A Tale of Tangles We Weave

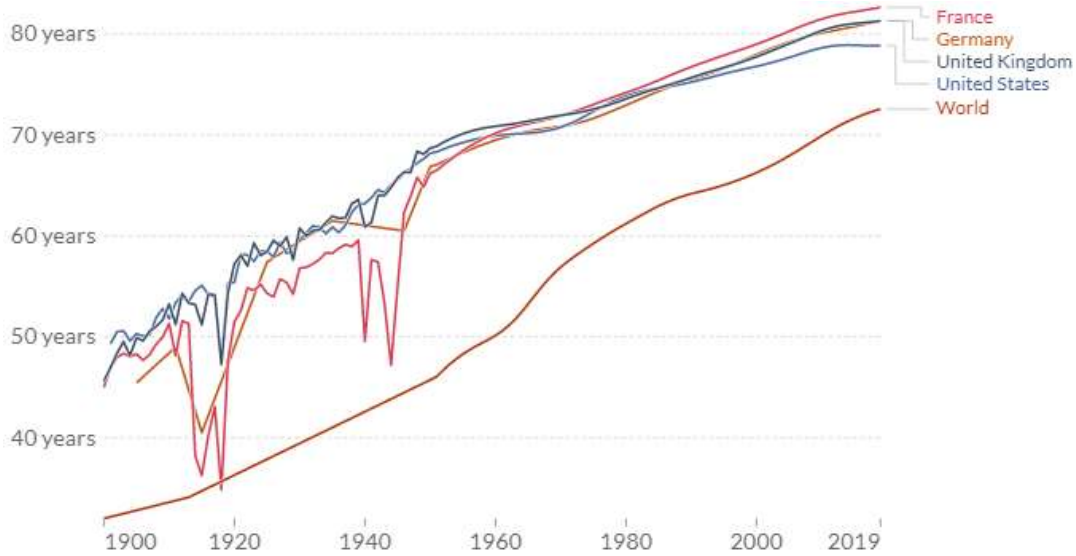
It has been over 100 years since Dr. Alois Alzheimer first described the case of August Deter, an early stage dementia patient committed to Frankfurt's Institution for the Mentally Ill and Epileptics. The German physician attended to this middle age woman with severe memory loss, paranoia and deteriorating psychology. Frau Deter died in 1906 after which Dr. Alzheimer performed an autopsy on her brain that first identified what we now call amyloid plaques and neurofibrillary tangles.

During his observations of Frau Deter, Dr. Alzheimer collaborated with other physicians and psychiatrists including Emil Kraepelin and went on to identify additional cases in 1909 and 1911. Dr. Alzheimer's findings did not attract much interest outside his small circle of associates at the time and he died a few years later in 1915 at age 51 leaving his work to be discovered by future researchers.

At the time, scant attention was paid to Alzheimer's disease (AD), as it was later coined by Emil Kraepelin. Despite the broader lack of interest, American psychiatrist Solomon Carter Fuller translated much of Dr. Alzheimer's work into English. Dr. Fuller had worked with Alzheimer in 1904 and was familiar with his methods. Dr. Fuller went on to observe and document additional cases of AD in the United States and publish a comprehensive review of the disease in 1912.

It wasn't until the 1970s when the collective attention of the medical community began to turn towards age-related disorders. Since AD is highly associated with age, especially individuals over 65, its prevalence was increasing during the 20th century along with extended life expectancy. In 1974, the National Institute on Aging (NIA) was established and in 1976 AD was recognized as the most common type of dementia.

Exhibit I – Average Life Expectancy in Select Western Countries 1900-2019[1]



[1] Source: Riley (2005), Clio Infra (2015) & UN Population Division (2019)

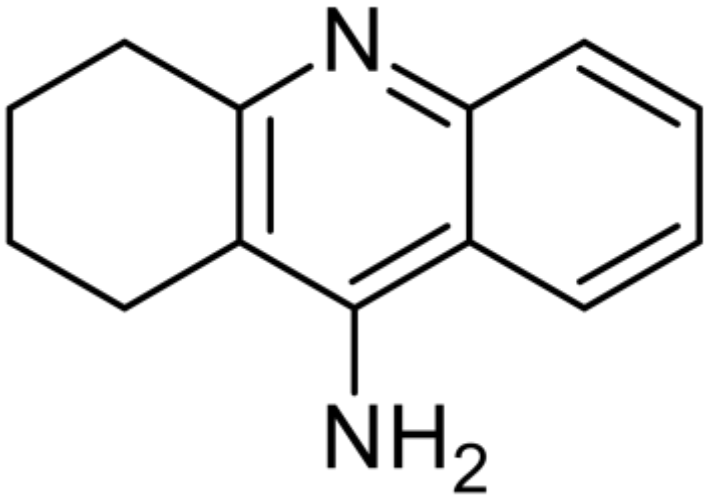
The pace of awareness and understanding accelerated in the 1980s as the Alzheimer's Association was founded in 1980, β-amyloid was identified in 1984 and funding for AD research from the NIA was allocated. Further clinical milestones were achieved in the following years leading to the first AD drug trial for tacrine, an acetylcholinesterase (AChE) inhibitor.

The First Round: Symptomatic Treatment

Tacrine

In the late 1970s, researchers embraced the cholinergic hypothesis which attributed the symptoms of AD to low levels of the neurotransmitter acetylcholine (ACh). They recognized that the enzyme AChE breaks down ACh, an important neurotransmitter and neuromodulator. ACh aids memory and learning and its deficit is associated with AD progression. This understanding led to the development of tacrine, a reversible AChE inhibitor originally developed by Warner Lambert. Scientists theorized that by blocking AChE, it would not interact with ACh and more neurotransmitter would be available for synaptic communications. The drug had previously been investigated in reviving patients from induced coma. In 1981, neuroscientist William Koopman Summers used tacrine to treat AD patients with favorable results. After an extended and arduous FDA review, the drug was approved in September 1993. While it did improve mental function in about 20% of AD patients, there were significant side effects such as elevated liver enzyme and gastrointestinal agitation.

Chemical Composition of Tacrine[2]



Tacrine's severe side effects stimulated the search for improved AChEIs leading to the development and approval of donepezil (Aricept) in 1996. Eisai had performed early research on donepezil in 1983 and continued to advance its work based on the assumption that ACh was linked to memory decline in AD patients. Rivastigmine (Exelon) was the next AChEI approved for AD. Patented in 1985, it was first approved in Switzerland and later given the FDA nod for AD in 2000. Novartis sponsored and commercialized the drug. A fast follower branded Razadyne (galantamine) was approved in 2001, emerging from a long history of use beginning in the 1960s for paralytic and neuropathic conditions.

Memantine was the fourth symptomatic therapy receiving US approval in 2003. It used an N-methyl-D-aspartate (NMDA) receptor antagonist initially synthesized and patented by Eli Lilly for use as an anti-

[2] Source: By User:Fuse809, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=28932496

diabetic agent with no success. Memantine had been researched since the 1960s and demonstrated the ability to protect healthy nerve cells from an excess of the neurotransmitter glutamate. As the field realized that NMDA receptors were involved in central synaptic pathways, researchers deduced the drug's potential in neurodegenerative disease. First marketed for dementia in Germany in 1989, memantine was developed with Forest Labs for AD in 2000 and eventually approved in the US.

In 2014, Forest Labs combined the leading AChEI and memantine to market a convenient combination therapy to patients called Namzaric. While not a new chemical entity, Namzaric would be the last drug approved for AD by the FDA for seven labyrinthine years as attention turned towards disease modifying therapies predominantly targeting amyloid-β and tau.

Stay tuned for the next chapter in our history of AD primer where we discuss the numerous trials that took place seeking a disease modifying therapy and how the approval of aducanumab may stimulate the next generation of AD therapies.

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