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# Alzheimer's Disease: From Clinical Tragedy to Reason for Hope

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# Alzheimer's Disease: From Clinical Tragedy to Reason for Hope

*Kenneth Adams*

**A**lzheimer's Disease (AD) is ruthless. At its earliest stage (Pre-Clinical AD), it begins wreaking havoc on the brains of patients without causing clinical symptoms, leaving them unaware that they need medical counsel. As the disease progresses, symptoms start to manifest as episodes of short-term memory impairment, which are often dismissed as normal cognitive decline during aging. If not dismissed, these episodes can instill fright and uncertainty about what the future holds. This period, referred to as Mild Cognitive Impairment (MCI) can last months or years before symptoms worsen to a degree that triggers alarm.

In this stage, referred to by clinicians as Mild AD, individuals' short-term memory is clearly impaired and new symptoms emerge, such as difficulty speaking and understanding language, alongside frequent mood swings. Here, formal diagnosis of AD becomes much more likely, forcing patients to endure the anticipation of their looming dementia. Moreover, the disease also begins to take a physical and emotional

toll on patients' loved ones, as assistance with some aspects of daily living becomes necessary. Mild AD typically lasts 1-2 years before worsening symptoms qualify it as Moderate AD, when individuals experience severe memory loss and exhibit behaviors that can be emotionally traumatizing to all involved, such as rambling speech, delusions, and uninhibited actions. In the process, patients are robbed of their

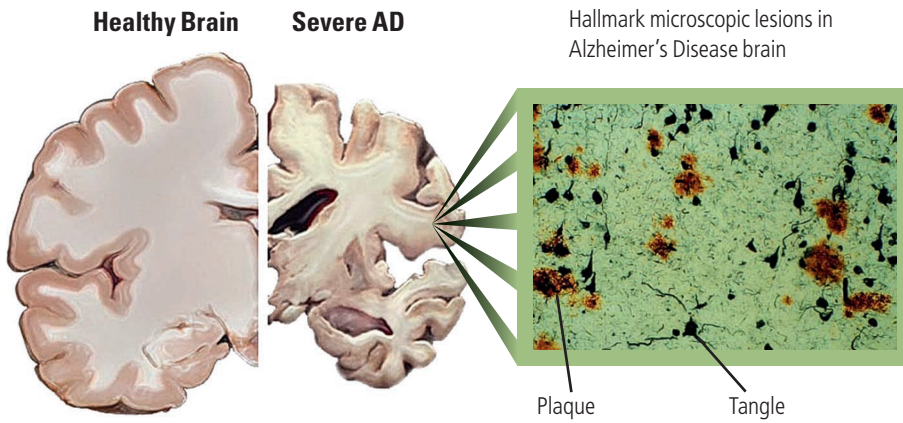
identities and their families are forced to watch helplessly. In its final stage, Severe AD, patients suffer a near complete loss of memory and the ability to communicate or process information; they lose their mobility and, eventually, even their capacity to swallow. From diagnosis to death, the disease's duration typically lasts 8-10 years and, sadly, we lack effective therapeutics to halt, let alone reverse, the disease's progression. As a budding cell biologist exiting graduate school in 2007 and in the process of discerning the next step in my career, this heartbreaking reality prompted me to seek research opportunities to contribute to the fight against this dreaded disease. This led to a research fellowship at the Massachusetts General Hospital Alzheimer's Disease Research Center, where I was inspired by a diverse and collaborative community of physicians, scientists, and philanthropists who are devoted to battling AD. We have much to learn about its underlying pathology and effective approaches for treatment, but the commitment and spirit of the AD research community gives us hope that one day we can eradicate the disease.

## Tracking the etiology of AD—from clinical dementia to plaques and tangles to beta-amyloid aggregation

Given its brutality and prevalence (more than 5 million people currently live with AD, a figure that is projected to rise to 13.5 million by 2050), enormous resources have been put into biomedical research focused on understanding and treating AD. Effective treatments have yet to be established; nonetheless we have learned a great deal about the pathology that takes place in the AD brain. The earliest insights were provided over a century ago by German physician Alois Alzheimer (1864-1915), after whom the disease is named (Figure 1). When his patient, Auguste Deter (a woman who was suffering



**FIGURE 1.** Dr. Alois Alzheimer (1864-1915) and his patient Auguste Deter (1850-1906). Source: Uncredited photos from Wikimedia Commons.



**FIGURE 2.** Coronal brain sections of healthy brain versus AD brain that has undergone severe atrophy (left) and microscopic analysis of AD brain tissue highlighting the hallmark lesions that develop in AD brain—plaques and tangles (right). Sources: National Institute of Health, Wikimedia Commons; LaDu Neurodegeneration Research Lab, University of Illinois Chicago.

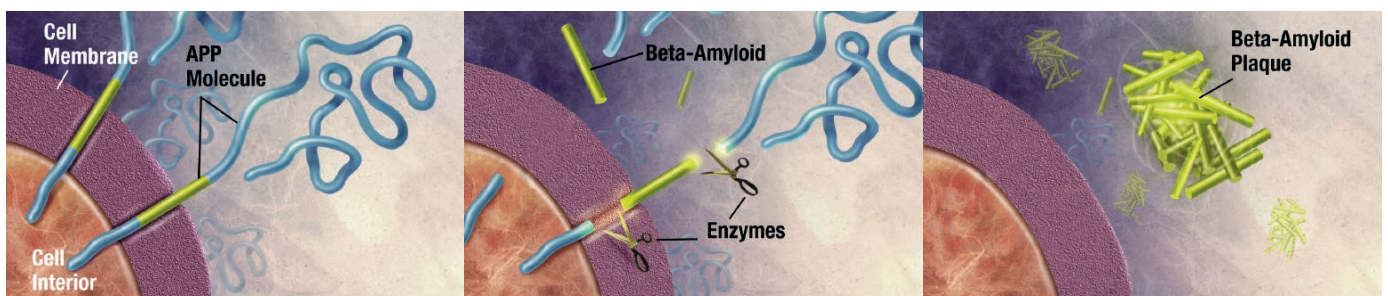
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from dementia) died in 1906, Dr. Alzheimer performed an autopsy on her brain and identified three abnormalities that to this day are regarded as hallmark features of AD pathology. On a macroscopic level, Alzheimer observed that Deter’s brain had undergone severe atrophy (Figure 2, left), which we now know results from extensive neurodegeneration (the death of brain cells called neurons) that occurs during AD. Neuron activities are central to the

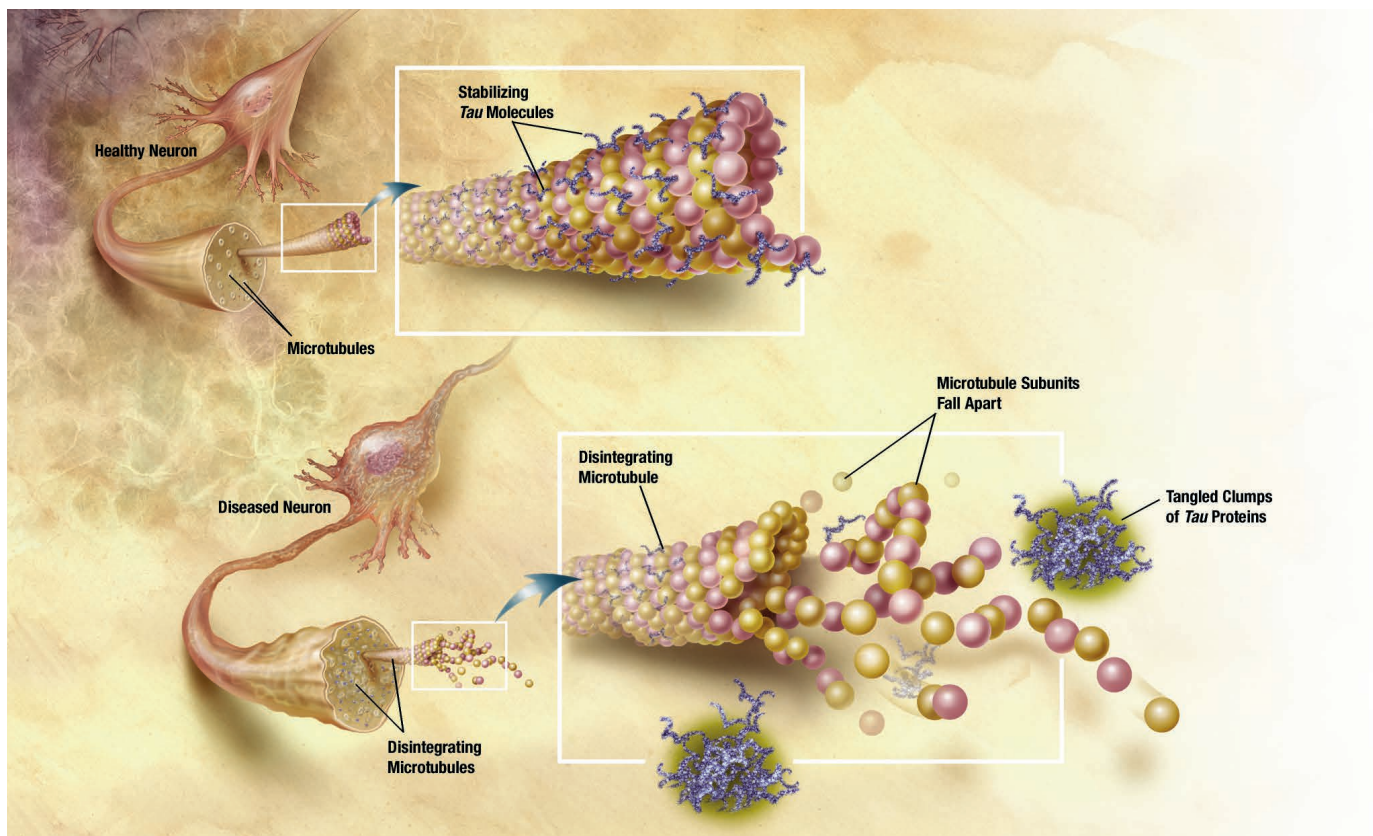
control and execution of virtually all human behaviors including those lost in AD (memory, language and communication skills, information processing, and mobility). His discovery provided a clear causal link between brain atrophy and the clinical symptoms that take place during the disease. On a microscopic level, Alzheimer determined that Deter’s brain also contained two abnormal lesions referred to as plaques and tangles (Figure 2, right). Importantly,

these observations alone suggested that Alzheimer’s Disease results from the accumulation of toxic plaques and tangles in the brain that cause neurodegeneration and the clinical symptoms associated with the disease. Testing this hypothesis, however, required answers to several fundamental questions that Alzheimer could not address due to the technological limitations of his time. These questions included: *What are plaques and tangles composed of? How do they form? Why do they form in brains of AD patients? Are plaques and tangles the toxic agents that cause the neurodegeneration during AD? Or, conversely, might they be an inconsequential side effect of the disease process?*

Perhaps surprisingly, addressing these fundamental questions awaited 80 years of progress in our understanding of biology, development of research technology, and national commitment to combating AD. Nevertheless, when these three developments converged in the 1980s, they ignited an explosion of AD research that has continued to present day. The explosion began in 1984 when researchers identified the core component of plaques—the protein beta-amyloid (aka, amyloid-beta and A $\beta$ )—which set the stage for researchers to determine where it comes from and how it forms plaques. Subsequent studies showed that beta-amyloid is first produced in brain cells as part of a larger, membrane-embedded protein called APP (Figure 3), which is regularly cleaved by enzymes, releasing beta-amyloid into the surrounding brain tissue. Critically, in Alzheimer’s Disease the released beta-amyloid



**FIGURE 3.** Schematic depiction of the process of amyloid plaque formation. Sources: National Institute on Aging and Wikispaces.



**FIGURE 4.** How microtubules disintegrate with Alzheimer's Disease. Sources: Alzheimer's Disease Education and Referral Center, National Institute on Aging and Wikimedia Commons.

readily aggregates into insoluble deposits—plaques. Parallel to these studies on beta-amyloid, researchers also determined that the core component of tangles is a protein called tau, which was already known to play an essential role in maintaining the health of neurons through binding (adhering to) and stabilizing structures called microtubules. As depicted in Figure 4, microtubules are elongated structures inside neurons that provide stability to neuronal extensions (called neurites), a function that is indispensable to neuronal health and function. During AD, tau dissociates from microtubules and aggregates into insoluble deposits—tangles—resulting in the disassembly of microtubules and consequent degeneration of neurites.

This characterization of beta-amyloid and tau aggregation into plaques and tangles, respectively, raised several new questions about AD pathology, many of which are still being investigated today.

One that is central not only to our understanding of the disease, but also to the development of AD therapeutics is this: *Can the root cause of AD be attributed to either beta-amyloid aggregation into plaques or tau aggregation into tangles?* If one of these events can be identified as the root cause, then we can focus resources on therapeutics that can intervene in that event. In other words, if beta-amyloid aggregation represents the triggering event in AD, then blocking beta-amyloid aggregation may represent the most promising approach to treating AD patients; likewise, if tau aggregation is the causative event in AD, then blocking it may prove more effective.

Major progress toward answering this question started in the early 1990s, stemming from genetic studies on several families whose members exhibited a rare, inherited form of AD called familial Alzheimer's Disease (or FAD). FAD differs from the most common form of AD (called sporadic

AD because it arises sporadically in population without a clear genetic cause) in that it is passed on through generations of a family due to the inheritance of a genetic mutation.

Starting in the 1990s, researchers began performing genetic analyses on families with FAD in an attempt to identify the mutation(s) responsible for the disease. Since then, more than 200 mutations have been discovered. Strikingly, all of these mutations are located within one of two genes: the gene that produces APP (see Figure 3); or the one that produces the protein presenilin, a key enzyme that cleaves APP to produce beta-amyloid. Moreover, experimental analysis of these mutations demonstrated that they cause a common, critical effect in the brain: they increase beta-amyloid aggregation into plaques. These discoveries, along with studies proving that plaques and smaller aggregates of beta-amyloid are toxic to neurons, led researchers to formulate

the amyloid cascade hypothesis (Figure 5), the most significant guiding force in AD research for the past 20 years.

The amyloid hypothesis posits that Alzheimer's Disease is triggered by the accumulation of small beta-amyloid aggregates and larger plaques that exert pathological stress on the surrounding brain tissue. This stress, in turn, causes additional pathology, including tangle formation, leading to widespread neuronal dysfunction and, ultimately, dementia. Importantly, while inheritance of the APP and presenilin mutations explain why beta-amyloid aggregates in the brains of patients with FAD, the cause of beta-amyloid aggregation in sporadic AD is not yet fully understood. Given the fact that sporadic AD constitutes greater than 95% of all cases, determining its cause is a major focus of ongoing research.

### Three paths to beta-amyloid aggregation in sporadic Alzheimer's Disease

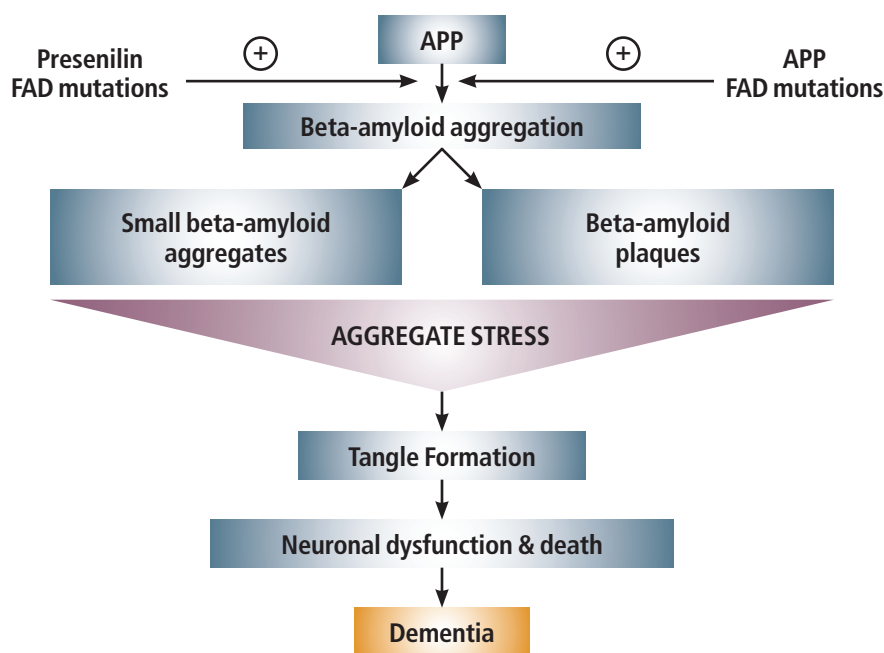
In 1992, an important discovery was made that now frames our growing understanding of beta-amyloid

pathology. The discovery was that although beta-amyloid represents the major toxic agent in AD, its presence in the brain is not limited to individuals with the disease. Rather, beta-amyloid is produced in the brains of all individuals—young and old, healthy and diseased—through continuous synthesis and cleavage of APP (see Figure 3). This is important because it dismisses simple explanations for AD etiology. Researchers need to pursue more nuanced explanations for the cause of

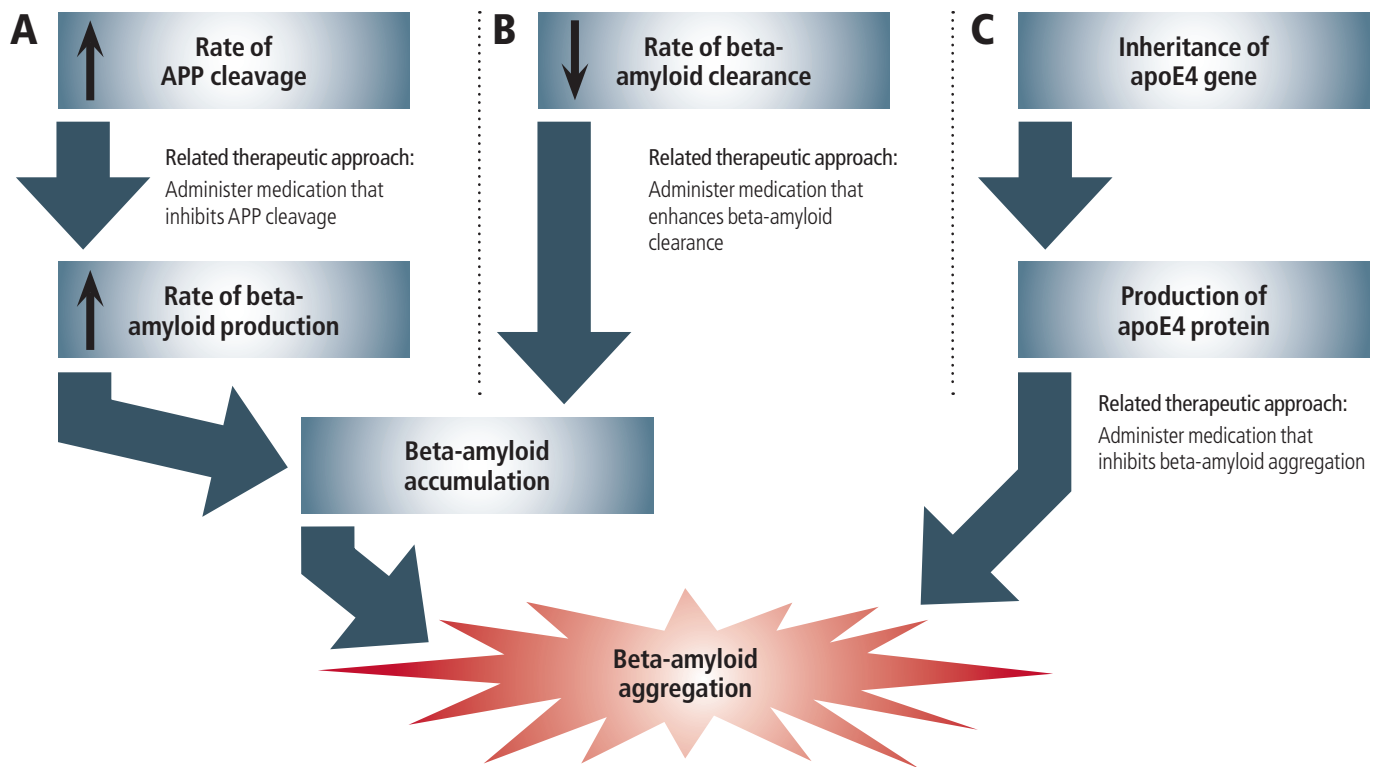
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beta-amyloid aggregation in AD. In doing so, three fundamental “paths” that contribute to beta-amyloid aggregation in sporadic AD have been defined.

First, while cleavage of APP occurs continuously in brain tissue, the rate of cleavage can vary and is affected by numerous factors that we now know contribute to AD pathology. More specifically, factors that increase the rate of APP cleavage cause increased rates of beta-amyloid production, leading to its accumulation, which can in turn drive its aggregation (Figure 6A). Second, to balance the ongoing production of beta-amyloid, brain cells have concurrent processes to continuously remove or “clear” it from tissue. Thus, factors that decrease the rate of beta-amyloid clearance can also cause its accumulation and aggregation (Figure 6B). Lastly, while no clear genetic cause for sporadic AD has been identified, one gene—apolipoprotein E (or, apoE)—has been demonstrated to influence a person's chance of developing the disease. The apoE gene exists in population as three variants referred to as apoE2, apoE3, and apoE4, all of which produce a protein that transports cholesterol throughout the brain. In 1993, it was discovered that individuals who inherit apoE4 have a 5-10 times greater risk of developing AD. In addition, brains of AD patients carrying



**FIGURE 5.** The amyloid cascade hypothesis. Adapted from Figure 1 in Karran et al., “The Amyloid Cascade Hypothesis for Alzheimer's Disease” *Nature Reviews* 10 (2011) 699.



**FIGURE 6.** Three paths to beta-amyloid aggregation in Sporadic Alzheimer's Disease (Author's scheme).

apoE4 exhibit significantly more beta-amyloid plaques than those of patients carrying apoE2 or apoE3, suggesting that apoE4 promotes AD by increasing beta-amyloid aggregation. Subsequent studies have demonstrated that, rather than affecting beta-amyloid generation or clearance, apoE4 protein binds and enhances its aggregation (Figure 6C). From patient to patient, it is likely that one or a combination of these three paths to beta-amyloid aggregation—increased production, decreased clearance, and inheritance of apoE4—explains the onset of AD.

### Treating Alzheimer's Disease—Where are we? Where aren't we?

Alongside research directed at characterizing the cause(s) of AD, enormous effort has also been focused on developing compounds with which to treat or prevent the disease. Based on the amyloid cascade hypothesis, the therapeutic approaches considered most promising

entail administering medications that will block or reverse beta-amyloid aggregation in the brain. Of the compounds generated and tested to date, many have been designed using our knowledge of the three paths to beta-amyloid aggregation. For example, several compounds have been created that inhibit the enzymes responsible for APP cleavage (see Figure 6A), whereas others enhance beta-amyloid clearance (see Figure 6B). A third class of compounds has been designed to interfere with beta-amyloid aggregation directly (see Figure 6C). Sadly, however, while many of these compounds have shown promise in laboratory models of AD, we have yet to establish one that has proved effective as a medication in human clinical trials (due either to insufficient reduction in beta-amyloid aggregation or to intolerable toxic side effects). Therefore, patients and their families continue to wait for the discovery of a compound that will alleviate their tragic fear and suffering.

Will the discovery come in form of a novel medication that blocks the toxic effects of beta-amyloid aggregates? Or will it come from advances in our knowledge of AD pathology that push our focus beyond beta-amyloid and its toxic aggregation? For now, it is impossible to predict it with much certainty. I nevertheless remain optimistic that the spirit and commitment I encountered within the AD research community when I entered it in 2007 is stronger than ever and will one day prevail.



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