Michel Goedert
The Alzheimer tangle – 100 years on.

Michel Goedert, Maria Grazia Spillantini¹, Bernardino Ghetti², R. Anthony Crowther, and Aaron Klug

Discovery of the tangle

On 3 November 1906 Alois Alzheimer, head of the Anatomical Laboratory of the Royal Psychiatric Clinic at the University of Munich, described a novel form of dementia at the 37th meeting of the Society of Southwest German Psychiatrists in Tübingen. He published these findings in the short paper of 1907 and the more extensive article of 1911 (Alzheimer 1907, 1911). In 1912, Alzheimer became Professor of Psychiatry at the University of Breslau (now Wroclaw). He died in 1915, aged 51.

The paper published in early 1907 is essentially a transcript of the lecture presented at the meeting in Tübingen. It gives the clinicopathological description of Auguste D., a patient who developed symptoms at age 51 and died aged 56. In her cerebral cortex, Alzheimer saw abundant plaques and tangles using the reduced silver staining method of M. Bielschowsky (1902). The clinical file and histological preparations of Auguste D. were recently recovered (Maurer et al. 1997; Graeber et al. 1998).

In normal brain, the Bielschowsky method visualizes what were named “neurofibrils” towards the end of the 19th century, a network of fine filaments that traverses the nerve cell and corresponds most closely to what we now know as the neuronal cytoskeleton. S. Ramón y Cajal also referred to the “neurofibrillar skeleton” (Ramón y Cajal, 1917). The ability to visualize neurofibrils provided some of the evidence in favor of the Neuron Doctrine, for which Ramón y Cajal was awarded the Nobel Prize in Physiology or Medicine in 1906 (together with C. Golgi).

Alzheimer saw increased silver staining in many nerve cells of the cerebral cortex from Auguste D., which he attributed to an abnormal thickening of neurofibrils and their alignment into bundles (the term “neurofibril” still survives in the expression “neurofibrillary tangle”). Indeed they were found to survive the degeneration of nerve cells (as extracellular or ghost tangles). Alzheimer states that he could also stain these bundles with dyes that did not label normal neurofibrils, thus underscoring their pathological nature.

In April 1907, the American psychiatrist S.C. Fuller, a former collaborator of Alzheimer, reported on neurofibrils in a number of conditions, including three cases of senile dementia (Fuller 1907; he had presented his findings at the June 1906 meeting of the American Medico-Psychological Association). It has been suggested that Fuller may have been the first to describe the tangle (Berrios 1990). However, unlike...