From the amyloid $\beta$ protein (A4) to isolation of the first Alzheimer’s disease gene: amyloid $\beta$ (A4) precursor protein (APP)

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Introduction

As life expectancy continues to increase, so will the prevalence and incidence of Alzheimer’s disease (AD) in our elderly population; by 2050, as many as 14 million AD cases are expected in the USA, alone. AD is characterized by global cognitive decline in association with specific brain pathological lesions, neuronal loss, and synaptic pruning. The disease takes its name from Dr. Alois Alzheimer, a German psychiatrist who in the fall of 1906 suggested that specific physical aberrations in the brain were driving dementia in his female patient, Auguste D (Alzheimer 1907a). Alzheimer had been treating Auguste D since she was first admitted at age 51 to the Hospital for the Mentally Ill and Epileptics in Frankfurt for “frenzied delirium.” Shortly after the patient’s death at age 56, Alzheimer presented the results of his post-mortem examination of her brain at a meeting in Tubingen. He wisely took advantage of Camillo Golgi’s new silver staining technique to examine the neurons in his patient’s brain tissue. Alzheimer was not the first to describe the appearance of senile plaques (clusters he called “miliary bodies”); neither did he know that the core was made of amyloid, despite Virchow’s description of “amyloid” decades earlier. However, with the help of Golgi’s silver stain, Alzheimer does appear to have been the first to suggest that the plaques were associated with “dense bundles of fibrils” choking the inside of cortical neurons, i.e., neurofibrillary tangles, and that these lesions were the cause of dementia in Auguste D. Thus, the pathogenic mechanism presented by Alzheimer in 1906 can in some ways be considered the earliest form of the “amyloid hypothesis.”

It was not until the 1960s that Robert Terry, Michael Kidd, Henry Wisniewski, and others would employ both light and electron microscopy to reveal the ultrastructural details of plaques and tangles (reviewed in Tanzi and Parson 2000). However, the question of primacy remained. Did plaques or tangles come first, and which lesion, if either, was killing off neurons? While these questions could not be immediately addressed, by the late-60s, Bernard Tomlinson, Gary Blessed, and Martin Roth provided the next boost for the emerging amyloid hypothesis when they suggested for the first time that dementia was correlated with senile plaque counts in the cerebral gray matter (Roth et al. 1966). Later, in 1968, these same investigators showed that over 60% of the demented elderly (the “senile”) harbored the same lesions observed by Alzheimer in his

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