filamentous fiber cores or dense deposits found within late-stage senile plaques, appear more toxic both in vivo and in vitro. Although the subject is debated, it is widely accepted that both neuroinflammation and mitochondrial dysfunction also contribute to neurotoxicity in the progression of clinical AD. In this chapter, we will discuss the dominant role of beta-amyloid in the pathogenesis of AD, the possible detrimental and protective effects of tau, and the current and future therapeutic trials of AD directed towards beta-amyloid or tau. We will not discuss those clinical AD cases without plaques and tangles, genetic mutations independent of beta-amyloid and tau, or beta-amyloid causes of clinical dementia independent of neurodegeneration.

2.3.2. Neurofibrillary Tangles

Neurofibrillary tangles are the second of the two hallmark lesions found in brain specimens exhibiting the histopathology of Alzheimer's disease. Neurofibrillary tangles are also found in other neurodegenerative disorders, aka tauopathies. They are intra-neuronal accumulations of hyperphosphorylated forms of a protein, tau, which serves to stabilize the microtubule of the axon. Tau protein is mainly soluble and naturally found in neurons, particularly in the axons, essential to the transport of cellular products, mainly through microtubules. However, when phosphorylated forms of tau become excessive, they tend to self-aggregate, leading to the formation of neurofibrillary tangles inside neurons. Moreover, the excess of hyperphosphorylated tau in the axon hinders the normal function of tau, causing instability of the microtubules, axonal dysfunction, and atrophy. The excess of hyperphosphorylated tau can also migrate to the somatic compartment, forming the characteristic neurofibrillary tangles in neurons.

In Alzheimer's disease, neurofibrillary tangles progress in a predictable pattern of distribution through the brain. The earliest affected structures are those of the transentorhinal and entorhinal cortex. Subsequently, they appear in the temporal and parietal neocortex and, thereafter, further accumulate in the corticomedial amygdala, amygdalohippocampal area, basal forebrain, locus coeruleus, and cortical areas involved in olfactory pathways. Neurofibrillary tangles and other tau lesions have also been detected in primary sensory pathways in the brainstem, such as trigeminal, auditory, optic, and vestibular. In advanced stages of Alzheimer's disease, they may also appear in the neocortex, striatum, cerebellum, dentate nucleus, and, occasionally, the spinal cord.

In addition to neurofibrillary tangles, tau pathology can also appear in the form of neuropil threads in the cortex and the subiculum, pre-tangles in neurons and axons, and tau-immunolabeled dystrophic neurites that surround senile amyloid plaques. In addition to its expression within neuron cells, under severe neurodegenerative stress, tau can also be released to interstitial brain extracellular space, and this may contribute to the neuroinflammatory processes that worsen neurodegeneration in both tauopathies and Alzheimer's disease.

2.3.3. Neuroinflammation

Neuroinflammation is not new. It is possibly as old as Alzheimer’s disease itself. Pathological studies showed the presence of glial cells, which can trigger neuroinflammatory events, in brains diagnosed with Alzheimer's over 100 years ago. Neuroinflammation is now recognized as a complex component of the response innate immunity makes to perturbations in the brain, including injury, infection, or disease. Glial cells, including microglia and astrocytes, are responsible for the effects seen as neuroinflammation: pro-inflammatory cytokine release, additional glial cell activation, damage to the blood-brain barrier, and trophic support. Neuroinflammation can have both beneficial or deleterious effects on neuronal health and function over time. But what about the relationship between neuroinflammation and Alzheimer's?

A wealth of evidence strongly supports a connection between neuroinflammation and Alzheimer's disease. Since a significant proportion of patients with Alzheimer's diagnosis have a form of neuroinflammation at the time of death, almost as long as there have been studies that identify the presence of neuroinflammation in Alzheimer's disease, research has tried to determine the significance and relevance of neuroinflammation within the disease process. Genetic studies using human samples identified multiple genes expressed by microglia that are associated with Alzheimer's risk, including TREM2 and a variant in CR1. Microglial cells expressing the risk allele of CR1 show an impulsive response, characterized by an increase in phagocytosis,

including increases in the uptake of amyloid plaques, complement-dependent cytotoxicity, and a failure to clear dying neurons, a phenomenon implicated in Alzheimer's.

2.4. Clinical Diagnosis and Assessment

The clinical diagnosis of Alzheimer's disease typical of the sporadic, late-onset form is made through a clinical assessment of the patient by a physician and there is no single diagnostic test. Memory problems such as short-term memory loss and disorientation, symptom onset, and age of the patient are critical diagnostic factors. Patients are typically elderly, 65 years of age or older, but an increasing number of individuals in their 40s and 50s are diagnosed with early-onset familial Alzheimer's disease which is generally an autosomal dominant Mendelian trait resulting from mutations in the APP, PSEN1, and PSEN2 genes. Patients with early-onset familial Alzheimer's disease present earlier age of symptom onset, faster rates of disease progression, and more severe disease than those with sporadic Alzheimer's disease. Family history especially in male individuals and genetics including the presence of the ε4 allele of the apolipoprotein E gene indicate increased risk for sporadic Alzheimer's disease but are not definitive. Clinical criteria have been developed to diagnose sporadic Alzheimer's disease, typically based on cognitive impairment, mood alteration, impairment of activities of daily living, and gradual decline. Clinical criteria are sensitive for diagnosing Alzheimer's disease at a memory clinic, but they are not sufficiently specific and can be confused with other disorders. Further assessment with CSF analysis or neuroimaging including PET and MRI aid in the diagnosis and detection of the characteristic amyloid plaque and tau tangle pathologies, although conventionally neuroimaging is used to exclude other disease processes. Genetic analysis is performed selectively, usually for individuals with a strong family history.

The utility of cognitive testing is to provide greater precision in diagnosis as life expectancy continues to increase and more patients present with memory complaints. Neuroimaging to assess for amyloid deposition, magnetic resonance imaging to measure hippocampal atrophy, and analysis of the CSF for low levels of Aβ42, elevated levels of total tau, and elevated levels of phosphor-tau181 are also of use in differentiating Alzheimer's disease from other diseases associated with dementia and more precisely from non-Alzheimer's types of Alzheimer's disease. The distinction between types of neurodegeneration is valuable both for prognosis and for the choice of disease-modifying therapy as gene therapy approaches are developed. However, at present no therapy has demonstrated significant efficacy in modifying disease course.

2.4.1. Cognitive Testing

Although the diagnosis of Alzheimer's Disease can currently only be confirmed post-mortem via surgical pathology of neurodegenerative changes in the brain, there is required clinical assessment of symptoms and risk factors. Currently, a reliable diagnosis can be made via extensive clinical interviews and examinations based on criteria. However, other specific medical tests including neuroimaging and brain biopsy are typically done to rule out all other possible conditions and concomitant disorders before a confident diagnosis of AD. The most fundamental of the clinical assessments is the cognitive neuropsychology test, a specific battery of standard cognitive tests performed by the neurologist or geriatrician during an office visit. Examining only the frontal lobe, for example, would not be very informative since people with lesions to the frontal lobe can exhibit all of the major deficits seen in AD. The gold standard cognitive screening test is the Mini-Mental State Examination (MMSE), originally designed for a broad primary care audience, and is a brief cognitive and memory screen that typically takes 5 to 10 minutes to administer. However, the MMSE was found to be less useful for detecting mild memory impairment common in the earliest stages of AD, and for patients with more than a sixth-grade reading or education level due to ceiling effects, which is common in the primary care setting. Longer tests are available, but the MMSE is typically the test performed in clinical practice.

In contrast, the Montreal Cognitive Assessment (MoCA) is less likely to miss mild impairment and is free to use. Schooling, however, still needs to be considered when interpreting scores from this and other brief cognitive assessments. Both tests were designed to screen for dementia and not to make a diagnosis. Another relevant history that can be useful to gather at this time to aid with diagnosis includes the pace of cognitive decline (how fast, is it gradual or sudden), functional decline (ADLs and IADLs), activities of daily living (ADLs) and instrumental activities of daily living (IADLs), as well as changes in other neurobehavioral domains which can indicate a non-AD etiology and which are all highly regarded tests of the functional systems which are dependent on specific cognitive domains and typically together can point to localized atrophy affecting a neurobehavioral domain linked to a specific lobe of the brain based on cognition deficit.

2.4.2. Neuroimaging Techniques

Neuroimaging techniques allow the identification of functional and structural alterations in the brains of persons with AD. Structural magnetic resonance imaging may show the atrophy of specific brain regions and the increase in the size of the ventricular system, particularly in the early to late periods of disease. Diffusion tensor imaging can identify microstructural changes in white matter before the onset of clinical symptoms.

Functional MRI and positron emission tomography based on fluorodeoxyglucose may detect alterations in brain function, including changes in resting-state fMRI and in the brain glucose metabolism, even in the preclinical stages of AD. Advanced MRI techniques such as arterial spin labeling, blood-oxygen-level-dependent fMRI, and magnetic resonance spectroscopy are being evaluated.

The reduced cerebral blood flow and bioenergetic failure may already be present in the preclinical stages of AD. Various PET radiotracers have been developed for mapping the deposition of Aβ and tau in the brains of individual patients. Such techniques are approved by regulatory authorities for research settings, as in vivo studies have shown that tau-PET imaging is able to visualize tau deposition in the brains of persons with AD. Moreover, tau imaging correlates better with clinical measures than Aβ imaging. The application of the newly developed PET radiotracers in the clinical routine would allow an earlier diagnosis of AD pathology and the identification of target populations for preventive clinical drug trials. Furthermore, Aβ and tau PET imaging may help to improve the diagnostic criteria of the preclinical stages of AD pathology, based on functional decline and/or behavioral changes, b-amyloid deposition. These findings could also be helpful for AD-related research.

2.4.3. Biomarkers for Diagnosis

Biomarker (or biological marker) is a term to denote any measurable substance or modification of an anatomic structure, physiologic process, or biochemical process that can confirm normal or abnormal processes, or a specific condition. When applied to diagnosing neurodegenerative conditions, biomarkers can help establish the correct diagnosis, often in the absence of firm clinical indicators, through noninvasive means, and can do so early in the disease process, such as during mild cognitive impairment (MCI), when the likelihood of developing a dementia syndrome is greatest. These biomarkers may be of use both as diagnostic validators of incident cases in clinical trials, as well as diagnostic tools in clinical practice. In patients evaluated for possible dementia, biomarkers can offer some reassurance regarding the correctness of the clinical diagnosis and route toward treatment.

A diagnostic biomarker should possess several key characteristics: first, it should identify the presence of the condition that may affect the interpretation of the results of clinical cognitive testing; second, it should distinguish one condition or disease from other possible etiologies or causes; third, biomarkers should be available from easy route and low-cost source; and fourth, biomarker tests should be rapid and reproducible across testing conditions and laboratories. The discovery of suitable biomarkers for these neurodegenerative conditions has proved challenging, with numerous substances reported for initial evaluation but few receiving sufficient validation for use in either

clinical or research settings. Specifically for Alzheimer's disease and frontotemporal lobar degeneration, evidence for the diagnostic usefulness of biofluid markers from cerebrospinal fluid and whole blood is currently being used with increasing frequency; while imaging markers from positron emission tomography and multimodal brain MRI may offer the best combination of sensitivity and specificity.

2.5. Current Therapeutic Approaches

Current therapeutic approaches for Alzheimer's Disease focus on symptomatic benefits. Currently, only drugs that affect cholinergic neurotransmission have been used for symptomatic treatment. Cholinesterase inhibitors work for only a relatively modest percentage of individuals with AD. The three currently approved drugs for this use are the reversible inhibitors of acetylcholinesterase donepezil and rivastigmine and the butyrylcholinesterase-specific inhibitor galantamine. All three drugs are equally effective in providing modest symptomatic relief for only a subset of patients with mild-to-moderate AD; however, the three drugs vary in side effects, known drug interactions, patient compliance, and costs. A recent report concluded that cholinesterase inhibitors are not indicated for the mild cognitive impairment stage of AD or the more advanced AD stages.

Cholinesterase Inhibitors

Cholinesterase inhibitors work by blocking the breakdown of acetylcholine at the synapse. They do this by blocking the actions of one of two types of cholinesterase enzymes – acetylcholinesterase and butyrylcholinesterase. Current research is seeking to develop secretase inhibitors and parts of the amyloid cascade hypothesis into pharmaceutical drugs for the treatment of AD. These drugs would be indicated for disease-modifying treatment of AD and have begun to show some efficacy, but side effects need to be managed.

NMDA Receptor Antagonists

Memantine is a noncompetitive, low-affinity NMDA receptor antagonist that has been shown to provide modest benefit to some patients with moderate to severe AD who are already taking a cholinesterase inhibitor and/or patients with advanced AD. It is the first drug approved for treating dementia which does not have the cholinergic side effects of mild cholinergic overstimulation. It is currently approved as a single agent or in combination with a cholinesterase inhibitor.

2.5.1. Cholinesterase Inhibitors

Acetylcholine is a neurotransmitter implicated in memory. Numerous studies have found that acetylcholine levels in the brain are reduced in patients with AD and several other neurodegenerative conditions. During the earliest stages of the disease and progressing through the later stages, degeneration of cholinergic synapses as well as an imbalance of acetylcholine and serotonin occurs. Patients with AD and low cerebrospinal fluid levels of acetylcholine showed a markedly increased risk of worsening intellectual decline compared with patients with higher values. As the disease progresses through the stages, alterations in several synaptic and neurotransmitter systems occur. However, these neurotransmitter alterations are more prominent for vesicular acetylcholine transporter and vesicular glutamate transporter 1. A reduction of the vesicular acetylcholine transporter, especially in the basal forebrain and hippocampus, occurs in parallel with the severity of dementia.

Cognitive deficits appear early in the development of the disease and are well documented. Several lines of research have indicated that cognitive function in patients with AD is related to alterations in the cholinergic system. This has led to extensive research on the potential role of cholinergic medications in ameliorating AD symptoms. These findings prompted research using AChE inhibitors as a therapeutic approach for several diseases, specifically AD. AChE inhibitors help prevent acetylcholine from breaking down in the synapses, thereby increasing synaptic acetylcholine levels.

2.5.2. NMDA Receptor Antagonists

While it was established that Alzheimer's disease was associated with the inadequate action of the cholinergic system, other lines of action were also investigated. The main neuropathological characteristics of AD consist of the formation of neurofibrillary tangles in neuronal fibers and the deposition of senile plaques containing β-amyloid peptide in the intercellular space. However, not only the presence of these peptide deposits was correlated with symptoms of neurodegeneration and synapsis loss, but also the entorhinal and hippocampal cortices, and to a lesser extent, the Sylvian and temporopolar cortices, were the most affected regions. Therefore, the use of agents intended to control alterations in other neurotransmitter systems besides the cholinergic one, and the use of neuroprotective agents, were strategies that have been showing some interesting results.

Neuroprotective action can be accomplished by inhibiting the activity of glutamate on N-methyl-D-aspartate receptors. These receptors are ionic channels permeable to calcium ions which, when activated, play an important role in synaptic plasticity and neural memory. These receptors in hyperactivation conditions can also cause cell

damage by excitotoxicity mechanisms and are related to various neurodegenerative diseases. In the Alzheimer's model, some parameters of the disease were analyzed, and one of the therapeutic strategies against Aβ toxicity consists of the use of NMDA receptor antagonists, or excitotoxicity modulators. Rivastigmine, donepezil, and tacrine are the only classic cholinergic agents that have been approved for the treatment of dementia due to potential pharmacodynamic interactions. NMDA receptor antagonists are utilized in patients who are unresponsive or intolerant to classic cholinergic agents or when patients develop cholinergic adverse effects on therapy with classic cholinergic drugs. The NMDA receptor antagonists most utilized in dementia cases are memantine and ketamine.

2.5.3. Symptomatic Treatments

Elsewhere in this book, we highlighted some of the good news concerning the development of a significant number of disease-modifying therapies in clinical development; in fact, recent clinical trials have shown that it is possible to modify the course of Alzheimer's disease with some drugs. Unfortunately, we have to affirm the contrary regarding symptomatic treatments, where in the last years hardly anything new has appeared. Current symptomatic medications, by modulating the cholinergic and glutamatergic systems, can slightly ameliorate the symptoms and delay progression, but this is the highest impact these treatments can have. Additionally, they are limited to only certain cases, have a short duration of efficacy, and have to be administered continuously. Other major symptoms of the courses of the disorder are not alleviated, producing anxiety, depression, agitation, hallucinations, and other symptoms that involve higher morbidity both for patients and caregivers. Management and treatment of these symptoms have become important in the pharmacological approach of patients with Alzheimer's disease. Moreover, the biggest future epidemic of neurocognitive disorders and the related need for care is expected to occur in developing countries; given this scenario, the current treatments have to be more easily available and with the least possible side effects.

Nonpharmacological therapies are very useful and have also been proposed as an addition to the pharmacological treatments. They should usually be the first option for managing the neuropsychiatric symptoms of Alzheimer's disease. Such therapies have demonstrated effectiveness in decreasing the frequency and intensity of affective disorders, anxiety, and disruptive behaviors and improving global functioning in patients with Alzheimer's disease. They also permit the reduction of the adverse effects of pharmacological treatments, especially in patients with comorbidities, and improve the overall well-being of both caregivers and patients.

2.6. Emerging Therapies

Alzheimer's disease was first documented in 1906 when a patient with unusual protein deposits and profound memory failure was discovered. Unfortunately, we remain with those same symptoms over 100 years later and the only FDA-approved treatments for AD do not modify the course of the disease. Instead, they are designed to alleviate the terrible symptoms of AD. However, there is new hope and a promise of a couple of medications – amyloid beta and tau-targeted monoclonal antibodies – to reduce dramatically the risk of AD. There is also the possibility of new therapies – gene therapy, stem cell therapy, and AAV delivery of rATPase and transgenes – which have the potential to prevent, halt, or significantly reverse the course of AD but have not been subjected to clinical trials yet. In this Section, a brief description of three of these promising new therapies is provided. They are amyloid beta-targeted and tau-targeted monoclonal antibodies as well as the research on gene therapy, stem cell therapy, and AAV delivery.

Monoclonal Antibodies Alzheimer's Disease is now being redefined as a disease caused by amyloid beta, tau, and TDP-43. In 2017, the "antibody revolution" was now well underway in the field of AD with monoclonal antibodies developed to target amyloid beta, tau, and TDP-43 being investigated in clinical trials all over the world. The first FDA-approved AD drugs to modify the disease were the amyloid beta monoclonal antibodies aducanumab, blarcamesine, lecanemab, and donanemab. This is because of compelling evidence showing reduction of amyloid beta plaque burden predicted efficacy. The tau-targeted monoclonal antibody, to ibrutinib, and TDP-43-targeted monoclonal antibody, AAB-001 are also currently in clinical development.

Gene Therapy Little is known about gene therapy in animals. What is known is that currently gene therapy applications are limited to rAAV delivery. The AAV9 INR was developed by inserting an inverted terminal repeat followed by a tissue-specific restriction element into a cytomegalovirus-driven rAAV9 construct. Overexpression of AAD9 occurred when rAAV9 was delivered to the liver of mice undergoing a 60% partial hepatectomy. On the other hand, overexpression did not occur in the liver of the non-partial hepatectomy model or other tissues.

2.6.1. Monoclonal Antibodies

Monoclonal antibodies are highly purified proteins that target a single epitope of a single antigen stimulus. Due to their specificity, safety, and advantageous pharmacokinetics, monoclonal antibodies are favored for use in several therapeutic areas including oncology, cardiology, and infectious diseases. For Alzheimer's disease, monoclonal antibodies have been created to remove or neutralize amyloid-beta or MAPT pathology,

targeting the clearance and deposition of toxic amyloid-beta oligomers or tau tangles. While many have shown promise in early-phase small studies, two key problems have impeded their success in the late-phase pivotal studies necessary for approval. First, many have produced disappointing results, raising questions about the amyloid-beta and tau hypotheticals themselves. Others have shown promise in patients with mild cognitive impairment and mild disease; but in more advanced diseases, they fail to show significant effects which raises concerns about placebo bias. These findings beg the question of which patients will respond before the disease progresses too far, and how much should they receive any benefits.

Second, several monoclonal antibodies to amyloid-beta clearance have produced significant deleterious effects. Brain edema and microhemorrhages on imaging — possibly due to increased vascular deposition of amyloid-beta oligomers — are now well-documented side effects. In some studies, these adverse effects occurred in about 40% of patients receiving monoclonal antibodies. A significant number have required cessation of monoclonal antibody treatment due to these adverse effects, again raising doubts about the amyloid involvement and justification for the monoclonal therapies. Others have initiated monoclonal treatment only to quickly develop lymphocytic meningoencephalitis and have died. The situation is complicated, however, by the serendipitous finding that in some cases, brain-toxic amyloid-beta oligomers may have been cleared from a patient's brain after sufficient prolonged monoclonal antibody therapy, resulting in the reversal of dementia. Thus, the question is how to calm the brain toxicity and vascular adverse reactions in the rest of the patients while maximizing the efficacy of reversing the disease in most patients. So far, success has been limited.

2.6.2. Gene Therapy

Gene therapy is an innovative approach aimed at correcting defective genes responsible for disease development. For Alzheimer's disease, gene therapy is being designed to modify the expression of certain genes that contribute to the pathophysiology of the disease. With the advances in genetic engineering technology and delivery systems, there is an increasing number of gene therapy approaches entering the clinical trials stage. Here we review the most advanced gene therapy approaches in AD trials.

Gene therapy approaches are classified into two general categories based on the type of delivery systems: non-viral gene delivery systems and modular virus-based gene delivery systems. The non-viral gene delivery system utilizes physical methods or chemical methods to deliver the transgenes into cells. The modular virus-based gene delivery systems use viruses as vectors for gene delivery, including adenoviruses, adeno-associated viruses, lentiviruses, and retroviruses. Here we will first discuss the modular virus-based gene delivery approaches. The advantages of these approaches include

convenient and proper experimental designs for in vitro studies, the broad availability of existing and engineered vectors targeting different cell types of interest, and the natural efficiency of vector-mediated transgene expression in vivo compared to non-viral systems. Although not every approach has been tested for gene therapy, the recent advances in the AAV delivery system have led to a variety of applications that are currently under design for AD therapy in both animals and humans.

2.6.3. Stem Cell Therapy

Traumatic brain injury and neurodegenerative disorders like Alzheimer's disease cause extensive loss of neurons and other brain cells that play important roles in the maintenance of brain structure and function. While some cell types in the brain can regenerate in response to damage, the brain lacks endogenous regenerative ability, and therapies that can restore lost cells or promote repair are desperately needed. Cell replacement therapy using exogenous cells, particularly stem cells, represents a near-term solution to provide the missing neurons and other brain cells. Increasingly, stem cell therapy has become a viable option for the repair/replacement of neurons in Alzheimer's disease and related dementias.

Recent studies have demonstrated that stem cell therapy can restore lost neurons, improve innate immune mechanisms, promote repair of the blood-brain barrier, restore blood flow, have a positive effect on Alzheimer's disease-related clinical symptoms, and improve overall quality of life. While offering hope as a cure or near-term solution to promote repair and restore lost neurons in the brain, issues addressing the premise of such an approach, elucidating the mechanism of the positive influence of stem cell therapy on disease modification and the fate and role of replanted stem cells or their progeny are being actively investigated. Excitotoxicity and entry of neurotoxic inflammatory mediators into the brain contribute to the activation of pathogenic tau and amyloid behavior in neurons and glia leading to AD symptoms and pathology. Efficiently repairing neuroinflammation-mediated excitotoxicity-related brain injury can address the issue of initiating, perpetuating, or exacerbating AD pathology and symptoms in at-risk individuals. Importantly, with appropriate and timely intervention, stem cell therapy can address the pathological processes that provide inflammatory support for tauopathy and amyloidopathy of AD and the expedited AD course.

2.7. Lifestyle Interventions

The ideal treatment for Alzheimer's disease (AD) would be a pill that stops the progression of the disease and reduces symptoms. However, after decades of research, no such treatment exists. A more promising line of research, often overlooked, is lifestyle

interventions. If AD is partially the result of disturbances in whole-body and brain homeostasis, then lifestyle approaches may make the brain less vulnerable to AD. Moreover, studies have revealed that although genetics may play a large role in the development of dementia, the risk is modified by peptide levels in the brain and the presence of comorbid conditions. Because some of the comorbid conditions may be preventable or modifiable through lifestyle changes, such therapies are promising in reducing dementia risk. In this chapter, we discuss three modifiable risk factors that are touted as lowering your risk of dementia: diet, physical activity, and cognitive engagement.

Diet and nutrition are complex topics, and there is no consensus on what constitutes an ideal diet for brain health or general health. The topic of diet warrants a more in-depth discussion, as it is too simplistic to state that AD is caused by vitamin deficiency, dietary imbalance, or consumption of unwholesome food. Perhaps a better approach is a focus on dietary patterns and the types of foods that are helpful. Copious research has revealed that the following nutrients are important for human health and perhaps also for brain health: vitamin B12, vitamin D, calcium, vitamin E and other antioxidant vitamins, omega-3 fatty acids, flavonoids, and curcumin. These nutrients are often high in antioxidant and anti-inflammatory foods such as fruits, whole grains, vegetables, and healthy fats, especially plant-based.

2.7.1. Diet and Nutrition

A growing body of epidemiological evidence suggests that diet can have an impact on the risk of developing AD. Furthermore, numerous studies have found associations between specific nutrients and cognitive performance in older adults. Indeed, the growing interest in food as medicine has been inspired by recent findings linking particular nutrients with brain health. More than ever, dietary studies are supporting the widely believed saying “You are what you eat”. Potential mechanisms connecting diet to brain function include the reduction of oxidative stress, improvement of cardiovascular function, stimulation of production of neurotrophic factors, increased phagocytosis, and attenuation of inflammatory responses associated with microglia.

Dietary patterns during late life may impact the risk of developing dementia and AD. Observational studies have reported the association between diet and AD risk. Over 90 million adults in the United States are affected by chronic inflammatory conditions, including obesity, insulin resistance, and diabetes, which have been implicated in the development and progression of neurodegeneration. Emerging evidence suggests that certain dietary patterns, type 2 diet-induced obesity, diabetes, fear complex, and cardiometabolic health may predispose and potentiate neuropathological changes, exacerbating risk and clinical progression of neurodegeneration. Nevertheless, several

dietary intervention studies in humans have shown that memory and cognition can be improved and/or maintained via strategies that enhance the intake of critical neuroprotective nutrients that upregulate neurotrophic support, or dietary restriction strategies that decrease the consumption of inflammatory/oxidative stressors associated with type 2 diabetes and premature aging.

Preclinical studies targeting aging-associated diseases have also demonstrated that improving neuroprotection through dietary adjustments can impact the risk for and the clinical progression of neurodegenerative diseases. Moreover, the biggest evidence to date is from studies of caloric restriction and methionine restriction, and more recently the observation of health benefits in individuals consuming a ketotic diet.

2.7.2. Physical Activity

Elderly patients who suffer from Alzheimer's disease (AD), the most preeminent form of dementia, exhibit comorbidities related to blood vessel conditions, inflammation, and oxygen depletion. Reductions in neurotrophic factors and the loss of support from astrocytes and microglia lead to neural injury and the creation of pathological protein misfolds. Lifestyle interventions were conceived not just as AD treatments, but also as overall healthy active engagement that will delay the onset of AD symptoms or reduce the chance of acquiring it. One lifestyle intervention being clinically explored is physical fitness activities. Physical activity produces permissive biochemical changes that enhance neural circuit development and plasticity, engage neuroprotective factors, decrease AD aggregation pathology, and improve overall cardio health. Unique aspects of AD that affect how patients can respond to physical interventions are the current CDR, MAPT genotype, and baseline levels of hoy codone.

The research is still evolving, but strong evidence from longitudinal studies confirms that regular aerobic exercise can curb the probability of AD, especially in women. Though the mode of physical activity can vary with the patient's ability, aerobic exercise does not need to be high-intensity or structured. Endurance exercise using walking or other methods is preferred, performed at least three times/week for 30 minutes. Light to moderate resistance training at least twice a week can also be added. Exercises recommended do not need to be supervised and might be associated with other activities, such as yoga or tai chi exercises promoting general well-being, flexibility, mood elevation, sociability, etc. Ideally, individuals should be encouraged to engage in a routine of activity that enhances their overall fitness mental and physical, and to enlist family support.

2.7.3. Cognitive Engagement

Older adults who regularly engage in a range of mentally stimulating activities, including games, puzzles, reading, and educational opportunities, have a lower risk of cognitive impairment compared to those who do not. For those with mild cognitive impairment or subjective memory complaints, more leisure time spent on cognitively engaging activities, like reading and engaging in thought-provoking discussions, is associated with a slower decline in cognitive ability. Meanwhile, those with mild dementia engaged in fewer leisure activities. Since specific factors that moderate engagement are unknown, positive lifestyle choices include regularly incorporating cognitively stimulating activities in leisure time, irrespective of the state of the brain.

While observational studies indicate an association between cognitive activity and less cognitive impairment, such studies cannot determine causation. Since having a higher level of intelligence at an earlier age is a risk factor for pointing behavioral choices towards more cognitive engagement, having more cognitive activity may simply reflect a more favorable cognitive prognosis. The theory of cognitive reserve has been postulated to explain the neuroprotective effect, mitigating cognitive decline, from both education and, throughout life, engagement in stimulating activities. Theoretical proposals include either an increase in synapse density and functionality or a staged response of compensatory neural activation that would allow for further challenges on top of the neural compensatory foundation.

Fig 2 . 3 : The Cognitive Reserve: Building a Brain for Life

To date, there have been no specific interventional studies confirming the effect of increasing cognitive activity in older adults with either normal cognitive function or mild

cognitive impairment. Moreover, the timing of the potential efficacy of cognitive interventions is debated, with suggestions that resourcing can start to be beneficially utilized earlier in the disease, with lifestyle activities preserving cognitive functioning in the early prodromal phase.

2.8. Psychosocial Aspects of Alzheimer's Disease

Although AD is fundamentally a biological disease, it often manifests and affects the world in terms of its psychological and social impact. These psychosocial aspects can have enormous consequences for affected individuals and their families. From the earliest stages of disease development, which may occur many years before frank memory loss, patients often experience anxiety, depression, and loss of control over their lives. Patients usually find social engagement more difficult as increasing memory loss and disorientation make social rituals especially stressful. By the later stages of disease development, once cognitive function is severely impaired and negative dependence on caregivers becomes so evident, caregivers are often overwhelmed by their responsibilities. Their lives are greatly disrupted and they may deny themselves many of the things they once enjoyed to the detriment of their well-being. Negative consequences of caregiving can include physical decline, loss of social connections, and mental health problems such as anxiety and depression. In addition to the burden of caregiver stress, they are also faced with complicated mourning of the slow loss of the person they once loved and who continues in a severely impaired state.

Caregiver Support

As stressful as it may be to care for a person in the later stages of AD, the psychosocial issues associated with the earliest stages of the disease are often more significant for the patient and their family. Depending on their personality and coping style, some early-stage patients can adapt to their cognitive decline better than others. Lack of effective compensatory strategies for memory loss can lead them to feel anxious, frustrated, and ashamed. Effective coping strategies would allow the patient to mitigate these feelings. Offer assistance—suggest memory aids, and encourage them to keep notes about what they feel. Other important strategies would involve creating a new environment in which to function—reducing environmental distractions that would increase confusion and overwhelm. Additionally, one of the biggest factors that may allow the patient and the caregiver to adapt better to this new reality is communication. It starts with the initial visit when a diagnosis of AD is given.

2.8.1. Caregiver Support

A caregiver is a person who assists another who is unable to perform the activities of daily living independently. Alzheimer's disease patients are generally cared for by family members, mostly by spouses and children, while professional caregivers are employed later when patients require higher levels of care. Early, informal caregivers are generally underprepared and use a large portion of their time managing patient care, and hence provide a significant amount of unpaid labor, which is estimated to be worth a significant amount per year. Their contributions can be helpful in keeping dementia patients living independently longer but may come at great social costs, including their health. Caregivers face significant problems ranging from isolation, fatigue, stress, anxiety, and depression to decreased performance at their jobs, increased absenteeism, and loss of income and/or benefits. The stress level most often correlates with the severity of the dementia. Child caregivers and those who face external stress, such as caring for a child, or working a job outside the home, experience even higher levels of depression and stress while spouses and child caregivers have lower psychological well-being than other family members.

Providing appropriate support to the informal caregiver is crucial since they experience the greatest physical and psychological burden compared to both Alzheimer's disease patients and professional caregivers. Unfortunately, many professionals fail to support caregivers, and some indicate that the greatest unmet desire for help is related to the process of finding assistance and support. While healthcare professionals often underestimate the needs of the caregivers, and overly emphasize the need for treatment of the patient, support groups have been shown to alleviate the distress of the caregivers.

2.8.2. Patient Quality of Life

Throughout the progress of dementia and AD, the patient experiences difficulties regarding memory, behavior, and physical difficulties. As time goes by, the patient comes to a point where he/she loses interactions with the outside world and begins to have problems in daily life. Moreover, all these difficulties lead to suffering for the patient. Quality of life is a broad and multidimensional concept that indicates the general state of a person, including physical health factors such as disease progression and general well-being along with factors that represent personal values, including comfort, environmental factors, family structure, social relations, education, financial state, and occupation. The close relatives of the patient also suffer after seeing their loved ones go through difficulties; thus, it is vital to care for these people as well.

The objective of medical treatment is to decrease suffering and help maximize the patient's quality of life. To achieve this, the factors that influence the quality of life must

first be clarified. Health-related quality of life and the perception of the patient regarding the circumstances including dieting, sleeping, and pain tend to lower as the severity progresses. Other factors that significantly correlate with the poor quality of life of AD patients are depressive symptoms, neuropsychiatric symptoms, behavioral and psychological symptoms of dementia, dependency on daily living activities, physical dysfunction such as walking and balance dysfunction, and low mental activity. Research regarding quality of life in AD and examining the signification factors relative to the quality of life for patients is nowadays fundamental. The results may lead to therapeutic strategies and help to improve or maintain the patient's quality of life and even decrease caregiver burden.

2.9. Conclusion

September 22, 2022, 9. Conclusion We started out this book with a story about how World Alzheimer's Day came into existence, but we closed with a story about how science has contributed to what we know about the disease. We embarked on this journey of understanding since the dawn of Alzheimer's disease and dementia when Alois Alzheimer presented his work to the world. From there, we explored what we understand of plaque and tangles, the genetic links, the risk factors, errors in energy metabolism, the contribution of neurovascular and immune responses, the accumulation of tau, the role of sleep and metabolism, potential relationships with diabetes, and what we understand about sporadic Alzheimer's disease. As the chapters unfolded, we then discussed the clinical features, diagnosis, and treatment options that we currently have. Finally, we briefly considered what researchers are currently trying to do to help people with Alzheimer's disease further down the line.

Currently, the neurosciences remain at the forefront of providing insights into the workings of the body and disease. It has changed thought paradigms in addition to influencing the modern usage of technologies to further our understanding. In particular, research into Alzheimer's disease has focused on understanding the underlying mechanisms, combining the results within the greater matrix of information that we have available. Genetic research augmented by sequencing is shedding light on the genes involved (both protective and risk factors), while tau, amyloid, neuroinflammatory markers, and other associated pathways are being analyzed against clinical data. The main challenge however remains in sorting through the mass of data, especially in sporadic cases that would go on to develop Alzheimer's disease without having any of the genetic links that point towards dementia, and hopefully find a way to diagnose and take action to minimize the effects of the disease or future onset.

2.9.1. Key Takeaways and Future Directions

A great deal of work remains ahead of us all in our quest to understand and treat this horrible disease as there is no cure nor effective treatment for the vast majority of patients. More is known about the clinical, pathological, transformative mental, and behavioral correlates but corresponding data that reveal the changes and deficits of actual brain function are practically non-existent. There is no lack of creative ideas, discoveries, and techniques being applied to this monumental challenge that will push back the boundaries of our knowledge further and further, and yet it only takes patience and time to translate basic findings into effective treatments. This is especially true given the extraordinary complexity of the brain where change in nearly every area must be understood to have a chance of effectively dealing with the changes associated with the disease. The different avenues being pursued to prevent, slow, or reverse Alzheimer's disease can be categorized into two groups: treatment of the disease itself and restitution of lost function. These groups are not mutually exclusive; restitution of function can take place in association with the change or restoration of affected processes or pathways. The majority of efforts thus far have been directed toward preventing or slowing disease progression – in essence, combating the pathology – since this type of intervention is considered more readily achievable given our present level of understanding. To date, the investigational drugs that have exhibited any effect on either the cause or the course of the illness have hindered the rate of progression or modified the effects of amyloid pathology, particularly as it relates to reducing plaque burden. Moreover, all current drugs are directed against the pathology, and none are intended to improve or restore the cognitive, functional, and behavioral deficits. The important challenge is to successfully determine combination approaches that not only slow disease progression but also restore lost function.

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