

Auguste D and Alzheimer's disease

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On Nov 4, 1906, Alois Alzheimer gave a remarkable lecture,¹ in which he described for the first time a form of dementia that subsequently, at the suggestion of Emil Kraepelin,² became known as Alzheimer's disease. In his lecture, at the 37th Conference of South-West German Psychiatrists in Tübingen, Alzheimer described a patient called Auguste D, a 51-year-old woman from Frankfurt who had shown progressive cognitive impairment, focal symptoms, hallucinations, delusions, and psychosocial incompetence. At necropsy, there were plaques, neurofibrillary tangles, and arteriosclerotic changes. The eponym Alzheimer, originally used to refer to presenile dementia, came into later use for the largest cause of primary dementia—senile dementia of the Alzheimer type (SDAT). Here, we describe the discovery and contents of the file of Auguste D, which had not been seen since 1909.

Alzheimer and Auguste D

Alzheimer was born on June 14, 1864, in Marktbreit, Germany, a small village near Würzburg. He studied medicine at the universities of Berlin, Tübingen, and Würzburg, where he wrote his doctoral thesis *Über die Ohrenschmalzdrüsen* (on ceruminous glands) in 1887, producing his first histological plates. In December, 1888, he began his medical career as a resident at the Hospital for the Mentally Ill and Epileptics, Frankfurt am Main, and subsequently was promoted to senior physician.

Alzheimer's research interests were wide ranging and included not only dementia of degenerative and vascular (arteriosclerotic) origin but also psychoses, forensic psychiatry, epilepsy, and birth control. His interest in the neuropathology of dementing disorders was shared by his colleague Franz Nissl, who came to Frankfurt in March, 1889. It was Nissl who provided Alzheimer with new histopathological techniques for studying nervous disorders.

On Nov 25, 1901, Auguste D was admitted to the Frankfurt hospital, where she was examined by Alzheimer. She had a striking cluster of symptoms that

included reduced comprehension and memory, as well as aphasia, disorientation, unpredictable behaviour, paranoia, auditory hallucinations, and pronounced psychosocial impairment.

In 1903, Alzheimer left Frankfurt, and, after a short stay in Heidelberg, moved to the Royal Psychiatric Clinic, Munich, whose director was Kraepelin. There, Alzheimer continued to follow Auguste D's case until her death in Frankfurt on April 8, 1906, after which he went on to study the neuropathological features of her illness.

Auguste D and her file

On Dec 19, 1995, the 80th anniversary of Alzheimer's death was commemorated at his birthplace in Marktbreit with the inauguration of his house as a museum and conference centre. Eli Lilly purchased the house, which has been renovated under the direction of Ulrike Maurer. Previously, we had conducted an intensive search for the file of Auguste D, which had been lost since its description by Perusini³ in 1909. We had been looking for it for many years; only 2 days after the 80th anniversary we found it in the archives of our own

department in Frankfurt.⁴

After 90 years, the blue-coloured cardboard file was still in good condition (figure 1); it contained a total of 32 sheets with the patient's admission report, an attestation, and three versions of the case history—one in Latin script and two in the now outdated German "Sütterlin" script. The first Latin script, already published by Perusini³ and subsequently translated,⁵ begins with questions about her husband, followed by clinical findings, the details of the course of her disease, and a report on her death, including a histopathological diagnosis. The part written in Latin is followed by a nearly identical copy in Sütterlin. A small sheet of paper with the handwriting of Auguste D dated by Alzheimer shows "amnesic writing disorder" so named by Alzheimer himself (figure 2). Alzheimer's handwritten



Figure 1: Cover of the file of Auguste D. Admitted Nov 25, 1901, died April 8, 1906. 36 × 23.5 cm.

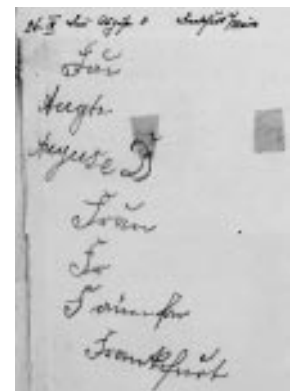


Figure 2: Auguste D's handwriting. Dated by Alzheimer (26. XI. Frau Auguste D Frankfurt/Main).

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Figure 3: **Auguste D**
Photograph dated November, 1902.

notes, also in Sütterlin, document in detail his patient's symptoms during the first 4 days of her stay in hospital. In between Alzheimer's notes are additional samples of Auguste D's attempts to write her name. The file also contains four photographs of her (the most impressive is shown in figure 3) and a report about the course of the disease, which consisted of concise notes starting on June 29, 1905, and ending on the day of her death on April 8, 1906. Several attestations and an application form for hospitalisation of a mentally ill person together with a one-page case report from the Royal Psychiatric Department, Munich, conclude the file.

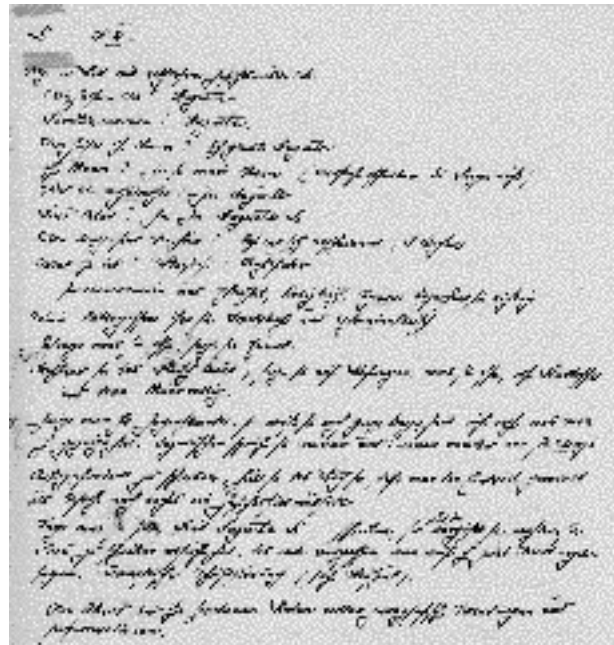
Alzheimer's notes in the file begin on Nov 26, 1901. He asked simple questions and wrote down Auguste D's answers systematically. He resumed questioning on Nov 28, 29, and 30 on four handwritten pages.

The file begins as follows (our italics denote Auguste D's answers, and each translated passage is followed by figures of the original pages in the file):

Nov 26, 1901

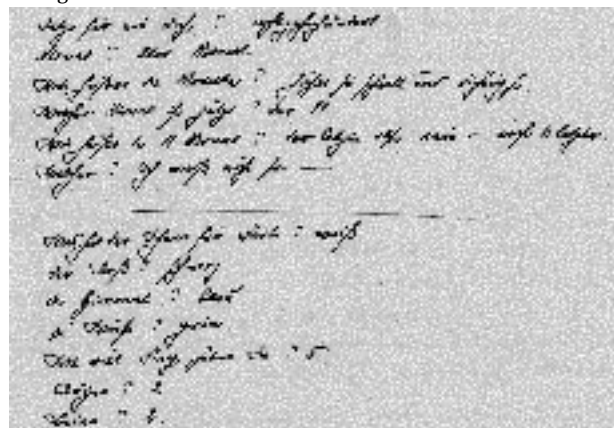
She sits on the bed with a helpless expression. What is your name? *Auguste*. Last name? *Auguste*. What is your husband's name? *Auguste, I think*. Your husband? *Ah, my husband*. She looks as if she didn't understand the question. Are you married? *To Auguste*. Mrs D? *Yes, yes, Auguste D*. How long have you been here? She seems to be trying to remember. *Three weeks*. What is this? I show her a pencil. *A pen*. A purse and key, diary, cigar are identified correctly. At lunch she eats cauliflower and pork. Asked what she is eating she answers *spinach*. When she was

chewing meat and asked what she was doing, she answered *potatoes* and then *horseradish*. When objects are shown to her, she does not remember after a short time which objects have been shown. In between she always speaks about twins. When she is asked to write, she holds the book in such a way that one has the impression that she has a loss in the right visual field. Asked to write Auguste D, she tries to write Mrs and forgets the rest. It is necessary to repeat every word. Amnesic writing disorder. In the evening her spontaneous speech is full of paraphrastic derailments and perseverations.

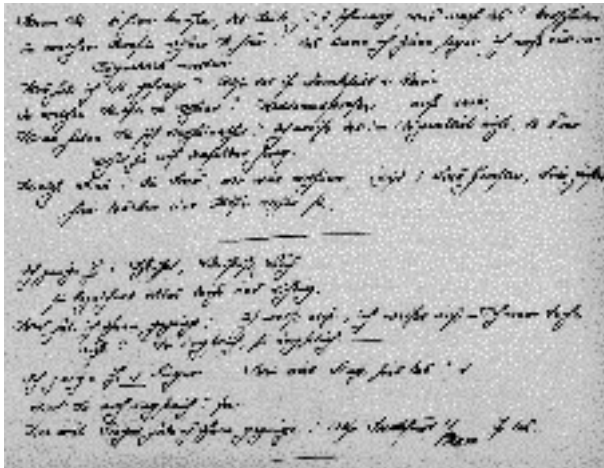


Extracts from Nov 29, 1901

...What year is it? *Eighteen hundred*. Are you ill? *Second month*. What are the names of the patients? She answers quickly and correctly. What month is it now? *The 11th*. What is the name of the 11th month? *The last one, if not the last one*. Which one? *I don't know*. What colour is snow? *White*. Soot? *Black*. The sky? *Blue*. Meadows? *Green*. How many fingers do you have? *5*. Eyes? *2*. Legs? *2*.



... If you buy 6 eggs, at 7 dimes each, how much is it? *Differently*. On what street do you live? *I can tell you, I must wait a bit*. What did I ask you? *Well, this is Frankfurt am Main*. On what street do you live? *Waldemarstreet, not, no...* When did you marry? *I don't know at present*. The woman lives on the same floor. Which woman? *The woman where we are living*. The patient calls Mrs G, Mrs G, here a step deeper, she lives... I show her a key, a pencil and a book and she names them correctly. What did I show you? *I don't know, I don't know*. It's difficult isn't it? *So anxious, so anxious*. I show her 3 fingers; how many fingers? *3*. Are you still anxious? *Yes*. How many fingers did I show you? *Well this is Frankfurt am Main*.



The patient is asked to recognise objects by touch, with her eyes closed. A toothbrush, sponge, bread, breadroll, spoon, brush, glass, knife, fork, plate, purse, Mark, cigar, key. She recognises them quickly and correctly. By touch she calls a brass cup a *milk jug*, a *tea-spoon*, but when she opens her eyes she immediately says a *cup*.

Writing, she does it as already described. When she has to write Mrs Auguste D, she writes Mrs and we must repeat the other words because she forgets them. The patient is not able to progress in writing and repeats, *I have lost myself*.

Reading, she passes from one line to the next and repeats the same line three times. But, she correctly reads the letters. She seems not to understand what she reads. She stresses the words in an unusual way. Suddenly she says *twins*. *I know Mr Twin*. She repeats the word twin during the whole interview.

The reactions of the pupils to light and accommodation are instantaneous. Tongue has normal mobility, dry, yellow-red-brown. No disturbance in speech articulation. She frequently interrupts herself in the articulation of words during the interview (as if she did not know whether she had said something correctly or not). She has dentures. No facial nerve differences. Muscular strength: at the left side considerably reduced compared with the right side. Patellar reflex normal. Radial reflex is slightly (but not relevantly) rigid. Cardiac ictus is not felt. Cardiac obtusity not enlarged. The second pulmonary and aortic tones are not accentuated.

During physical examination she cooperates and is not anxious. She suddenly says *Just now a child called, is he there?* She hears him calling. . . she knows Mrs Twin. When she was brought from the isolation room to the bed she became agitated, screamed, was non-cooperative; showed great fear and repeated *I will not be cut. I do not cut myself*.

Alzheimer's report in Sütterlin ends on Nov 30, 1901. The two other versions, in Sütterlin and Latin, continue to document the course of Auguste's disease. In the Latin version, an entry from Nov 7, 1905, states: "Tendency to develop a decubitus since the beginning of 1906. Ulcerations at the sacral and left trochanteric area with a size of about 5 cm. Very weak, high fever up to 40°C within the last days. Pneumonia in both inferior lobes".

The day of Auguste's death on April 8, 1906, was not mentioned by Alzheimer but by his other two (unnamed) colleagues, who wrote the following report (in Latin) about the decay and the neuropathological diagnosis:

April 8, 1906

During the morning *exitus letalis*; cause of death: septicaemia due to decubitus; anatomical diagnosis: moderate hydrocephalus (external internal); cerebral atrophy; arteriosclerosis of the small cerebral vessels; ? ; pneumonia of both inferior lobes; nephritis.

The eponym Alzheimer

After Auguste D's death, Alzheimer asked for her records and brain to be sent to Munich, to where he had moved in 1903. Within 6 months he presented his findings to the Tübingen meeting, the abstracts of which were published in the same year.¹ Alzheimer's was the 11th contribution. However, only the title of his presentation was announced with a statement in parentheses that the lecture "was not appropriate for a short publication".

11. Herr Alzheimer (München): Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde (zu kurzem Referat nicht geeignet).

It was not until the following year, in 1907, that Alzheimer published his lecture⁶ under the title "A characteristic serious disease of the cerebral cortex". He described "the case of a patient who was kept under close observation during institutionalisation at the Frankfurt Hospital and whose central nervous system had been given to me by director Sioli for further examination". Alzheimer described, without identifying her, a "51-year-old woman" who showed "as one of her first disease symptoms a strong feeling of jealousy towards her husband. Very soon she showed rapidly increasing memory impairments; she was disoriented carrying objects to and fro in her flat and hid them. Sometimes she felt that someone wanted to kill her and began to scream loudly. . . After 4½ years of sickness she died".

Alzheimer also described the histopathological findings of this disease. He reported peculiar changes in the neurofibrils: "In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability". He went on to describe the typical plaques, later named after him: "Numerous small miliary foci are found in the superior layers. They are determined by the storage of a peculiar material in the cortex". Alzheimer continues: "all in all we have to face a peculiar disease process. Such peculiar disease processes have been verified recently in considerable numbers".

We learn more about this patient in an article by Perusini, "On histological and clinical findings of some psychiatric diseases of older people", published in 1909.³ On Alzheimer's suggestion, Perusini "examined four cases characterised by clinical and especially histopathological signs". In this article, Auguste D was reinvestigated with respect to her symptoms and histopathology as case No 1. For the first time the initials of her surname, complete given name, and profession of her husband were mentioned ("D Auguste, wife of an office clerk, aged 51½ years"). Perusini thanked Sioli from Frankfurt am Main for the use of the case history and the brain for microscopic research. Thus, Perusini's case No 1 is identical with the case described by Alzheimer in his 1907 paper,⁶ a fact that was not completely clear until now.

Perusini referred to the Latin version of Auguste D's case history; he presented detailed histopathological findings together with six illustrations showing amyloid plaques and neurofibrillary tangles. In summary, he stated:³ "The pathological process recalls main features of senile dementia; however, the alterations in the cases described are more far reaching, although some of them represent presenile diseases".

Besides the two important publications of Alzheimer in 1907 and Perusini in 1909 on Auguste D, Kraepelin must have known of other reports: Bonfiglio⁷ reported in 1908

on a similar patient, aged 60, who had similar symptoms and histopathology; in 1907, Fischer⁸ had published a detailed description of histopathological changes in dementia; and then there was Alzheimer's 1911 report⁹ (which appeared 1 year after the eponym had been introduced by Kraepelin) in which he described his second case of dementia (Johann F). In the discussion were drawings of typical changes in the neurofibrils (figure 5), which were from his first case (Auguste D).

In the 8th edition (1910) of *Handbook of Psychiatry*, Kraepelin² stated that "a particular group of cases with extremely serious cell alterations was described by Alzheimer". The necropsy findings showed changes that "represent the most serious forms of senile dementia. The plaques were excessively numerous and almost one-third of the cortical cells had died off. In their places were peculiar, deeply stained bundles of neurofibrils". He mentioned "Alzheimer's disease" for the first time, stating, "The clinical interpretation of this Alzheimer's

Disease is still unclear. Although the anatomical findings suggest that we are dealing with a particularly serious form of senile dementia, the fact is that this disease sometimes starts as early as in the late forties". In the chapter on senile dementia, there is an illustration of "fibrillary patterns in Alzheimer's disease" from the third layer of the frontal cortex. The neurofibrillary tangles in this figure resemble those drawn in 1911 by Alzheimer.⁹

Kraepelin introduced the eponym Alzheimer's disease, but why did he use Alzheimer's name, and not Perusini's, Bonfiglio's, or Fischer's? Since Alzheimer described the two cases, and since Perusini republished the Auguste D case (with photographs and drawings of the histopathological findings), we are convinced that the eponym was based on Alzheimer's 1907 report of Auguste D's case. Moreover, she only showed neuritic plaques and neurofibrillary tangles typical of the disease.

Several hypotheses to account for the haste with which Kraepelin created the new eponym have been put forward.^{10,11} Beach¹¹ says that Kraepelin did so for scientific reasons, because he believed that Alzheimer had discovered a new disease. Another reason might have been the existing rivalry between his department and that of Pick in Prague (where Fischer also worked) and the desire for prestige for his Munich laboratory. Also plausible is Kraepelin's wish to show the superiority of his school over psychoanalytical theories and to show (vis-à-vis Freud) that some mental disorders were organically based. The most likely explanation, however, is the close collaboration between Kraepelin and Alzheimer, and Kraepelin's awareness of Alzheimer's clinical and scientific work on presenile cases.

Auguste D's dementia

There are doubts about the diagnosis of Auguste D's illness, and other diagnoses have been put forward, especially arteriosclerosis of the brain.

Both descriptions of Auguste D's dementia by Alzheimer and Perusini confirm that Auguste D had a

degenerative and not a vascular form of dementia. Alzheimer mentioned the miliary foci (later called senile plaques), which represented the sites of deposition of a peculiar substance in the cerebral cortex. This substance has since turned out to be β -amyloid protein. Alzheimer showed clumps and condensations of intracellular fibrils and called them "neurofibrillary degeneration".

At Alzheimer's suggestion, Perusini restudied the brain of Auguste D and found "that the large cerebral vessels, the arterial circle of Willis and the Sylvian arteries showed no significant signs of arteriosclerosis"; only "some regressive alterations of the arterial wall" were noted. Perusini confirmed the presence in Auguste D of neuritic plaques and neurofibrillary tangles.

In summary, the clinical and histopathological findings of Auguste D accord with the ICD-10, DSM-III-R, and CERAD¹² definitions of Alzheimer's disease. There can be little further doubt in view of Alzheimer's observations published in 1911, in which he refers to the presence of neurofibrillary tangles in the second and third layers of the cortex in a brain slice of his first case (ie, Auguste D) (figure 5).

Alzheimer anticipated the debate about which type of dementia Auguste D may have had by his remark in 1907:⁶ "a histopathological analysis at a later point will show the peculiarity of this case". Our next goal is to find the brain sections of Auguste D so that we can corroborate Alzheimer's original findings.

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Figure 5: Neurofibrillary tangles from Auguste D, drawn by Alzheimer
From ref 9.

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