Title: 100 Years of Alzheimer Research

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Just over a century ago, Alois Alzheimer described a case of dementia in a middle aged woman who, at autopsy, had plaques and tangles. For the next 70 years, Alzheimer's disease (AD) was considered to be a rare and untreatable disease of middle age, a "pre-senile" dementia. But in the mid-1970's, through the ground-breaking work of Robert Katzman and others, AD was recognized as the major cause of dementia in aging individuals world-wide. In response to this newly appreciated public health need, research funded by NIH and other agencies identified therapeutic targets and established the methodology necessary to develop treatments for AD. The cholinergic hypothesis of AD suggested that memory impairment might be treatable, and led to the first successful trial of a cholinesterase inhibitor in 1985; the approval of four drugs in this class followed. In 2003, a new class was established with the approval of memantine, targeting the glutamatergic system, for the management of moderate to severe AD. All current treatments thus modulate synaptic function, but do not change the underlying pathophysiological processes. But the main focus of therapeutic research today is the development of disease-modifying therapies that aim to ameliorate amyloid dysregulation and toxicity, tangle formation or other aspects of the neurodegenerative cascade. While most of the early disease-modifying studies have had disappointing results, at least one new drug may be close to approval, and many others are advancing through the late phases of testing. A major challenge today is moving beyond the trial methodology that successfully launched current symptomatic treatments toward new study designs that will facilitate the development of disease-modifying treatments. This trial design evolution, essential to advancing many promising therapeutic programs, will involve much earlier diagnosis of AD and incorporation of biological markers to facilitate efficacy studies. Such methodological advances, along with the rich pipeline of anti-amyloid, anti-tangle and neuroprotective therapies, make the outlook for major therapeutic advance in the coming decade very bright indeed.