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The discovery of Alzheimer's disease

Hanns Hippus, MD; Gabriele Neundörfer, MD



On November 3, 1906, a clinical psychiatrist and neuro-anatomist, Alois Alzheimer, reported "A peculiar severe disease process of the cerebral cortex" to the 37th Meeting of South-West German Psychiatrists in Tübingen. He described a 50-year-old woman whom he had followed from her admission for paranoia, progressive sleep and memory disturbance, aggression, and confusion, until her death 5 years later. His report noted distinctive plaques and neurofibrillary tangles in the brain histology. It excited little interest despite an enthusiastic response from Kraepelin, who promptly included "Alzheimer's disease" in the 8th edition of his text *Psychiatrie* in 1910. Alzheimer published three further cases in 1909 and a "plaque-only" variant in 1911, which reexamination of the original specimens in 1998 showed to be a different stage of the same process. Alzheimer died in 1915, aged 51, soon after gaining the chair of psychiatry in Breslau, and long before his name became a household word.

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The 37th Meeting of South-West German Psychiatrists (37 *Versammlung Südwestdeutscher Irrenärzte*) was held in Tübingen on November 3, 1906. At the meeting, Alois Alzheimer (Figure 1), who was a lecturer (*Privatdozent*) at the Munich University Hospital and a coworker of Emil Kraepelin, reported on an unusual case study involving a "peculiar severe disease process of the cerebral cortex" (*Über einen eigenartigen, schweren Erkrankungsprozeß der Hirnrinde*).

Prelude

Alzheimer described the long-term study of the female patient Auguste D., whom he had observed and investigated at the Frankfurt Psychiatric Hospital in November 1901, when he was a senior assistant there. Alzheimer had been interested in the symptomatology, progression, and course of the illness of Auguste D. from the time of her admission, and he documented the development of her unusual disease very precisely from the beginning.

In March 1901, the husband of the 50-year-old woman had noticed an untreatable paranoid symptomatology in his wife and then—in fast progression and with increasing intensity—sleep disorders, disturbances of memory, aggressiveness, crying, and progressive confusion. Eventually, the husband was forced to take his wife to the Community Psychiatric Hospital at Frankfurt am Main. The symptomatology increasingly deteriorated and so Auguste D. remained an inpatient of the hospital up to her death on April 8, 1906. After the autopsy, Alzheimer was able to investigate the brain of Auguste D. both morphologically and histologically. These results and their relationship with the clinical findings recorded over more than 4 years were the basis for Alzheimer's lecture at the Tübingen meeting. The chairman of the session was the very prominent psychiatrist from the University of Freiburg, Alfred Hoche

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(1865–1943). Hoche was a scientific opponent of Kraepelin and his nosological concept and classification of psychiatric diseases. Kraepelin was not in the audience during Alzheimer's presentation. After Alzheimer's lecture, Hoche, departing from the usual role of a chairman, did not comment on Alzheimer's presentation and only once or twice asked the audience for comments or questions. He stated that there was no need for discussion and invited the next speakers to continue with their lectures. These were two contributions to psychoanalytical topics, and were followed by long and very lively discussions, including some active comments from the chairman. The lack of interest from the numerous and well-known scientists in the audience was a great disappointment for Alzheimer. Moreover, only a very short abstract was printed in the official proceedings of the meeting.¹ Tübingen's public press commented extensively on the psychoanalytical lectures, whereas only two lines were devoted to Alzheimer's lecture. Such was the beginning of communication on research into Alzheimer's disease!²

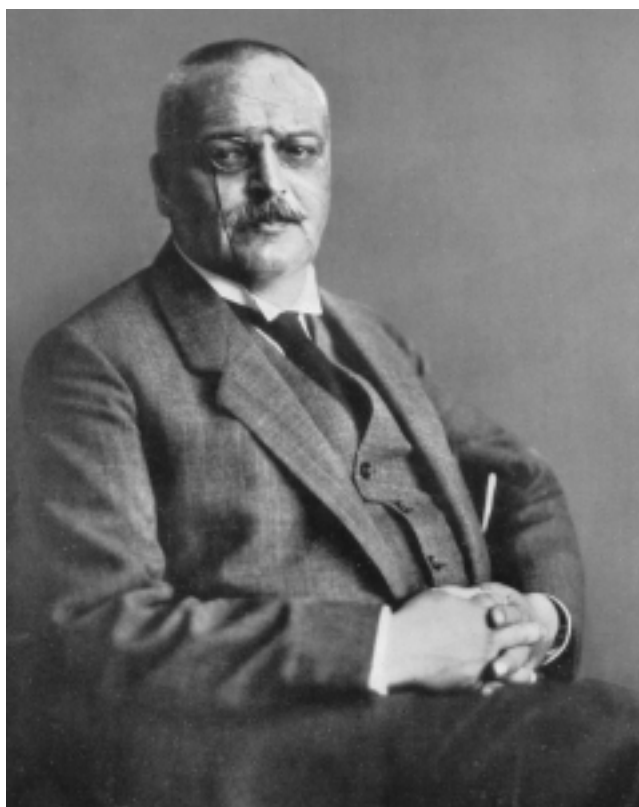


Figure 1. Alois Alzheimer. About 1909.

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Alois Alzheimer

Alois Alzheimer was born into a Catholic family on June 14, 1864, in the small town of Marktbreit in Lower Frankonia close to Würzburg on the river Main.²⁻⁴ His father was a royal notary in the Kingdom of Bavaria who had lost his first wife 2 years previously to puerperal fever after giving birth to their first son. Alzheimer's father married the sister of his dead wife and had six more children with her—the eldest child was Alois Alzheimer.

Alois Alzheimer went to elementary school in Marktbreit and later to classic secondary school in Aschaffenburg. After he left school, Alzheimer became a college student in Berlin, Freiburg, and Würzburg (1883–1885). Very early on, in the first few academic trimesters, he became interested in anatomy and learned to work with microscopes. As a young student, he attended some lectures on forensic psychiatry, but later during clinical training he was extensively occupied in all clinical disciplines, with one notable exception: he probably never attended clinical lectures in psychiatry! After a dissertation in anatomy, he finished his studies at Würzburg and obtained the official diploma in medicine with *magna cum laude*.

At this time, there were no indications that Alzheimer was destined to follow a career in psychiatry. However, a more or less accidental event after the end of his studies in medicine may have influenced him in this direction. At the end of the 19th century, some very wealthy German families had an unusual approach to the care of a mentally ill relative: they engaged a young medical doctor to travel with the patient. Alzheimer had such an offer and traveled for 5 months (May to October 1888) with a mentally ill female patient. Unfortunately, no information is known regarding this patient's illness or identity, or the travel itinerary.

Upon returning from this journey, at the age of 24 years, Alzheimer applied for a position as assistant in the Community Hospital for Mental and Epileptic Patients (*Städtische Anstalt für Irre und Epileptiker*) in Frankfurt am Main. The director of the Frankfurt Hospital, Emil Sioli (1852–1922), accepted Alzheimer's application. Alzheimer worked with Sioli for 15 years (1888–1903) and was strongly influenced by him: Alzheimer thus became an all-round skilled clinician.

Sioli had held this position in Frankfurt since 1888 and he was the successor of the pediatrician H. Hoffmann (well known as the author of *Shock-Headed Peter* [*Der Struwwelpeter*]). As a psychiatrist, Sioli directed the hos-

pital with the main idea of nonrestraint psychiatry, an idea introduced from Great Britain, but at that time still controversial in Germany.

Today, many people believe that Alzheimer was a pure neuropathologist, but all information on his own self-assessment, as well as the summary of his scientific publications—after working with Sioli—demonstrate that he identified himself primarily as a clinical psychiatrist responsible for patients.

In addition to his development as a clinician in Frankfurt, Alzheimer did not neglect his interest in anatomy dating from his time as a young student in Berlin and Würzburg. This interest was enhanced by Franz Nissl (1860–1919), who came from Munich to work with Sioli in Frankfurt 1 year after Alzheimer. Nissl had already worked in neuroanatomy and neuropathology as a student, and had discovered a special histological staining technique (Nissl stain), which is still in use today. In Munich, Nissl had been a coworker of B. von Gudden in his brain research laboratory. After the tragic death of von Gudden, who was found drowned with his patient Ludwig II, King of Bavaria, in 1886, Nissl sought a new comparable position and, with the help of Sioli, became senior assistant at the Frankfurt Hospital in 1889.

From the beginning, Nissl and Alzheimer became good colleagues and close friends. The more senior Nissl encouraged young Alzheimer to actively continue research alongside his clinical work. Alzheimer followed Nissl's advice and worked on topics such as general paresis in children and young adults,⁵ and brain atrophy in patients with cerebral arteriosclerosis,⁶ epilepsy,⁷ or demential diseases.⁸ He also published pioneering ideas on the contribution of the cortex to pathology, as the anatomical basis of some psychotic diseases.⁹

During his Frankfurt years, in 1895, Alzheimer married the very wealthy Cecilia Geisenheimer (née Wallerstein); Nissl was a witness at the marriage ceremony. Due to the prosperous financial background of his wife, Alzheimer was henceforth financially independent. His aim was to become an independent clinical director of a psychiatric hospital in which he could do research, but not exclusively. Nissl left Frankfurt in 1896 because he had been invited by Emil Kraepelin (1856–1926) to work at the University Hospital of Heidelberg, which was directed by Kraepelin between 1890 and 1903. Nissl accepted the invitation because he thus achieved a position at a university with better conditions for research. Both Nissl and Alzheimer regretted that they could no longer work together at the

same hospital. However, they continued their friendship and their scientific exchange for the rest of their lives.

On the other hand, Nissl's move to Heidelberg brought about an improvement in Alzheimer's position at the Frankfurt Hospital. Sioli recommended Alzheimer to the authorities as Nissl's successor as first assistant and deputy director of the hospital. The official appointment to this position was in July 1896. This appointment represented an important step for Alzheimer toward his professional target: to become the director of a psychiatric hospital.

The following years were satisfactory for Alzheimer not only with regard to his professional situation, but also with respect to his particularly harmonious family life with his wife and three children born between 1895 and 1900.²

1901

For Alzheimer, the year 1901 marked a difficult turning point in his life. Some months after the birth of their third child, his 41-year-old wife died. Alzheimer was now a widower and had to take care of three children. Although his income from his position at the hospital was small, he had his wife's extensive inheritance. One of his unmarried sisters moved to Frankfurt to look after the household because Alzheimer wanted to live with his family and to work at, or near to, Frankfurt. He planned to apply for leading positions in this area. To overcome the grief of his wife's death, Alzheimer worked more intensively at the hospital than ever before. He saw all newly admitted patients and made a detailed and extensive documentation of his findings. On November 26, 1901, he investigated the newly admitted female patient Auguste D., not imagining for one moment that the clinical investigation of this patient would be the starting point for a development that would make him famous throughout the world!

From Frankfurt to Munich via Heidelberg

Apart from his very intensive clinical work, Alzheimer—together with Sioli—organized the establishment of a special branch hospital for mental patients close to Frankfurt in the Taunus mountains. In addition, he began to write a so-called *Habilitationsschrift* (postdoctoral thesis for a university lecturing qualification) as a basis for an application at a medical faculty of a German university. He was in possession of the clinical and the postmortem findings of 320 patients with the diagnosis of “*Progressive Paralyse*” (gen-

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eral paresis), investigated at the Frankfurt Hospital since 1888. (Around 1900, more than 25% of chronic psychiatric inpatients suffered from this disease and were hospitalized up to their death. The relationship between syphilis and general paresis was still controversial: *Treponema pallidum* [*Spirochaeta pallida*] had not yet been discovered and no effective treatment was available.)

In the summer of 1902, little more than one year after the death of Alzheimer's wife, Emil Kraepelin invited him to join the Heidelberg research team as assistant to the Heidelberg Hospital. This was a great honor because Kraepelin was at the time one of the most prominent and influential psychiatrists in Germany. In addition, Alzheimer's great friend Nissl had then been working in the Heidelberg Hospital for 7 years. In spite of many reasons in favor of Heidelberg, Alzheimer refused Kraepelin's invitation and applied—unsuccessfully—for the leading position in a Hessian state hospital.

When Nissl heard about this, he persuaded Kraepelin to repeat his offer of a position at the Heidelberg Hospital to Alzheimer. Kraepelin did so and Alzheimer accepted; he moved to Heidelberg at the end of 1902.¹⁰

Sioli and the Frankfurt authorities explicitly regretted the departure of Alzheimer. However, Sioli approved of Alzheimer's decision, since it led to a university position (the University of Frankfurt was only established in 1914). Sioli promised Alzheimer that he would tell him of the fate of all the patients who had been of special interest to Alzheimer from a scientific point of view. Thus, some years later, Alzheimer obtained information on the course of Auguste D.'s illness and her death at the Frankfurt Hospital in April 1906.

Alzheimer moved to Heidelberg expecting to work there for a long time. However, just one month later in April 1903, the Professor of Psychiatry in Munich, A. Bumm (1849–1903), died at the age of 54. For some years, Bumm



Figure 2. Alzheimer's modern histopathological laboratory in the Psychiatric University Hospital in Munich, 1904.

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had been responsible for the planning and construction of a new modern, large university hospital for psychiatry. At the time of Bumm's unexpected death, the building was not yet finished and the Munich chair suddenly became vacant. On the recommendation of the Faculty of Medicine, the chair and directorship were offered to Kraepelin. After only momentary hesitation, Kraepelin agreed to soon take up the position and moved in autumn 1902. He was accompanied by three coworkers from his Heidelberg team, one of whom was Alzheimer. Kraepelin used the remaining year till the official opening of the hospital in November 1904 to work on his textbooks and undertook a long voyage to explore Indonesia. During this time, Alzheimer's task in Munich was the supervision of the completion of the building and the organization of hospital equipment. After his return, Kraepelin stated that Alzheimer had done an excellent job.¹⁰ With regard to hospital equipment, a very modern and spacious histopathological laboratory with the most modern microscopes and other apparatus was established (Figure 2), enabling Alzheimer to continue his histopathological research.

After the opening of the hospital in November 1904, R. Gaupp (1870–1953) (Figure 3) was appointed senior assistant and Alzheimer became Kraepelin's first research assistant. In this position, Alzheimer received no payment, but he could devote all his time to research. Alzheimer's remarkable private fortune enabled him to work under these peculiar conditions.

Alzheimer was head of the histopathological laboratory until 1912. During these 8 years, numerous young scientists from many countries were trained by Alzheimer and later became famous neuropathologists or clinical psychiatrists.



Figure 3. (Left to right) A. Alzheimer, E. Kraepelin, R. Gaupp, and F. Nissl. About 1906.

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The list of Alzheimer's coworkers (Figure 4) includes many prominent names—N. Achucarro, I. Bonfiglio, L. Casamaior, U. Cerletti, H-G. Creutzfeld, C. v. Economo, A. Jakob, K. Kleist, F. H. Lewy, L. Merzbacher, G. Perusini, and W. Spielmeyer—a who's who of contemporary neuropathology!

In October 1903, a short time after moving to Munich, Alzheimer arranged for his children to follow him and they all lived in a large house near the hospital, together with his sister as housekeeper. Furthermore, at the end of 1904, he bought a big weekend house beside a small lake near Munich.

An important step in Alzheimer's academic career came in November 1903 when he presented his *Habilitations-schrift* in Munich. The manuscript, entitled *Differential diagnosis of general paresis on the basis of histological studies (Histologische Studien zur Differentialdiagnose der progressiven Paralyse)*, was printed as an almost 300-page book soon afterwards¹¹ and Alzheimer was appointed *Privatdozent* (lecturer) in August 1904.

Discovery

The case of Auguste D.

After the Munich Hospital had opened (November 11, 1904), Alzheimer hoped to again have more time for his research. This happened only for a short time, but with great effect. In April 1906, Sioli, with whom Alzheimer worked in Frankfurt, informed him of the death of the



Figure 4. Alzheimer and coworkers in Munich. Back (left to right): F. Lotmar; unknown; St Rosental; Allers (?); unknown; A. Alzheimer; M. Achucarro, F. H. Levy. Front (left to right): Frau Grombach; U. Cerletti; unknown; F. Bonfiglio; G. Perusini. About 1909.

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patient Auguste D., arranged an autopsy, and gave him brain material for investigation. By this means, epoch-making research was enabled.^{12,13}

Alzheimer discovered and described the histological alterations later known as plaques and neurofibrillary tangles.¹⁴ He presented these findings to Kraepelin and the other scientists in the Munich research team, convincing all of them that such histopathological findings in connection with such a clinical symptomatology and course of illness had never been seen before. Kraepelin encouraged Alzheimer to present the case of Auguste D. as soon as possible at the next scientific congress of German psychiatrists in the autumn of 1906 in Tübingen. The lack of response to this discovery at this meeting was very disappointing for Alzheimer, but he did not give up his search for comparable cases. He felt satisfied that his lecture, which had not been mentioned at Tübingen, was published one year after the conference.¹⁵

Due to changes at the Munich Hospital, Alzheimer's hopes of being able to devote all his time to research in the histopathological laboratory were dashed. Robert Gaupp, who had moved together with Kraepelin and Alzheimer from Heidelberg to Munich, was offered the chair of psychiatry and the directorship of the Medical Faculty of the University of Tübingen (1906-1939). Gaupp accepted this appointment and left Munich in October 1906. Kraepelin entrusted Alzheimer, as Gaupp's successor, with the position of deputy director. Alzheimer was now occupied with many additional obligations: care of patients, training of young psychiatrists, teaching of students, expert reports in psychiatry, and administrative duties. Therefore, Alzheimer delegated the research in the histopathological laboratory to his team of coworkers, which every year was becoming bigger. Notably, Gaetano Perusini from Italy specialized in research on cases with dementing processes. After 1906, Perusini and Alzheimer observed three additional cases comparable to that of Auguste D., and Perusini published these four cases, together with all clinical and histopathological details in 1909.¹⁶

Between 1906 and 1909, Kraepelin prepared the 8th edition of his famous textbook *Psychiatrie*.¹⁷ As he had soon recognized the fundamental significance of Alzheimer's findings, he included a report on the case history of Auguste D. in the written text of 1908 and proposed calling this peculiar illness Alzheimer's disease. Both volumes of the new edition of Kraepelin's textbook came out in 1910. In this way, very soon after the description

of the first case, the diagnostic term Alzheimer's disease was introduced by Kraepelin's authority and, since that time, has been generally used. However, in spite of this fact, because this disease—presenile dementia with some unusual histological signs (plaques and neurofibrillary tangles)—was very rare, the name of Alois Alzheimer was almost forgotten for more than 50 years. During the last few decades, the situation has changed considerably.

The case of Josef F.

In 1911, Alzheimer himself published again in a broader context on presenile and senile dementing processes.¹⁸ He described how the male patient Josef F. died after 3 years of hospitalization in Munich in 1910. Kraepelin had already mentioned the case of Josef F. in his textbook, and had diagnosed him as having Alzheimer's disease¹⁷ before death. The histological investigation confirmed the clinical diagnosis, but there was one important difference. Alzheimer noticed that there were no neurofibrillary tangles in the slide preparations of Josef F.'s brain, only plaques. For a long time, it was considered to be contradictory if “plaque-only” cases belonged to the same category as cases with plaques and neurofibrillary tangles. A singular situation in research in recent years has provided a solution to this problem. In 1995, after an intensive search of the Frankfurt archives, K. Maurer discovered the documentation of the clinical findings of Auguste D.¹⁹ Histopathological slide preparations of her brain were subsequently found in the Munich Institute of Neuropathology. Documentation on the illness of Josef F. up to his death was found in clinical archives of the Munich Psychiatric Hospital and, after a long search, M. B. Graeber finally discovered the brain slide preparation in the depot of the Munich Institute of Neuropathology, where it had been stored since 1911.¹⁹

The material of both cases (Auguste D. and Josef F.) was reinvestigated with modern neurohistochemical techniques. The results of this investigation and analysis of all findings together with a summary on literature and conceptual interpretations were published by H.-J. Möller and M. B. Graeber.² Their conclusion was that plaque-only cases and cases with plaques and neurofibrillary tangles are simply different stages in the development of the same disease process.²⁰ This means that—in addition to his pioneering discovery of the case of Auguste D. in 1906—a few years later, Alzheimer was

the first person to describe an important stage of development of the illness associated with his name with the case of Josef F. also.

From Munich to Breslau

Kraepelin had promised Alzheimer that, after the departure of Gaupp (1906), he would only be in charge as deputy director for a short time. However, this state of affairs lasted 3 years until E. Rüdin (1874–1952) was appointed to take over all of Alzheimer's routine duties. Since he now had more time for research, Alzheimer was mainly occupied from 1909 onwards with histopathological studies on all kinds of psychotic mental diseases, including dementia praecox (schizophrenia) and manic-depressive psychoses. The aim was to also find a neuropathological basis for these so-called endogenous psychoses. Kraepelin was especially hopeful that Alzheimer would be successful, in order to demonstrate that his concept of dichotomy of these psychotic diseases was right.

Alzheimer intended to publish all his findings in a comprehensive book, but he was not able to finish this project. He was also occupied with more general problems of research in psychiatric illness, notably with the difficulties in correlating clinical diagnosis and postmortem findings.²¹

In addition, on Kraepelin's advice, in 1910, together with the neurologist M. Lewandowsky (1876–1918), Alzheimer established a new scientific journal *Zeitschrift für die gesamte Neurologie und Psychiatrie*. The first introductory contribution of this new journal was written by Alzheimer himself.²¹

In 1912, he was appointed Chair of Psychiatry at the University of Breslau. This position was the realization of his dreams as a young assistant at the psychiatric hospital at Frankfurt for his professional life: to work as clinician and director responsible for a psychiatric hospital. Unfortunately, he had very few years left to work in Breslau, for he died there at the age of 51 on December 19, 1915. □

Alois Alzheimer: el descubrimiento de la Enfermedad de Alzheimer

El día 3 de Noviembre de 1906 un psiquiatra clínico y neuroanatomista, Alois Alzheimer, dio cuenta en la 37ª Reunión de Psiquiatras del Sudoeste de Alemania en Tübingen del trabajo "A peculiar severe disease process of the cerebral cortex." Él describió el caso de una mujer de 50 años a quien él había seguido desde su ingreso por paranoia, progresivos trastornos del sueño y de la memoria, agresividad y confusión, hasta su muerte 5 años más tarde. Su informe de la histología cerebral describió placas distintivas y ovillos neurofibrilares. El informe provocó poco interés a pesar de una entusiasta respuesta de Kraepelin, quien prontamente incluyó la "Enfermedad de Alzheimer" en la 8ª Edición de su texto Psiquiatría en 1910. Alzheimer publicó posteriormente tres casos en 1909 y una variante de "sólo placa" en 1911; el reexamen en 1998 de las muestras originales demostró que correspondían a una etapa diferente del mismo proceso. Alzheimer falleció en 1915, a los 51 años, muy pronto después de ganar la cátedra de psiquiatría en Breslau, y mucho antes de que su nombre llegara a ser una palabra de uso habitual.

Alois Alzheimer : la découverte de la maladie d'Alzheimer

Le 3 novembre 1906, lors du 37^e congrès des psychiatres allemands du sud-ouest à Tübingen, un psychiatre clinicien et neuroanatomiste, Alois Alzheimer, rapporta « un processus morbide sévère et étrange du cortex cérébral ». Il décrit le cas d'une femme âgée de 50 ans qu'il avait suivie depuis son hospitalisation pour paranoia, perturbation progressive du sommeil et de la mémoire, agressivité et confusion jusqu'à sa mort 5 ans plus tard. Le compte rendu qu'il fit de l'examen histologique du cerveau faisait état de plaques caractéristiques et de dégénérescences neurofibrillaires. Ces observations ne soulevèrent que peu d'intérêt, seul Kraepelin réagit de façon enthousiaste en incluant sans délai, dès 1910, « la maladie d'Alzheimer » dans la 8^e édition de son ouvrage Psychiatrie. Alzheimer publia trois autres cas en 1909 et une variante « plaques seulement » en 1911 qui s'est révélée, après un réexamen des spécimens originaux en 1998, être une étape différente du même processus. Alzheimer mourut en 1915, âgé de 51 ans, peu de temps après l'obtention de la chaire de psychiatrie de Breslau et bien avant que son nom devienne connu de tous.

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