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A Brief Biography of Alois Alzheimer

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ABSTRACT

Although we are often aware of a few events in the private lives of specific doctors, we tend to express far more interest in their professional lives. Nevertheless, we should recognise that doctors' biographies often reveal the clues that led them to their discoveries and findings. While this is not always the case, we should also recognise the interest of looking beyond scientific research to gain a better understanding of a scientist as a person. Alzheimer is one of the most commonly-used eponyms in the field of neurology, but we rarely stop to ask ourselves who this doctor was, how he described the illness that still bears his name, and under what circumstances these events took place. The purpose of this article is to find answers to these questions.

KEYWORDS

Alois Alzheimer, biography, history, professional career, teaching

Alois Alzheimer was born on 14 June 1864 in his family's home at Würzburger Strasse 273, Marktbreit-am-Main. His family was deeply Catholic. His father Eduard had three wives; the first was Eva-Maria Busch who died young, and the second was her sister Theresia Busch, Alois's mother. Theresia also died, after which Eduard married Marta Katharina Maria Geiger. His three marriages resulted in eight children (Karl Eduard, Aloysius 'Alois', Anna Johanna Barbara Sabina, Eduard Roman, Max Theodor Alexander, Maria Crescentia Elisabeth, Johann Alfred, and Eugenia). Alois began his studies in 1870 at the Catholic primary school in Markbreit and continued on to the Royal Humanistic Secondary School in Aschaffenburg, graduating in 1883.

In April 1894, he married Cecilie Simonette Nathalie Geisenheimer, and they had three children: Gertrud (1895-1980), Hans (1896-1981), and Maria (1900-1977).[1-5] The economic independence which Alzheimer gained through his marriage meant that he was able to pay for a large part of his laboratory projects and costs himself.[6] Cecilie died on 28 February 1901 when she was only 41 years old. Alzheimer decided not to remarry and dedicated himself to his work.

The doctor's figure was robust and somewhat round; his facial features were set off by his full and well-kept moustache and a scar on his left cheek that resulted from a fencing accident during his youth. His personality was described as creative, good-humoured, optimistic, caring, fun-loving, and expansive, in contrast to the obsessive-compulsive tendencies of his good friend and colleague Nissl.[7] As a scientist, he was remarkably thoughtful and critical, mainly of himself, but also of those around him. His descriptions and research reveal the precision and objective approach employed in his quest for scientific truth, and he placed considerable importance on values such as honesty, constancy, and meticulousness. A careful observer, he checked every last detail in his histological slides, and also possessed excellent powers of deduction. He expressed his scientific opinions clearly and concisely, only doing so after a period of thorough and dedicated reflection so that his words would not contain any baseless or ill-considered speculations (Figure 1).

Kraeplin and other colleagues described Alzheimer as a workaholic, and his obsession became nearly an addiction after the death of his wife, when he would work well into the night, perhaps to avoid coming to terms with his grief. Nissl described him as "the enemy of all exaggeration, speculation, and fantastic invention...filled with burning enthusiasm for the ideas he supported, he not only defended this approach in research, but was also the

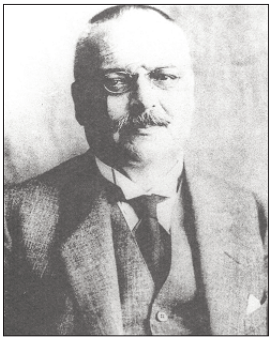

Figure 1.
Alois Alzheimer (1864-1915)

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strongest point in its favour".[8] Young's obituary note, written and published in the *Archives of Neurology and Psychiatry* in 1935 (years after Alzheimer's death), states "he was a clear-headed scientist who knew where research was needed and where it was most profitable. Confidence and self-criticism marked his work. Everyone who knew him felt the gentleness, the kindness, and the spirited force [of this man of genius]".[9] His scientific generosity was such that some of his cases (Bonfiglio's and Perusini's patients) and studies (Fuller's neurofibrillary tangles) were in fact published by his students.

Bonfiglio, who wrote the Italian obituary for his teacher, stated:

> Professor Alzheimer's passing deprives us of one of the main architects of histopathology of the nervous centres, especially that applied to solving the myriad and complex histopathological questions about mental illnesses...Today, Germany has lost one of its greatest men. This loss is more devastating than a lost battle. And yet, Germany has no time today to reflect on how much more the men like Alzheimer have contributed to civilisation compared to all of its generals who employ violence, terror, and devastation with the stated aim of civilising the world.[10]

There were darker pages in his biography, however, such as his defence of the Great War, for which there was no possible justification, even considering the circumstances in Germany at the time. At the outbreak of that war, he wrote the following:

> Although the war will harm some nerves, it may also benefit them by forming a more determined, daring, enterprising race […] The Fatherland was threatened on all sides, and we knew only too well that we would be shown no mercy unless we were victorious.[1]

While on the subject, I must also point out that he was a member of the German Racial Hygiene Society (*Deutschen Gesellschaft für Rassen-Hygiene*). This society was founded by Alzheimer's colleague and locum clinical chief in Munich, E. Rüdin, who went on to become a consultant on Racial Policy for the Third Reich Home Office.

Career as a scientist, researcher, and teacher

Alzheimer's activity as a doctor covered all three facets of the profession, and as a clinician, teacher, and researcher, he made important contributions.

On 15 October 1883, he began his medical programme at Friedrich-Wilhelms Universität in Berlin, where he remained until his transfer to Julius-Maximilians-Universität Würzburg on 15 March 1884. Here, he would meet R. von Kölliker, one of his first mentors. He studied at this university until 20 October 1886, when he was granted another transfer to Eberhard Karls Universität Tübingen. In the end, he returned to Würzburg, where he completed his studies and defended his thesis *Über die Ohrenschmalzdrüsen* (On the ceruminal glands of the ear) with von Kölliker as his advisor. He passed the state examination for doctor certification summa cum laude.[1]

For no apparent reason, he left his work with von Kölliker to accompany a woman who suffered from a mental illness on a 5-month journey.[2] This experience may have sparked his professional interest in the study and treatment of disorders of this type. As a result, in December 1888 he joined the Frankfurt hospital for mentally ill and epileptic patients (Städtischen Heilanstalt fur Irre und Epileptisch), where he met Emil Sioli and Franz Nissl. In March 1903, he left for the Heidelberg Psychiatric Clinic directed by Kraepelin, but in October of the same year, when Kraepelin was made Chair of Psychiatry at Ludwig-Maximilians-Universität in Munich, Alzheimer moved to Munich as well. He was hired as a neuropathologist and head of the neuroanatomy laboratory by the Munich Institute of Psychiatry.[3]

In August 1912, Alzheimer was named Chair of Psychiatry and Neurology by the University of Breslau, leading him to change cities yet again. In the process of moving to Breslau, Alzheimer developed symptoms compatible with tonsillitis. The illness did not heal completely and gave rise to bacteraemia which in turn caused endocarditis and heart failure.[4] Following that episode, his health declined continuously and he suffered from frequent bouts of angina and dyspnoea. As a result, he was forced to restrict his professional activities, especially in the last two years of his life. Alzheimer died of heart and kidney failure in Breslau on 19 December 1915, only 11 days after his friend and student Gaetano Perusini was killed in the war.[5]

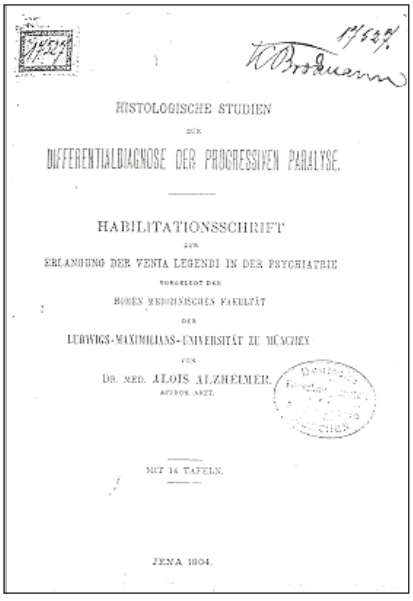
Scientific and research activities

Although von Kölliker is sometimes regarded as the first person who encouraged Alzheimer to study the cerebral cortex, his influences in this field of study were Sioli and especially Nissl. The latter left his mark on Alzheimer's training in neuropathology. In any case, Alzheimer always referred to himself as a clinician as well as a neuropathologist. In Kraepelin's words, he "wanted to help psychiatry with the microscope"[6] and one of his objectives was "enlarging scientific knowledge of psychiatry"[11] and finding clinical-anatomical correlations in mental illnesses. Nissl was his chief mentor as well as his

best friend. Under his direction and influence, Alzheimer learned the most cutting-edge histopathological techniques of his time, and used them to complete his first investigations of microscopic changes in different mental illnesses. The two doctors formed an exceptional scientific team. Nissl provided innovation, imagination, and his interest in new experimental and methodological problems in neuropathology, while Alzheimer's many strong points made him the right candidate to put new ideas into practice. These character traits, some of which are listed above, included consistency, meticulousness, well-developed powers of observation, and a gift for deduction and analysis. The precision and accuracy of his descriptions, and his ability as an anatomical illustrator, also contributed to the dissemination of his scientific studies.

The key stage in Alzheimer's career was the time he spent in Munich working with Kraepelin. Here, we can further subdivide the period using the pivotal event in the doctor's life: his description in 1906 of the first case of Alzheimer disease. His first scientific publication, dated 1892 when he was working at the hospital in Frankfurt, was *Über einen Fall von spinaler progressiver Muskelatrophie mit hinzutretender Erkrankung bulbärer Kerne und der Rinde* [On a case of spinal progressive muscular atrophy with additional disease of bulbar nuclei and the cortex]. In 1903, E. Kraepelin convinced Alzheimer to travel to Heidelberg to further his academic studies. There, he wrote his *Habilitationsschrift* or inaugural dissertation, which was titled *Histologische Studien zur Differentialdiagnose der progressiven Paralyse* [Histological studies on the differential diagnosis of progressive paralysis][12] (Figure 2). It took him four years to complete the dissertation, which comprised 297 pages with numerous photographs and 14 illustrations drawn and coloured by the author. In this text, Alzheimer presented post-mortem findings from 170 patients with general progressive paralysis whose anatomical pathology studies he completed himself while living in Frankfurt. The neuropathological descriptions ring true even today. With his dissertation, prepared with the guidance of his friend W.H. Erb and under the direction of E. Kraeplin, he launched his career as a researcher, although he had written several earlier articles about the same process. Examples include *Die Frühform der progressiven Paralyse* [General progressive paralysis in its early stages] presented before the LXVI Meeting of German Scientists and Doctors (Vienna, 24-30 September 1895); *Über die anatomische Ausbreitung des paralytischen Degenerationsprozesses* [On the anatomical spreading of the paralytic degeneration process], presented at the LXVII Meeting of German Scientists and Doctors (Frankfurt, 1896); and *Ein Fall von luetischer Meningomyelitis und Encephalitis* [A case of syphilitic meningomyelitis and encephalitis] (1897). This last topic continued to fascinate him, and was probably his most-published subject. Examples of his articles include *Progressive Paralyse und endarteriitische Lues des gehirns* [Progressive paralysis and endarteritic lues cerebri] (1905); *Zur pathologischen Anatomie der Paralyse und der paralyseähnlichen Erkrankungen* [On the anatomical pathology of paralysis and paralytic diseases] (1906); *Die stationäre Paralyse* (1906) [Stationary paralysis]; *Die Frage der stationären Paralyse der Irren* [The question of stationary paralysis in lunatics] (1907); and *Die syphilitischen Geistesstörungen* [Syphilitic mental illnesses] (1909).

In Breslau, Alzheimer continued working as a professor and researcher, but his main activity was the search for organic causes underlying mental processes. To this end, he began a compilation, which he never finished, of neuropathological findings in endogenous forms of psychosis. He believed that these psychoses were caused by cerebral degeneration.[13,14] Alzheimer was convinced that mental illnesses were specific cerebral conditions resulting from changes on the neuronal level.[9] He always maintained that these disorders had an organic cause, especially *Dementia praecox* (schizophrenia).[15,16] Kraepelin also held this belief, as we see in his book *Dementia praecox und Paraphrenia* (1919). Alzheimer dedicated considerable effort to searching for neuropathological findings and an organic cause in schizophrenia. He described glial bands, regressive pigment changes, neuronal cell body degeneration, and neuronal loss in a number of cortical strata.[9] In fact, one of his last projects as a professor was to


HISTOLOGISCHE STUDIEN

ZUR

DIFFERENTIALDIAGNOSE DER PROGRESSIVEN PARALYSE.

HABILITATIONSSCHRIFT

ZUR

ERLANGUNG DER VENIA LEGENDI IN DER PSYCHIATRIE

VORGELEGT DER

HOHEN MEDICINISCHEN FAKULTÄT

DER

LUDWIGS-MAXIMILIANS-UNIVERSITÄT ZU MÜNCHEN

VON

DR. MED. ALOIS ALZHEIMER,

ASSIST. ARZT.

MIT 14 TAFELN.

JENA 1904.

Figure 2. Alzheimer's inaugural thesis

elaborate a neuropathology textbook, *Die Anatomie der Geisteskrankheiten* [The anatomy of mental illness].

Alzheimer's first two years in his new position in Breslau may well have been his most productive in terms of scientific output. It is quite likely that his new position as a department chair and the independence it provided would have sparked his enthusiasm. In 1911, counting publications and presentations at conferences, he completed 11 studies. In his lifetime, he would publish more than 70 medical articles. In addition to those on dementia and neurosyphilis listed above, he also addressed anatomical pathology in Huntington disease (*Über die anatomische Grundlage der Huntingtonschen Chorea und der choreatischen Bewegungen überhaupt*); epilepsy, including neuronal loss in the hippocampus or Ammon's horn sclerosis in a group of epileptic patients (*Über rückschreitende Amnesie bei der Epilepsie*, *Ein Beitrag zur pathologischen Anatomie der Epilepsie*, and *Die Gruppierung der Epilepsie*); forensic psychiatry (*Ein geborener Verbrecher*); psychiatric epidemiology; birth control in women with mental illnesses (*Über die Indikationen für eine künstliche Schwangerschaftsunterbrechung bei Geisteskranken*); neuroglia (*Beiträge zur Kenntnis der pathologischen Neuroglia und ihre Beziehungen zu den Abbauvorgängen im Nervengewebe*), peripheral nervous system regeneration (*Über die Degeneration und Regeneration an der peripheren Nervenfaser*); diagnostic techniques (*Einige Methoden zur Fixierung der zelligen Elemente der Cerebrospinalflüssigkeit*); diagnostic difficulties in psychiatry (*Die diagnostischen Schwierigkeiten in der Psychiatrie*), neurological pedagogy (*Über den gegenwärtigen Stand der Lehre von der Epilepsia*); alcoholism (*Das Delirium alcoholicum febrile Magnan's*, *Faelle von Methylalkoholvergiftung*); mental retardation (*Einiges über die anatomischen Grundlagen der Idiotie*); hysteria (*Über einen Fall von hysterischer Bulbaerparalyse*, *Die hysterischen Geistesstörungen*); schizophrenia (*Beiträge zur pathologischen Anatomie der Dementia praecox*), the correlation between anatomical pathology and mental illness (*Haben wir bei den verschiedenen Geisteskrankheiten mit anatomischem Befund einen histologisch annähernd gleichen Krankheitsprozess vorauszusetzen?*, *Einiges zur pathologischen Anatomie der chronischen Geistesstorungen*, *Beitrag zur pathologischen Anatomie der Seelenstörungen des Greisenalters*, *Ergebnisse auf dem Gebiete der pathologischen Histologie der Geistesstörungen*); delirium (*Das Delirium acutum*); care management in psychiatry (*Ist die Einrichtung einer psychiatrischen Abteilung im Reichsgesundheitsamt erstrebenswert?*); war and neurological and psychiatric diseases (*Tödliche auswirkungen des Krieges auf Nervensystem und Psyche*, *Der Krieg und die Nerven*); and others.

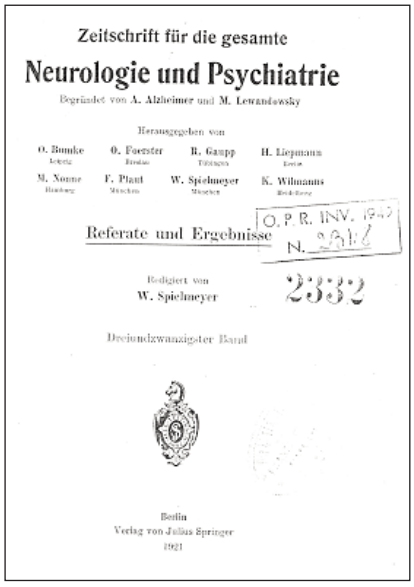
Activity as a professor

Teaching was one of Alzheimer's passions, and we can distinguish between three major phases in his professional career. The first phase is that prior to 1904 when he achieved full professorship, the second covers the time between completion of his inaugural dissertation and being named department chair in Breslau (1904-1912), and the third phase spans his time as chair until his death in 1915. During this last phase, his health declined, which curtailed his teaching and research activities considerably.

On 23 July 1904, he presented a lecture on *Die hysterischen Geistesstörungen* (Hysterical forms of dementia). He was made an associate professor (*ausserordentlicher*) at the Faculty of Medicine at Ludwig-Maximilians-Universität in Munich on 10 August 1904. On 30 December 1909, the university named Alzheimer an honorary chair, and on 16 July 1912, he became Chair of Neurology and Psychiatry at Friedrich-Wilhelms Universität in Breslau (now Wroclaw, Poland). He was also appointed director of that city's Clinical Hospital for Psychiatric and Nervous Diseases. When he left Munich, W. Spielmeyer became the head of the neuropathology laboratory. He was accompanied by his student F. Lewy on his journey to Breslau on 15 August 1912.

In addition to publishing articles and presenting research in scientific meetings, he and Max Lewandowsky, with Kraepelin's support, co-founded the medical journal *Zeitschrift für die gesamte Neurologie und Psychiatrie*. Alzheimer acted as a medical writer and later became editor; he handled the psychiatry section, while Lewandowsky was entrusted with the neurology section (Figure 3).[4] Most of his neuropathological studies were published by this journal. In partnership with Nissl, he also edited all six volumes of *Histologische und histopathologische Arbeiten uber die Grosshirnrinde*, published between 1904 and 1918.[17] The purpose of these books was to present specific neuropathological findings in different mental processes that would demonstrate their organic cause (Figure 4).

His valiant efforts as a teacher were beneficial to more than just medical students. He also prepared and directed the Munich Hospital's yearly postgraduate course on neuropathology, which lasted 20 days (100 hours of theory and practice). This course was designed to refresh


Zeitschrift für die gesamte

Neurologie und Psychiatrie

Begründet von A. Alzheimer und M. Lewandowsky

Herausgegeben von

O. Bumke · O. Foerster · R. Gaupp · H. Liepmann

M. Nonne · F. Plaut · W. Spielmeyer · K. Wilmanns

Referate und Ergebnisse

Redigiert von W. Spielmeyer

Dreiundzwanzigster Band

Berlin
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1921

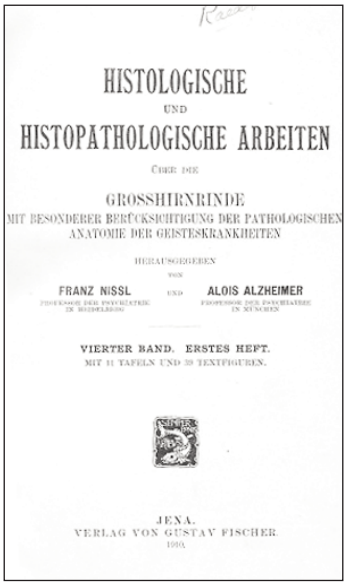

HISTOLOGISCHE
UND
HISTOPATHOLOGISCHE ARBEITEN
ÜBER DIE
GROSSHIRNRINDE
MIT BESONDERER BERÜCKSICHTIGUNG DER PATHOLOGISCHEN ANATOMIE DER GEISTESKRANKHEITEN
HERAUSGEGEBEN
VON
FRANZ NISSL UND ALOIS ALZHEIMER
VIERTER BAND. ERSTES HEFT.
MIT 11 TAFELN UND 39 TEXTFIGUREN.
JENA.
VERLAG VON GUSTAV FISCHER

Figure 3. Cover of *Zeitschrift für gesamte Neurologie und Psychiatrie*, the journal founded by Alzheimer and Lewandowsky

Figure 4. Journal published in partnership with Nissl and belonging to his colleague Raecker

clinical and anatomical pathology concepts in mental diseases, and it was open to all scholars with an interest in the neurosciences. The course also fostered contact between scientists trained in different schools of neurology, resulting in widespread awareness of Alzheimer's neuropathological findings and observations, and interest in his neurohistological techniques. He also played a fundamental role in training the numerous distinguished specialists who flocked to his laboratory from all across the globe to learn his techniques and neuropathological diagnostic procedures.

Figure 5. Photograph of Alzheimer[7] with his most assiduous students: Lotmar,[1] head technical assistant Mrs Grombach,[2] Rosenthal,[3] Cerletti,[4] Allers,[5] Bonfiglio,[6] Achúcarro,[8] Perusini,[9] and Lewy.[10] The individual between Lotmar and Rosenthal may be laboratory assistant Karl G.

His prestige as a clinician and anatomist led many neurologists and neuropathologists to request work at the Munich laboratory, which had a capacity of 20 researchers, and its slots were always full. His students included C. Von Hoesslin, F. H. Lewy, K. Kleist, H. G. Creutzfeldt, and A. M. Jakob of Germany; F. Bonfiglio, G. Perusini, U. Cerletti, and F. Fulci of Italy; T. Simchowicz and St. Rosenthal of Poland; B. Doinikow, A. Farworsky, and L. Omorokow of Russia; S. Fuller, L. Casamajor, C. Farrar, H. A. Cotton, and S. E. Jelliffe of the United States; F. Lotmar and G. Biondi of Switzerland; H. Evensen of Norway; M.C. Campbell of Great Britain; A Debaux of France; L. Merzbacher of Argentina; and many more (Figure 5). He had Spanish students as well: N. Achúcarro and G. R. Lafora.[18] In fact, Achúcarro was the first doctor to describe Alzheimer disease in the United States, during his time working in Washington, D.C.[19] (Figure 6).

Figure 6. N. Achúcarro

Alzheimer was always selfless and generous in his dealings with his students. For example, he allowed Fuller,[20] whose research he directed, to describe neurofibrillary tangles a few months before Alzheimer himself was to do so at a conference in Tübingen. He also provided Bonfiglio[21] and Perusini[22] with the material they needed in order to analyse and publish cases of Alzheimer disease. Teaching was a lifelong passion for Alzheimer; in fact, one of his last projects, a treatise on anatomical pathology in mental illnesses (*Die Anatomie der Geisteskrankheiten*) was conceived as a psychiatry textbook. Last of all, Alzheimer gave all of his students two important pieces of advice: be resolute, and be open-minded rather than dogmatic.

Clinical activity

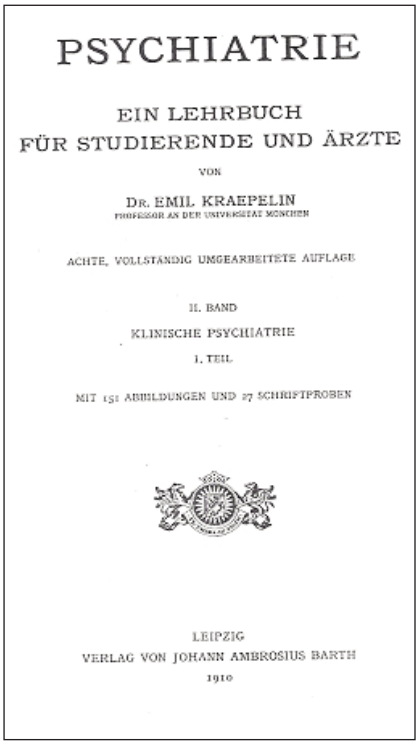
Alzheimer's clinical activity had two fundamental facets, which were clinical care and neuropathology. Recall that Kraepelin said that he "wanted to help psychiatry with the microscope",[23] and that Alzheimer joined Kraepelin's institute as a neuropathologist. And

yet, while Alzheimer always worked in both facets of medicine, he was first and foremost a clinician interested in illnesses originating in the brain itself, whether they were psychiatric or purely neurological. Although his name went down in history because of the eponymous form of dementia, he also showed considerable interest in other conditions, such as epilepsy, general paralysis, stroke, and more.

While in Frankfurt, he worked with figures including Lilienstein, J. Raecke, K. Brodmann, A. Friedländer, M. Sander, and F. Resch, but most of all with Franz Nissl, who remained in Frankfurt until October 1895, when he moved to Heidelberg. It was due to the change in Nissl's situation that Alzheimer applied for the position of clinical chief at the hospital in Frankfurt on 6 October 1895. He began his new duties on 21 July 1896 and held the position for 15 years, until 1 March 1903. The paths of Nissl and Alzheimer crossed once again when Kraepelin, at Nissl's request, asked him to come work with them in Heidelberg. On 25 October 1906, nine days before the Tübingen medical conference, Alzheimer was named vice-director and clinical chief of the Munich Psychiatric Hospital, upon Kraepelin's recommendation. Kraepelin's trust in him was such that Alzheimer also acted as locum clinical and administrative director whenever Kraepelin was absent.[5,24,25] Nevertheless, three years later on 22 February 1909, he willingly ceded his position as clinical chief to Rüdin, indicating that he wished to devote more of his time to teaching and research.[1] In August 1912, he transferred to the University of Breslau as its chair of neurology and psychiatry, and as director of the Breslau Clinical Hospital for Psychiatric and Nervous Diseases.

From a clinical viewpoint, the people who most influenced Alzheimer were Sioli, Nissl, Binswanger, and Kraepelin. Rather than just his mentors, these four were his intimate friends, especially Nissl, who was best man at his wedding and godfather to one of his daughters. Each of the doctors listed above contributed to a specific area in Alzheimer's medical and scientific training. E. Sioli sparked Alzheimer's clinical interest in mental illnesses and processes involving cognitive decline, and he was also the first to teach him neuropsychiatric pathology. F. Nissl showed Alzheimer his microscope neurohistology techniques and awakened his love of microscopic studies of mental processes and the search for anatomical and clinical correlations. These two doctors were so closely linked that it would be hard to say who influenced whom the most.[26-28] O. Binswanger urged him to study cerebrovascular processes, and E. Kraepelin promoted his interest in researching the organic causes of mental illness.[29] There can be no doubt that Kraepelin contributed the most to Alzheimer's professional career and helped him make medical history by featuring 'Alzheimer disease' as an eponym in his 1910 psychiatry textbook titled *Psychiatrie: ein Lehrbuch für Studierende und Ärzte* (Figures 7 and 8).

Kraepelin, influenced by the biological current, was attempting to determine the topography of cerebral functions and determine clinico-pathological correlations with mental illnesses. From his small laboratory on the third floor of the Munich Institute, Alzheimer made great strides in the study of dementia, from both an anatomical pathology and clinical point of view. He introduced new histological techniques[17] permitting detailed analysis of changes in brain structures and ultimately enabling him to describe the disease that bears his name. In light of the above, he is regarded as the founding father of neuropathology in mental illnesses.[14]


PSYCHIATRIE

EIN LEHRBUCH
FÜR STUDIERENDE UND ÄRZTE

VON

DR. EMIL KRAEPELIN
PROFESSOR AN DER UNIVERSITÄT MÜNCHEN

ACHTE, VOLLSTÄNDIG UMGEARBEITETE AUFLAGE

II. BAND

KLINISCHE PSYCHIATRIE

1. TEIL

MIT 151 ABBILDUNGEN UND 27 SCHRIFTPROBEN

LEIPZIG
VERLAG VON JOHANN AMBROSIUS BARTH
1910

Figure 7. The 1910 edition of Kraepelin's psychiatry textbook, the first text to refer to 'Alzheimer disease'

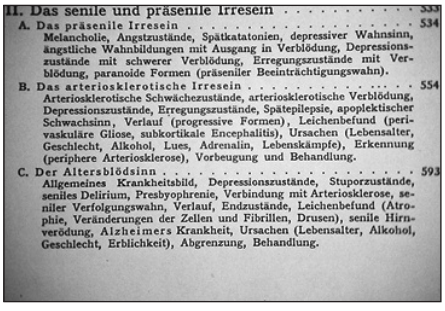

II. Das senile und präsenile Irresein 533
A. Das präsenile Irresein 534
Melancholie, Angstzustände, Spätkatatonien, depressiver Wahnsinn, ängstliche Wahnbildungen mit Ausgang in Verblödung, Depressionszustände mit schwerer Verblödung, Erregungszustände mit Verblödung, paranoide Formen (präseniler Beeinträchtigungswahn).
B. Das arteriosklerotische Irresein 554
Arteriosklerotische Schwächezustände, arteriosklerotische Verblödung, Depressionszustände, Erregungszustände, Spätepilepsie, apoplektischer Schwachsinn, Verlauf (progressive Formen), Leichenbefund (perivaskuläre Gliose, subkortikale Encephalitis), Ursachen (Lebensalter, Geschlecht, Alkohol, Lues, Adrenalin, Lebenskämpfe), Erkennung (periphere Arteriosklerose), Vorbeugung und Behandlung.
C. Der Altersblödsinn 593
Allgemeines Krankheitsbild, Depressionszustände, Stuporzustände, seniles Delirium, Presbyophrenie, Verbindung mit Arteriosklerose, seniler Verfolgungswahn, Verlauf, Endzustände, Leichenbefund (Atrophie, Veränderungen der Zellen und Fibrillen, Drusen), senile Hirnverödung, Alzheimers Krankheit, Ursachen (Lebensalter, Alkohol, Geschlecht, Erblichkeit), Abgrenzung, Behandlung.

Figure 8. Table of contents from Kraepelin's psychiatry textbook, the first text to employ the term 'Alzheimer disease'

From a clinical standpoint, his career can be divided into four periods, but all are marked by a common feature, i.e. his interest in mental illness. The first period (1888-1903) spans his stay in Frankfurt. During this time, he wrote more than 20 important articles. In these early years, guided in his investigation of mental illness by Sioli and Nissl, and also influenced by Binswanger and by Notzli's vascular theory, he completed a number of studies on vascular dementia. Dating from this period are such writings as *Die arteriosklerostische Atrophie des Gehirns* [Arteriosclerotic atrophy of the brain], presented in the Annual Meeting of the Association of German Psychiatrists (Dresden, 20 September 1894), and published the following year. This study analysed clinical and neuropathological factors in vascular dementia in 12 patients and listed the differences between that entity and general progressive paralysis.[30] This publication was followed by others on vascular dementia completed in 1895, 1898, 1899, and 1902. Along with Binswanger, Alzheimer was one of the first German authors to present an in-depth study of arteriosclerotic atrophy of the brain. He recognised Klippel's significant contributions to research into this process, and believed that it should be called Klippel disease.

Meanwhile, especially in his articles appearing in 1898 and 1902, he also categorised cerebral processes associated with arteriosclerosis in four groups: Binswanger's chronic progressive subcortical encephalopathy (arteriosclerotic white matter atrophy); senile cortical atrophy (small-vessel vascular dementia, which he believed was frequently associated with senile dementia); perivascular neurogliosis (a form of dementia associated with arteriosclerosis and severe narrowing of large vessels leading to chronic ischaemia); and postapoplectic dementia.[27] In 1902, he published an exhaustive microscopic description of the entity described by Binswanger (chronic progressive subcortical encephalopathy) in which he confirmed the presence disease and referred to it using the eponym "Binswanger". He wrote that it corresponded to a "peculiar form of subcortical atrophy due to atherosclerosis of cerebral arteries, a trait distinguishing it from other types of arteriosclerotic atrophy" and that it was due to arteriosclerosis of white-matter vessels. ("It was caused by a specific form of severe arteriosclerosis of the long vessels of the deep white matter showing advanced atrophy of the white matter in both hemispheres").[31] This cause was first suggested by Binswanger in 1894 and confirmed in 1920 by Nissl.[32]

Alzheimer first raised the question of whether senile dementia might be a primary process of cerebral atrophy independent from arteriosclerotic changes in 1898, in the following words:

> Previously, I believed this opinion [the vascular cause of senile dementia] to be correct. Nevertheless, I recently examined a case that could be described as pre-senile dementia which revealed severe nerve cell atrophy with only minimal atheromatous changes to the vessels. This case supports the hypothesis that hereditary weakness of the central nervous system may result in early atrophy of nerve cells.[33]

This description, appearing in 1898, may have been the doctor's first recorded case of what was later called Alzheimer disease. It was published nearly eight years before what is now considered the first report of a case of AD. Alzheimer may not have been fully aware of the significance of this observation, but he did have it in mind when he analysed the other case in 1906 and found scarce cerebrovascular changes once again. He then realised that the finding was not casual, and that it might indicate a different type of process from those understood at the time. This was expressed in the conclusion of the report in 1906.

In this period, he also published well-regarded articles on neurosyphilis, and was recognised as one of the leading experts on progressive general paralysis.[34] The discovery that anatomical pathology changes were present in diseases with cognitive impairment made Alzheimer critical of the purely psychiatric currents supported by Lombroso in Italy and Freud in Austria. However, he did defend some of his French colleague Morel's theories.

The second period in Alzheimer's career (1903-1912) spans his time in Heidelberg and Munich and includes two well-defined phases. Although he was still working with cerebrovascular disease during the first phase, he placed particular emphasis on general paralysis and wrote *Histologische Studien zur Differentialdiagnose der progressiven Paralyse*, mentioned previously, in 1904. Alzheimer attempted to find correlations between symptoms and anatomical pathology findings in the different stages of general progressive paralysis. Proof of his interest and continued research into the topic is that on 11 June 1913, he informed the secretary of the University that he had discovered the syphilis microbe

in general progressive paralysis and that a serological diagnostic procedure could be performed. On this basis, he requested funding,[1] which was awarded on 21 July 1913. In the second part of this period, which was the most fructiferous and significant of his entire career, he expanded his initial studies from 1894 and 1898 to focus on senile dementia and its anatomical pathology changes in particular. He presented what would become his best-known case in the lecture *Über eine eigenartige Erkrankung der Hirnrinde* in which he also described senile plaques and neurofibrillary tangles. In this period, he also addressed the potential histopathological changes in depression and manic-depressive disorder,[2] described Pick bodies and the balloon-shaped neurons typical of Pick disease,[35] and published one of the first neuropathological studies of Huntington chorea in 1911.[17]

In the third period of his career (1912-1915), while he was living in Breslau, he continued his study of senile dementia with an emphasis on the organic causes of psychosis. He also researched dementia associated with Parkinson's disease with the assistance of his student Friedrich H. Lewy. Lewy presented the first description of the eponymous bodies in patients with Parkinson's disease while working under Alzheimer's tutelage in the latter's neuropathology laboratory in Munich.[36] Alzheimer's most productive year of all may have been 1913, during which he published and presented a total of eleven studies.

Apart from his clinical and pathological description of general paralysis (1904)[12] and the case of the disease that now bears his name (1906),[37] his best-known anatomical pathology studies are those on senile plaques[38] and neurofibrillary tangles.[39] According to Alzheimer, senile plaques were a phenomenon that invariably accompanied CNS degeneration and could therefore be regarded as an essential histological finding in senile dementia. Plaques consist of two distinct parts: a homogeneous central region or core (*Kern*) due to reactive phenomena secondary to an unknown substance being deposited on the cortex, plus a peripheral fibrillary part or halo (*Hof*) caused by degenerative and proliferative changes to the axons. Based on the type of halo and core, Alzheimer categorised senile plaque in 1911 as *Hof ohne Kern* (halo without core) or primitive/diffuse senile plaque showing no neuronal cell damage and no fibrillary or amyloid structures; *Höfe mit Kern* (halo with core) or classical/typical senile plaque; and lastly, *Kerne ohne Höfe* (core without halo) or compact plaque. Alzheimer showed that senile plaque was aetiologically independent from vascular factors. He believed that rather than causing senile dementia, it was a manifestation of senile cerebral degeneration. Alzheimer was also the first author to describe senile plaque outside of the brain, in the spinal cord.

Some debate exists over who first described neurofibrillary tangles using the Bielschowsky technique; the description was initially attributed to Alzheimer in his case study of 1906.[39] The issue is that a few months before, in June 1906, his student S. Fuller[20] presented a study on alterations in neurofibrils in senile dementia, indicating their potential diagnostic utility in this entity. The study, directed by Alzheimer himself, was presented at the meeting of the American Medical Psychological Association in Boston. Nevertheless, well-deserved credit for this anatomical pathology finding has been given to Alzheimer. We see that the other anatomical pathologists of his time used the eponym 'Alzheimer' to refer to neurofibrillary tangles ever since they were first described. Examples include Alterazione di Alzheimer (Ziveri, 1912; Lugaro, 1916); Alzheimer's degeneration of intracellular neurofibrils (Fuller, 1912); Alzheimer's intracellular neurofibril alteration (Tiffany, 1913), and others. The term may even appear in more recent works, as we see in the study by Harada (1988)[40] that refers to "Alzheimer's tangles".

Lastly, we must not overlook Alzheimer's contributions to the study of other types of primary degenerative dementia, such as Pick disease and dementia with Lewy bodies, in the latter case as Lewy's mentor. It should be recalled that several of his students made important contributions to both neuropathology and clinical neurology.

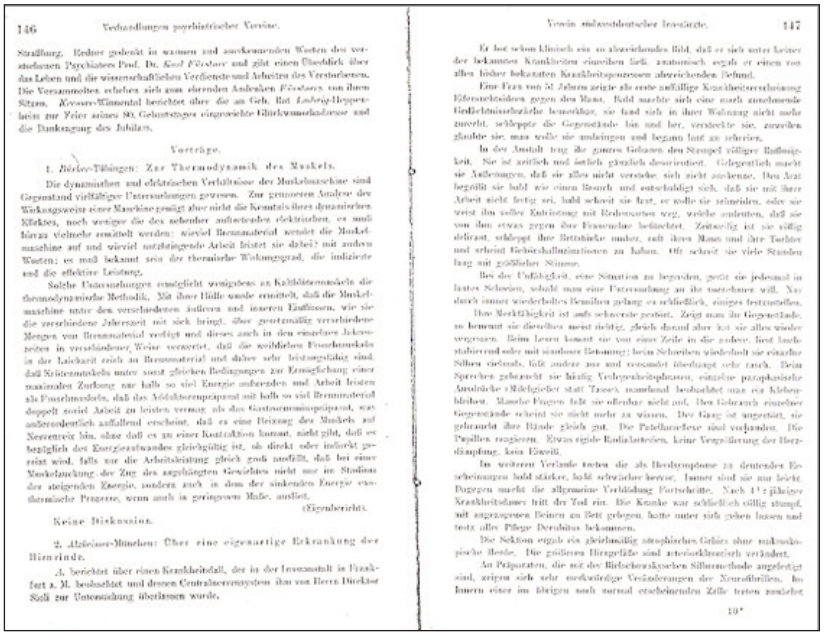
The eponym 'Alzheimer' has been used to describe a number of different anatomical pathology findings, as in Alzheimer tangles, Nissl-Alzheimer arteritis, Alzheimer baskets, Alzheimer gliosis types I and II, Alzheimer-related cortical destruction, Alzheimer sclerosis, Alzheimer stain (a stain used to detect Negri bodies in rabies), Alzheimer cells, Alzheimer neurons, Alzheimer rod cells (*Stabchenzellen*) and type I and II Alzheimer astrocytes, which he described in partnership with C. von Hoesslin in 1912.

The description of Alzheimer disease

On the afternoon of Saturday, 3 November 1906, Alzheimer gave a presentation titled *Über einen eigenartigen, schweren Erkrankungsprozess der Hirnrinde* [On a peculiar, severe disease of the cerebral cortex] at the 37th Assembly of Southwest German Psychiatrists held in Tübingen. The session was presided over by Alfred Hoche of Freiburg. The case report was published the following year in the annals of the conference, with a minor change to the title (About a peculiar disease of the cerebral cortex), in the journal *Zentralblatt für Nervenheilkunde und Psychiatrie*. The lecture was published in *Allgemeine Zeitschrift für Psychiatrie und Psychisch-gerichtliche Medizin*.[37] The lecture provided a description of the disease that today bears his name. The lecture appears in the annals as "inappropriate for a brief presentation". It is worth highlighting the fact that the members of the conference's scientific committee branded as 'inappropriate' a lecture that would weather the years to become one of the most frequently cited and relevant articles in the field of neurology. The following figures in neurology, psychiatry, and neuropathology also attended the conference: Binswanger, Bürker, Romberg, Fleischer, Nissl, Merzbacher, Bumke, Curschmann, Döderlein, Gaupp, Bezzola, Wollenberg-Strassburg, Hoche, Jung, and others (Figures 9 and 10).

The folder containing the original medical history of Auguste D. (Auguste Deter), consisting of 32 pages and 4 photographs,[11] was discovered by Maurer in 1995 in the basement of a Frankfurt hospital. It had been misfiled with documents from 1920. In 1998, Möller discovered the histology slides prepared with the same patient's brain tissue in Munich.[42] It seems nearly miraculous that the patient's medical history and original slides would have survived the two world wars that left Germany in ruins.

At the age of 51, the patient was admitted to the Frankfurt Hospital for Nervous Diseases on 25 November 1901. She died of bilateral basal pneumonia with septicaemia on 8 April 1906. Autopsy revealed significant cortical atrophy, hydrocephalus, discrete cerebrovascular changes, and presence of neurofibrillary anomalies and senile plaques. The patient had been examined by Nitsche, Alzheimer and Friedländer in Frankfurt; when she died, Alzheimer, who was in Munich, asked Sioli to send him her brain for research. The laboratory recorded its arrival on 28 April 1906,[11] only 20 days after the patient's death, which indicates just how interested Alzheimer was in the case. Bonfiglio and Perusini completed the anatomical pathology study under Alzheimer's supervision.[43] Since Perusini played an important role in the initial description and authored the first review of AD,[22] the disease is also known in Italy as Alzheimer-Perusini disease.[44]



146 Verhandlungen psychiatrischer Vereine.

Sitzung. Redner gedenkt in warmen und anerkennenden Worten des verstorbenen Psychiaters Prof. Dr. *Karl Förstner* und gibt einen Überblick über das Leben und die wissenschaftlichen Verdienste und Arbeiten des Verstorbenen. Die Versammelten erhoben sich zum ehrenden Andenken *Förstners* von ihren Sitzen. *Kreuser*-Winnental berichtet über die an Geh. Rat *Ludwig*-Hoppenheim zur Feier seines 80. Geburtstages eingereichte Glückwunschadresse und die Dankesgabe des Jubilars.

Vorträge.

1. *Bürker*-Tübingen: Zur Thermodynamik des Muskels.

Die dynamischen und elektrischen Verhältnisse der Muskelmaschine sind Gegenstand vielfältiger Untersuchungen gewesen. Zur genaueren Analyse der Wirkungsweise einer Maschine genügt aber nicht die Kenntnis ihrer dynamischen Effekte, noch weniger die des nebenher auftretenden elektrischen, es muß hierzu vielmehr ermittelt werden: wieviel Brennmaterial wendet die Muskelmaschine auf und wieviel nutzbringende Arbeit leistet sie dabei? mit anderen Worten: es muß bekannt sein der thermische Wirkungsgrad, die indizierte und die effektive Leistung.

Solche Untersuchungen ermöglicht wenigstens an Kaltblütermuskeln die thermodynamische Methodik. Mit ihrer Hilfe wurde ermittelt, daß die Muskelmaschine unter den verschiedenen äußeren und inneren Einflüssen, wie sie die verschiedene Jahreszeit mit sich bringt, aber gewissenhaft verschiedene Mengen von Brennmaterial verfügt und dieses auch in den einzelnen Jahreszeiten in verschiedener Weise verwertet, daß die weißlichen Froschmuskeln in der Laichzeit reich an Brennmaterial und daher sehr leistungsfähig sind, daß Krötenmuskeln unter sonst gleichen Bedingungen zur Ermöglichung einer maximalen Zuckung nur halb so viel Energie aufwenden und Arbeit leisten als Froschmuskeln, daß das Adduktorenpräparat mit halb so viel Brennmaterial doppelt soviel Arbeit zu leisten vermag als das Gastrocnemiuspräparat, was außerordentlich auffallend erscheint, daß es eine Heizung des Muskels auf Nervenreiz hin, ohne daß es zu einer Kontraktion kommt, nicht gibt, daß es bezüglich des Energieaufwandes gleichgültig ist, ob direkt oder indirekt gereizt wird, falls nur die Arbeitsleistung gleich groß ausfällt, daß bei einer Muskelzuckung der Zug des angehängten Gewichtes nicht nur im Stadium der steigenden Energie, sondern auch in dem der sinkenden Energie exothermische Prozesse, wenn auch in geringerem Maße, auslöst.

(Eigenbericht).

Keine Diskussion.

2. *Alzheimer*-München: Über eine eigenartige Erkrankung der Hirnrinde.

A. berichtet über einen Krankheitsfall, der in der Irrenanstalt in Frankfurt a. M. beobachtet und dessen Centralnervensystem ihm von Herrn Direktor *Sioli* zur Untersuchung überlassen wurde.

Verein südwestdeutscher Irrenärzte. 147

Er hob schon klinisch ein an abweichendes Bild, daß er sich unter keiner der bekannten Krankheiten einreihen ließ, anatomisch ergab er einen von allen bisher bekannten Krankheitsprozessen abweichenden Befund.

Eine Frau von 51 Jahren zeigte als erste auffällige Krankheitserscheinung Eifersuchtsideen gegen den Mann. Bald machte sich eine stark zunehmende Gedächtnisschwäche bemerkbar, sie fand sich in ihrer Wohnung nicht mehr zurecht, schleppte die Gegenstände hin und her, verlegte sie, zuweilen glaubte sie, man wolle sie ankleiden und begann laut zu schreien.

In der Anstalt trug ihr ganzes Gebaren den Stempel völliger Ratlosigkeit. Sie ist zeitlich und örtlich gänzlich desorientiert. Gelegentlich macht sie Äußerungen, daß sie alles nicht verstehe, sich nicht auskenne. Den Arzt begrüßt sie bald wie einen Bruch und entschuldigt sich, daß sie mit ihrer Arbeit nicht fertig sei, bald schreit sie ihn, er solle sie schneiden, oder sie weist ihn voller Entrüstung mit Redensarten weg, welche andeuten, daß sie von ihm etwas gegen ihre Ehrsamkeit befürchtet. Zeitweilig ist sie völlig delirant, schlägt ihre Bettnässe umher, ruft ihren Mann und ihre Tochter und scheint Halluzinationen zu haben. Oft schreit sie viele Stunden lang mit größter Stimme.

Bei der Unfähigkeit, eine Situation zu begreifen, greift sie jedesmal in letzten Schwierigkeiten, sobald man eine Unterredung an sie anknüpfen will. Nur durch immer wiederholtes Benennen gelang es schließlich, einiges festzustellen.

Ihre Merkfähigkeit ist auch schwerste gestört. Zeigt man ihr Gegenstände, so benennt sie dieselben meist richtig, gleich darauf aber hat sie alles wieder vergessen. Beim Lesen kommt sie von einer Zeile in die andere, liest buchstabierend oder mit sinnlosen Betonung; beim Schreiben wiederholt sie einzelne Silben vielmals, läßt andere aus und verwandelt überhaupt sehr rasch. Beim Sprechen gebraucht sie häufig Verlegenheitsphrasen, entwirft paraphasische Ausdrücke (Milchgießer statt Tasse), monologisiert beobachtet man sie häufig. Manche Fingen faßt sie allerdings nicht mal. Den Gebrauch einzelner Gegenstände scheint sie nicht mehr zu wissen. Der Gang ist ungestört, sie gebraucht ihre Hände gleich gut. Die Patellarreflexe sind vorhanden. Die Pupillen reagieren. Etwas rigide Radialarterien, keine Vergrößerung der Herzdämpfung, kein Eiweiß.

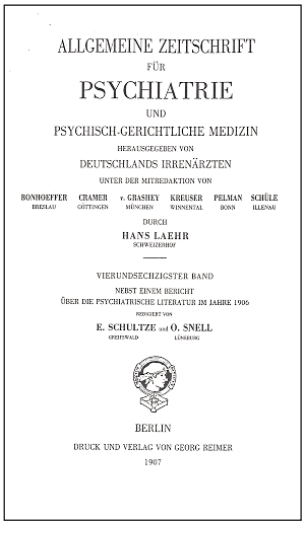
Im weiteren Verlaufe treten die als Herdsymptome zu deutenden Erscheinungen bald stärker, bald schwächer hervor. Immer sind sie nur leicht. Dagegen macht die allgemeine Verblödung Fortschritte. Nach 4½ jähriger Krankheitsdauer tritt der Tod ein. Die Kranke war schließlich völlig stumpf, mit angezogenen Beinen zu Bett gelegen, hatte unter sich gehen lassen und trotz aller Pflege Decubitus bekommen.

Die Sektion ergab ein gleichmäßig atrophisches Gehirn ohne makroskopische Herde. Die größeren Hirngefäße sind arteriosklerotisch verändert.

An Präparaten, die mit der Bielschowskyschen Silbermethode angefertigt sind, zeigen sich sehr merkwürdige Veränderungen der Neurofibrillen. In Innern einer im übrigen noch normal erscheinenden Zelle treten zunächst

10*

Figure 9. Original article reporting the first case of Alzheimer disease



ALLGEMEINE ZEITSCHRIFT
FÜR
PSYCHIATRIE
UND
PSYCHISCH-GERICHTLICHE MEDIZIN
HERAUSGEGEBEN VON
DEUTSCHLANDS IRRENÄRZTEN
UNTER DER MITREDAKTION VON
BONHOEFFER BRESLAU · CRAMER GÖTTINGEN · v. GRASHEY MÜNCHEN · KREUSER WINNENTAL · PELMAN BONN · SCHÜLE ILLENAU
DURCH
HANS LAEHR
SCHWEIZERHOF
VIERUNDSECHZIGSTER BAND
NEBST EINEM BERICHT
ÜBER DIE PSYCHIATRISCHE LITERATUR IM JAHRE 1906
REDIGIERT VON
E. SCHULTZE GREIFSWALD und O. SNELL LÜNEBURG
BERLIN
DRUCK UND VERLAG VON GEORG REIMER
1907

Figure 10. Cover of the journal in which the first case of Alzheimer disease was published.

Before reading the original medical history, and most of all before viewing the histopathology slides, doctors believed that the case could well be explained by metachromic leukodystrophy, dementia with Lewy bodies, or other entities. It is true that there are some discrepancies between the clinical history presented by Alzheimer in 1906 and the version of the same case which Perusini published years later. The latter is more complete from a clinical and anatomical pathology viewpoint, and it includes photomicrographs which, oddly enough, were not found in the original folder. With his description, Alzheimer challenged the arteriosclerotic theory of senile dementia and the concepts of presbyophrenia and true senile dementia.[45] His findings also ran counter to the earlier notion that degenerative dementia correlated to the senile period, since this patient's age clearly represented the presenile period.

E. Kraepelin was the first to publish a reference to "Alzheimer disease" in the 1910 edition of his psychiatry textbook *Psychiatrie: ein Lehrbuch für Studierende und Ärzte*.[46] Strangely enough, Nissl, who was probably Alzheimer's best friend and closest neuropathologist colleague, never used the term 'Alzheimer disease'. Kraepelin, mentioned above as having coined the term, only employed it in his textbook.[1] According to accounts by his numerous students in Munich, Alzheimer initially believed the disease to be merely an atypical or peculiar (*eigenartige*) form of senile dementia. He maintained that belief for some time, since he was still using that adjective to describe the second case he reported in 1911.[35] We can deduce that Alzheimer clearly suspected the presence of a new entity from the following words in the conclusion of his first case report:

> On the whole, it is evident that we are dealing with a peculiar, little-known disease process...We must not be satisfied to force it into the existing group of well-known disease patterns. It is clear that there exist many more mental diseases than our textbooks indicate.[48,49]

The second case was a 56-year-old man (Johann F.) with dementia who was admitted to the clinic in Munich on 12 September 1907 and who died of pneumonia on 3 October 1910. The article was prepared in considerable haste, considering that it was submitted for publication in January 1911. Johann F was the first known case to be diagnosed with Alzheimer disease; this we know based on the patient's anatomical pathology studies, discovered in 1997. Alzheimer's own handwriting on the autopsy report in the patient's file informs us that the case was confirmed as Alzheimer disease (arteriosclerotic dementia was the initial clinical suspicion).[42]

It is certainly true that the disease existed prior to Alzheimer's description, but he was the one who clearly identified it for the medical community. With this in mind, I would like to end with a quote by Piazza, who in 1911 issued a rebuttal to contemporaries who did not believe Alzheimer's disease to be a distinct entity:

> It cannot be denied that Alzheimer's greatest achievement was not framing a new disease, but rather identifying a series of cases that had previously been mistaken for senile dementia or for a combination of senile and arteriosclerotic dementia.[47]

A translation of Alois Alzheimer's first case (K. L. Bick)

> Alzheimer, Munich. A Characteristic Disease of the Cerebral Cortex
>
> Alzheimer reports the case of a patient who was kept under close observation during institutionalization in Frankfurt am Main and whose central nervous system was examined by Director Sioli. The patient showed early clinical symptoms which deviated from the common ones and could not be classified under any well-known clinical patterns. The anatomical findings were also different from those of the usual disease processes. One of the first disease symptoms of a 51-year-old woman was a strong feeling of jealousy towards her husband. Very soon she showed rapidly increasing memory impairments; she could not find her way about her home, she dragged objects to and fro, hid herself, or sometimes thought that people were out to kill her, then she would start to scream loudly. During institutionalization her gestures showed a complete helplessness. She was disoriented as to time and place. From time to time she would state that she did not understand anything, that she felt confused and totally lost. Sometimes she considered the coming of the doctor as an official visit and apologized for not having finished her work, but other times she would start to yell in the fear that the doctor wanted to operate on her; or there were times that she would send him away in complete indignation, uttering phrases that indicated her fear that the doctor wanted to damage her woman's honour. From time to time she was completely delirious, dragging her blankets and sheets to and fro, 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 was unable to understand any particular situation, she got upset any time a doctor wanted

to examine her. Only after several efforts was it possible to obtain any data.

She suffered from serious perception disorders. When the doctor showed her some objects she first gave the right name for each one, but immediately afterwards she had already forgotten everything. While reading she would omit sentences, she would spell every word or read without intonation. In a writing test she often repeated the same syllables, omitting others, and became confused and absent-minded. In her conversation she often used confused phrases, single paraphrasic expressions (milk-jug instead of cup), sometimes she would suddenly stop talking completely. She evidently did not understand many questions. She did not remember the use of particular objects. She still walked normally and had full use of her hands. Patellar reflex was present. Pupils reacted normally. She had somewhat rigid radial arteries, no cardiac hypertrophy, no albumen.

During the course of the disease symptoms appeared which could be considered focal symptoms; sometimes these were very prominent and sometimes quite faint. Mental regression advanced quite steadily. After four and a half years of illness the patient died. She was completely apathetic in the end, and was confined to bed in a fetal position (with legs drawn up), was incontinent and in spite of all the care and attention given to her she suffered from decubitus. The autopsy showed an evenly affected atrophic brain without macroscopic foci. The larger cerebral vessels showed arteriosclerotic changes.

The Bielschowsky silver preparation showed very characteristic changes in the neurofibrils. However, inside an apparently normal-looking cell, one or more single fibers could be observed that became prominent through their striking thickness and specific impregnability. At a more advanced stage, many fibrils arranged parallel showed the same changes. Then they accumulated forming dense bundles and gradually advanced to the surface of the cell. Eventually, the nucleus and the cell disappeared and only a tangled bundle of fibrils indicated the site where once the neuron had been located.

As these fibrils can be stained with dyes different from the normal neurofibrils, a chemical transformation of the fibril substance must have taken place. This might be the reason why the fibrils survived the destruction of the cell. It seems that the transformation of the fibrils goes hand in hand with the storage of an as yet not closely examined pathological product of the metabolism in the neuron. About one-quarter to one-third of all the neurons of the cerebral cortex showed such alterations. Numerous neurons, especially in the upper cell layers, had totally disappeared.

Dispersed over the entire cortex, and in large numbers especially in the upper layers, miliary foci could be found which represented the sites of deposition of a peculiar substance in the cerebral cortex. It was even possible to recognize these without staining, but they were much more evident once stained.

The glia had abundant formed fibers; in addition, many glia cells showed large deposits.

There was no infiltration of the vessels. Against this, focal lesions in the endothelium could be observed, and in some sites new vessel formation could also be seen.

On the whole, it is evident that we are dealing with a peculiar, little-known disease process. In recent years these particular disease-processes have been detected in great numbers. This fact should stimulate us to further study and analysis of this particular disease. We must not be satisfied to force it into the existing group of well-known disease patterns. It is clear that there exist many more mental diseases than our text books indicate. In many such cases, a further histological examination must be effected to determine the characteristics of each single case. We must reach the stage in which the vast well-known disease groups must be subdivided into many smaller groups, each one with its own clinical and anatomical characteristics.[48,49]

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