

## INTRODUCTION AND OVERVIEW

# Alois Alzheimer: A short biography and a new translation of his key paper

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### Brief historical account of Alzheimer's life and professional career

In 1864, Aloysius (Alois) Alzheimer was born in the small Bavarian town of Marktbreit, which is situated about 16 miles south of Würzburg, the capital city of Lower Frankonia (one of the seven administrative districts within the German state of Bavaria). His father was a royal notary who moved with his family to the city of Aschaffenburg in the vicinity of Frankfurt two years after young Aloys' birth. It was only around 10 years ago, when worldwide interest began to focus on Alzheimer's disease, that the city elders of Marktbreit became aware of their famous son. In order to accommodate the increasing numbers of mostly Japanese and American visitors who began to roam the streets of Marktbreit in search of Alzheimer's birthplace, the city elders decided to designate one of the nicer little stone houses as such. It is quite possible that Alzheimer was in fact born in a less attractive house near the more western margin of town. The retired and now deceased town historian confided this privately to George M. Martin and myself when we visited Marktbreit in 1985. On the initiative of H. Beckmann, current chairman of the Department of Psychiatry at the University of Würzburg, the charming little house selected as Alzheimer's birthplace was officially recognized and decorated with a commemorative plaque by the University of Würzburg in 1987. That year marked the centennial anniversary of Alzheimer's M.D. degree which he received in 1887 from the University of Würzburg School of Medicine after having completed his studies at the Medical Schools of Berlin, Tübingen and Würzburg.

For a period of 14 years after his graduation, Alzheimer worked as an intern, resident, and chief resident in the 'lunatic asylum' operated by the city of Frankfurt. Most of the patients of that institution at that time suffered from so-called paralytic disease, a manifestation of late stage syphilis. It was during his Frankfurt years that Alzheimer's interest in neuropathology was kindled by his close friend and colleague Franz Nissl (who later became a well-known neuropathologist). A sad blow to his personal life was the early loss of his wife Cäcilia, who died in 1901 after only seven years of marriage. After Cäcilia's death, he asked his sister to manage his household and care for his three children. He was only too happy to leave the Frankfurt area when Nissl asked him to join the Department of Psychiatry at the University of Heidelberg. The chairman of the Heidelberg department was the godfather of German psychiatry, Emil Kraepelin. He moved to Munich shortly after Alzheimer's arrival in Heidelberg. Alzheimer accepted Kraepelin's offer to move with him to Munich, even though he had to work there for several months without pay. Kraepelin became very fond of Alzheimer and provided him with a well-equipped anatomical laboratory on the third floor of the famous Munich Department. He jokingly referred to Alzheimer as the 'psychiatrist with a microscope'. But Kraepelin was also worried about Alzheimer's heavy work-load, which comprised clinical duties, research, teaching, and (since 1906) a good deal of administration as the acting vice-chairman of that busy department. In 1904 Alzheimer fulfilled the requirements to become a university professor by submitting and defending a thesis entitled, 'Histological studies on the differential diagnosis of progressive

paralysis'. In this so-called 'Habilitationsschrift,' Alzheimer for the first time mentioned changes in senile brains ('miliary plaque formation') which clearly differ from those found in neurosyphilis. But it was his very short presentation at the 1906 convention of the southwest German psychiatrists in Tübingen that described the first clinical case of senile dementia exhibiting the now classical neuropathological changes. His mentor Kraepelin soon thereafter referred to these changes in the brains of demented older patients as 'Alzheimer's disease'.

Alzheimer himself cannot be credited with the first description of the senile plaque. This was provided by the neuroanatomist Redlich in 1898, whose work, however, was appropriately cited by Alzheimer in his 1904 thesis. Independent of Alzheimer, Mjake of Vienna and Oskar Fischer of Prague published early accounts of the senile plaques (in 1906 and 1907, respectively), but contrary to Alzheimer, Fischer believed that these changes in senile brains (which he called 'drusal necrosis') might be the result of bacterial infection. Both in his 1898 paper 'The colloidal degeneration of the brain' and in his 1906 patient report, Alzheimer makes reference to deposits of a 'peculiar substance' that proved resistant to staining with most conventional dyes. Was it amyloid that Alzheimer recognized as being different from the other 'colloids'?

During his Munich years, Alzheimer was totally devoted to his work, believing that many so-called psychic diseases would show evidence of neuropathological changes if one were only to perform careful and extensive histopathological examinations of the brain in each case. Together with Kraepelin, Alzheimer thus clearly belongs to the founding fathers of biologically oriented psychiatry. In his few hours of spare time he retreated to his home to be with his family, avoiding most social contacts with the Munich medical and social establishment. For his children, he bought a vacation home on a nearby lake, which is still owned by one of his granddaughters. His professional goal was to write a textbook on the 'Histopathology of psychotic disease', but due to his failing health, this never materialized. Alzheimer, in the meantime, had acquired an eminent position in German academic medicine. He was one of the four Editors of the prestigious *Zeitschrift für die gesamte Neurologie und Psychiatrie*, the leading journal of these fields at that time (Figure 1). Like many of his contemporaries, he was worried about the rising numbers of inpatients that populated the 'insane asylums'. In a most influential editorial in the *Zeitschrift*, he supported the addition of a division of psychiatry to the National Health Agency. Only research by such a high-powered and independent institution could, in his opinion, settle the question of whether the increase of insane patients resulted from

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Figure 1.

genetic 'degeneration' or from environmental and social causes. However, in contrast to his colleague, Hoche, who in 1922 published the infamous book advocating euthanasia, Alzheimer made no public statements which could be construed as outright support for the Eugenics Movement.

Against the advice of Kraepelin, who was concerned about his health, Alzheimer accepted, in 1912, the chairmanship of the Department of Psychiatry at the University of Breslau in then Upper Silesia (now Poland). During his train ride to Breslau he contracted what, in retrospect, might have been streptococcal angina, since his heart as well as his kidneys became affected. Alzheimer never completely recovered and, after three painful and ailing years, he died in Breslau in 1915, barely 52 years old.

### "On a peculiar disease of the cerebral cortex"

This is the title of Alzheimer's seminal paper which, however, was not an elaborate formal publication. Rather, the paper was nothing more than a two-page summary prepared by Alzheimer himself of his talk presented at the 37th meeting of the southwest German psychiatrists in Tübingen on 3 November 1906. Under the heading: 'Proceedings of the Psychiatric Societies' these meeting reports were published in the *Allgemeine Zeitschrift für Psychiatrie* the following year. The proceedings list a total of 88 members and guests attending the 37th meeting in Tübingen. Following business matters and the commemoration of a recently deceased member, Bürker of Tübingen opened the scientific part of the session with a report on the

'Thermodynamics of muscle'. The next talk was by Alzheimer. There was no discussion after his talk, but this was not at all unusual, since there were a number of other talks to follow, and the psychiatrists in that era typically wanted to move on to the social part of the session as quickly as possible.

A volume entitled *The early story of Alzheimer's disease*, edited by Katherine Bick, Luigi Amaducci and Giancarlo Pepeu (Liviana Press, Padova, 1987), contains the first English translation of Alzheimer's original report. The editors of this historical volume are to be commended for providing the scientific community with excellent and very readable translations of key papers of this early period of Alzheimer's research. As Bick notes in the foreword to her translation of Alzheimer's original report, she tried to 'reproduce the style and keep the substance as close as possible to the original in order to preserve the flavor of these (by present day standards) quite verbose and repetitive descriptions'. In comparing Alzheimer's original text to Bick's translation, a number of discrepancies were noted which render the text more appealing in English, but which tend to convey a meaning that occasionally deviates from what Alzheimer actually stated. This is already obvious in Bick's version of the title where she chooses to translate Alzheimer's term 'eine eigenartige Krankheit' by 'a characteristic disease' instead of 'a peculiar disease'. A more critical example is Alzheimer's description of the 'depositions of a peculiar substance in the cerebral cortex'. Here Bick's version reads: 'It was even possible to recognize these (depositions) without staining, but they were much more evident once stained', whereas Alzheimer wrote: '... but they were refractory towards staining'. This is a crucial point, since what Alzheimer probably meant by this 'peculiar substance' might have been deposits of amyloid at the center of the senile plaques. According to Mark Sumi and Earl Benditt, pathologists at the University of Washington, poor stainability is in fact a hallmark of the amyloid substance when subjected to conditions of fixation used by Alzheimer at his time. Considering these discrepancies and the historical significance of Alzheimer's original report, it seemed worthwhile to provide, as a complement to Bick's semantically more pleasing version, a strict literal translation. Even though such a stringent translation may sound awkward for native speakers of English, it is hoped that a word-by-word version may be as close as is possible to what Alzheimer meant to say. As mentioned before, Alzheimer wrote the report on his talk in the third person, which was customary for these proceedings.

#### Literal translation of Alzheimer's paper

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the *Allgemeine Zeitschrift für Psychiatrie*, Verlag Georg Reimer, Berlin, 1907)

#### ON A PECULIAR DISEASE OF THE CEREBRAL CORTEX

A. reports on a case of patient who had been observed in the lunatic asylum of Frankfurt, and whose central nervous system had been entrusted to him by Herrn Direktor Sioli for the purpose of investigation.

Already with regard to its clinical course, this case had been so different that it could not be fitted into any known disease category. With respect to its anatomy, the case yielded findings which were at variance with all presently known disease processes.

As the first conspicuous sign of disease the 51-year-old woman showed episodes of unwarranted jealousy towards her husband. Soon thereafter one could notice increasing weakness of her memory: she became disoriented in her apartment, she dragged objects to and fro, hiding them; now and then she believed that someone wanted to kill her, and she began to scream.

In the institution her behavior was marked by complete helplessness: she is totally disoriented with regard to time and location. Occasionally she would indicate that she did not understand what was going on, and that she felt lost. Sometimes she greets the attending physician like a strange visitor, apologizing for not having finished her work, but other times she yells at him and accuses him of wanting to do surgery on her; or there were times when she would send him away in complete indignation, using phrases which insinuated that he might infringe upon her honor as a woman. From time to time she is completely delirious, dragging her bedcovers around, calling for her husband and daughter, and seeming to have auditory hallucinations. Often she would scream for hours and hours in a horrible voice.

As she is unable to comprehend any given situation, she starts to scream at the top of her lungs each time someone wants to examine her. It was only through persistent efforts that it finally became possible to obtain a few facts.

Her sense of perception is severely impaired. If objects are shown to her, for the most part she first labels them correctly, but soon thereafter she forgets everything. While reading, she skips from line to line, reads as if she were spelling, or reads with a meaningless pattern of intonation. While writing, she repeats certain syllables many times, omits others, and in general gets stranded very quickly. While talking, she frequently uses stereotype phrases or paraphrases (milkdispenser instead of cup), sometimes one notes her getting stuck. She obviously does not comprehend a number of the questions asked. She seems not to know anymore how to use certain objects. Her walking is not impaired, and

she uses both hands equally well. Her patellar reflexes are present. Her pupils react. Somewhat rigid radial arteries, on auscultation no enlargement of the heart, no albumin.

During the progression of her disease, symptoms which must be considered focal in nature appear more or less clearly. They are always minor. In contrast, the general loss of intellectual capacity progresses continuously. Death occurs after a four and a half year duration of the illness. The patient ended up lying in bed completely mindless, with her legs drawn up, incontinent, and suffering from decubitus in spite of diligent care.

Autopsy revealed a uniformly atrophic brain without evidence for macroscopic foci. The larger cerebral vessels show arteriosclerotic changes.

Preparations obtained by using the silver-method of Bielschowsky show peculiar changes of the neurofibrils. Inside an otherwise still seemingly normal cell, one or more fibrils become more conspicuous due to their exceptional thickness and due to their exceptional stainability. During further stages, parallel arrays of these fibers show similar changes. Then they join together as dense bundles and gradually appear at the cell surface. Ultimately, the nucleus and the cell disintegrate, and only a tangled bundle of fibrils indicates the site where once the neuron had been located.

As these fibrils can be stained with other dyes than normal neurofibrils, a chemical transformation of the fibril substance must have taken place. This may well be the reason why the fibrils survive the destruction of the cell. It seems that the transformation of the fibrils goes

hand in hand with the storage, within the neuron, of an as yet not closely researched, pathological metabolic product. Approximately one quarter to one third of all the neurons of the cerebral cortex show such alterations. Numerous neurons, especially in the upper cell layers, have totally disappeared.

Dispersed over the entire cortex, and predominantly in the upper layers, small miliary foci are found which are caused by the deposition of a peculiar substance in the cerebral cortex. This substance can already be seen without staining, but it is refractory towards staining.

The glia has formed abundant fibers; in addition, many glia cells show large bags of fat.

There is not a hint of infiltration of the vessels. However, the endothelial layers show proliferative changes, and at some sites one notes the formation of new vessels.

Altogether, we are obviously dealing with a peculiar disease process. An increasing number of such peculiar disease processes has been noted during the past years. This observation must suggest to us that we should not be content to force any clinically ambiguous case into a category of diseases that is familiar to us. There is no doubt that a greater number of mental diseases exist than is listed in our textbooks. In a number of such instances, the ultimate histological examination will reveal the peculiar nature of a given case. Then we will gradually reach the stage in which we will be able to separate certain diseases from the major disease categories of our textbooks, and to delineate such diseases with much greater clinical precision.

## Pathogenetic mechanisms in dementias of the Alzheimer's type

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This review addresses two of the most intellectually challenging and socially important problems of contemporary biology and medicine: 1) *Why* do aging cohorts of many populations of human beings become so extraordinarily susceptible to the set of pathologies that currently define dementias of the Alzheimer's type? 2) *How* do these lesions develop—i.e. what are the detailed mechanistic steps that lead from etiology or etiologies to phenotypic expression? A plausible answer to the first question can be provided by the current conclusions of evolutionary biologists concerning nonadaptive mechanisms for the

evolution of senescence. The second question has at least a partial answer in that, in a few rare pedigrees, there is compelling evidence that a specific gene mutation, involving the  $\beta$ -amyloid precursor protein, is the primary cause of an early onset of the disease. Thus, we now have a metabolic pathway that serves as a working hypothesis for a candidate pathogenetic mechanism for all forms of the disorder. The major challenge is to elucidate how intrinsic biological aging impacts upon this pathway. An additional challenge is to discover environmental agents that can modulate the rates of development of specific