

OCCASIONAL PAPER

Oskar Fischer and the study of dementia

Michel Goedert

MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 0QH, UK

Correspondence to: Michel Goedert,
MRC Laboratory of Molecular Biology,
Hills Road, Cambridge CB2 0QH, UK
E-mail: mg@mrc-lmb.cam.ac.uk

The centenary of Alois Alzheimer's description of the case of Auguste Deter has renewed interest in the early history of dementia research. In his 1907 paper Alzheimer described the presence of plaques and tangles in one case of presenile dementia. In the same year, Oskar Fischer reported neuritic plaques in 12 cases of senile dementia. These were landmark findings in the history of research in dementia because they delineated the clinicopathological entity that is now known as Alzheimer's disease. Although much has been written about Alzheimer, only little is known about Fischer. The present article discusses Fischer's work on dementia in the context of his life and time.

Keywords: Alzheimer; dementia; Fischer; Kraepelin; presbyophrenia

Over the past 2 years, the centenary of Alois Alzheimer's description of the case of Auguste Deter has been marked repeatedly (Jucker *et al.*, 2006; Perry *et al.*, 2006). It seems clear that Alzheimer's name will be linked forever with one of the most common and feared diseases affecting the elderly population. Accordingly, there is much interest in his life and work. Two full-scale biographies and several articles presenting Alzheimer's work in the context of his life have been published in recent years (Maurer and Maurer, 1998; Jürgs, 1999; Dahm, 2006; Graeber, 2006; Jellinger, 2006; Goedert and Ghetti, 2007). His childhood home has been turned into a museum and conference centre. Furthermore, the clinical notes and histological slides of Auguste Deter (Alzheimer's first case) and the slides of Johann Feigl (Alzheimer's second case) have been recovered and reanalysed (Graeber *et al.*, 1997; Maurer *et al.*, 1997; Graeber, 1999; Klünemann *et al.*, 2006).

Emil Kraepelin, Director of the Royal Psychiatric Clinic in Munich, where Alzheimer worked from 1903 to 1912, named the disease after his colleague in the eighth edition of his textbook of Psychiatry, which was published in 1910 (Kraepelin, 1910). At that time, Alzheimer had published only one short paper on the subject (Alzheimer, 1907). In it, he described the combined presence of plaques and tangles in the brain of Auguste Deter, who

had suffered from presenile dementia. Four additional cases of dementia with plaques and tangles (Bonfiglio, 1908; Perusini, 1909; Sarteschi, 1909) were known to Kraepelin when he was revising his textbook. As discussed before (Amaducci *et al.*, 1986; Goedert and Ghetti, 2007), it is not entirely clear what compelled Kraepelin to separate this condition from senile dementia and to name it after Alzheimer. He mentioned the young age of the patients, language disturbances, focal signs and severe dementia as major distinguishing characteristics.

In the same year as Alzheimer, Oskar Fischer published a clinicopathological study of 16 cases of senile dementia, in which he provided the first description of the neuritic plaque (Fischer, 1907). Over the next 5 years, Alzheimer and Fischer collected additional cases and correlated clinical symptoms with neuropathological findings, extending their earlier work. Central was their use of the reduced silver staining technique developed by Max Bielschowsky a few years earlier (Bielschowsky, 1902, 1903). In view of Fischer's major contributions to the study of dementia, it is surprising how little is known about him, especially when compared with Alzheimer. In an attempt to correct this imbalance, the present article describes Fischer's work on dementia, discusses it in relation to that of his contemporaries, in particular Alzheimer, and provides some biographical information.

At the German University in Prague

Oskar Fischer (Fig. 1) was born in Slaný, a small town in central Bohemia located 25 km northwest of Prague, on April 12, 1876, where his father was the administrator of an agricultural estate. Following primary and secondary schools in Slaný, he attended the medical school at the Universities of Prague and Strasbourg. He obtained his MD degree in Prague in 1900.

At the time, what is now the Czech Republic, formed part of Austria–Hungary. In 1882, in the wake of growing Czech nationalism, the Charles University of Prague was divided into a Czech and a German University. Up to this point, there had only been a German University. The Czech University existed until 1939, when it was closed by the German occupant. It reopened in 1945. The German University was abolished in 1945 by a decree from the President of Czechoslovakia, with retroactive effect to November 17, 1939, the day the Germans had closed the Czech University (Míšková, 2007).

At the beginning of the 20th century, the majority of the population of Bohemia and Moravia used Czech as its first language, but ~25% of the population was German speaking. Prague was the third largest city of Austria–Hungary, with some 600 000 inhabitants, 30 000 of whom were German speaking. The cultural importance of the Prague Germans far outweighed their number. Besides a German University, Prague had two large German theatres, one German concert hall, five German secondary schools and two daily German newspapers (Wagenbach,



Figure 1 Oskar Fischer around the time of his 60th birthday in 1936.

1993). Rainer Maria Rilke, Franz Kafka, Egon Erwin Kisch and Franz Werfel were all born in Prague between 1875 and 1890 into families belonging to the German-speaking minority (Spector, 2000). Oskar Fischer, who spent his academic career at the German University, also belonged to this minority.

After obtaining his MD degree in May 1900, Fischer worked at the Department of Pathological Anatomy of the German University for 2 years, before he moved to the Department of Psychiatry, where he stayed until 1919. From 1886 to 1921, the Department of Psychiatry was directed by Arnold Pick, a major figure in behavioural neurology, who is now best remembered for his definition of frontotemporal dementia (Pick, 1892, 1906; Kertesz and Kalvach, 1996).

During World War I, Fischer was assigned as physician-in-chief to the Division of Neurology and Psychiatry of the second Garrison Hospital in Prague, where he treated many soldiers who had developed mental problems while fighting on the Eastern Front. It is here that he became involved in the so-called 'Halbhuber affair'. Halbhuber was a German doctor with the rank of colonel in the Austrian army and Fischer's superior. His behaviour towards soldiers traumatized at the front was brutal. He used electrotherapy with strong alternating currents on them and sent hundreds of soldiers who were in no fit state to fight, back to the front. This form of electrotherapy to treat so-called 'war neuroses' was developed in Germany by the psychiatrist Fritz Kaufmann, who used it in conjunction with strong verbal suggestion (Kaufmann, 1916). It was widely practiced by both Central and Allied powers, although only few of those treated in this manner were ever returned to the front. Most were employed instead in war-related clerical activities in their respective home countries (Eissler *et al.*, 1979; Lerner, 2003).

Fischer challenged Halbhuber, who enjoyed the support of German nationalist circles in Prague, and demanded his dismissal on grounds of sadistic behaviour and mental instability. Following a military tribunal, Halbhuber was declared insane and was removed from his post. For daring to criticize his superior, Fischer was transferred to the Barracks Hospital in Pardubice in eastern Bohemia, where he worked until the end of World War I. It was here that he met Franziska, his future wife, who was a voluntary nurse with the Red Cross. They were to have two children, the twins Lotte and Heinz. In the newly formed Czechoslovakia, Fischer was politically active, standing as a candidate for Parliament and Prague City Council on behalf of the German Democratic Liberal Party, a party with Social Democratic leanings. In 1923, while canvassing, he was beaten up by anti-Semitic students (Míšková, 2007).

It appears that Fischer had to leave his research position at the German University because he was denied tenure. During his last year at the University, he worked as an unpaid Assistant. Pick retired in 1921 and his successor was Otto Pözl. When Pözl returned to Vienna in 1928 to take up the Chair of Psychiatry, Eduard Gamper became his successor. In 1938, Gamper was dismissed during the 'Aryanization' measures enacted at the University. Two years later, he was replaced by Kurt Albrecht, a member of the SS, who became Rector of the German University in 1944. Albrecht's death in May 1945 marked the end of the

Department of Psychiatry and the German University as a whole (Hlaváčková and Svobodný, 1998; Mišková, 2007).

After his time at the University, Fischer opened a private practice for Neurology and Psychiatry in Prague. He lived in the same street as Vladimír Vondráček, Professor of Psychiatry at the Charles University from 1957 to 1970. In his memoirs, Vondráček described Fischer as 'a nice man with quite a distinctive personality who was very original' (Vondráček, 1977). Given his scientific achievements, it is difficult to understand why the newly formed and independent Czechoslovakia could not find a full Professorship for Fischer at the German University. During the time of the Austro-Hungarian Empire, he had been promoted to Assistant Professor of Psychiatry in 1907 and to Associate Professor in 1917. Fischer lectured at the German University until January 1939, when he was revoked by the University authorities. This was after the Munich Dictate of September 1938, when Czechoslovakia lost 30% of its territory, 33% of its population and 40% of its national income (Rothkirchen, 2005), and before the German invasion of Bohemia and Moravia of March 1939. The University was clearly doing the bidding of her German masters before they had even reached Prague.

Fischer continued to work in private practice until 1941, when he was arrested by the Gestapo. He was taken to the Small Fortress in Terezín (Theresienstadt) in northwestern Bohemia, that the National Socialists had turned into a political prison in 1939 (Huppert and Dori, 2005). It is located close to the garrison town of Terezín that became a Jewish ghetto in late 1941 (Adler, 1960). By 1945, overcrowding and the abysmal living conditions in the ghetto had led to the death of over 35 000 people. Furthermore, between 1942 and 1944, 83 000 people were taken from Terezín to concentration camps in the East, where only 3000 survived World War II. Despite its proximity, the Small Fortress was run separately from the ghetto. Its regime was extremely brutal and detention there for any length of time was equivalent to being handed a death sentence. Between 1940 and 1945, 2600 people died in the Small Fortress, mainly through torture and execution. With his arrest, Oskar Fischer's fate was sealed. He died in Terezín, apparently of a heart attack, on February 28, 1942.

It was at the Department of Psychiatry of the German University that Fischer carried out his groundbreaking research centred around clinicopathological correlations. Dementia was only one of the topics he worked on, although, when looking back, it probably led to his most important publications (Fischer, 1907, 1910, 1912). Other topics included tumours of the central nervous system and spongiform cortical atrophy, which Fischer named and was one of the first to describe (Fischer, 1911). Fischer's habilitation thesis was on the causes and relevance of cerebrospinal pleocytosis. Like Alzheimer, he devoted much of his work to the clinical and histological study of neurosyphilis, then a pressing problem in psychiatry. Alzheimer carried out the definitive study on the neuropathology of progressive paralysis (Alzheimer, 1904). Around this time, the artificial induction of inflammation and fever was shown to lead to clinical improvements in patients with progressive paralysis, then an incurable disease. Fischer developed a novel preparation of degraded

proteins (named phlogetan) that was used to this effect (Fischer, 1922). The best-known work in this area was by Julius Wagner-Jauregg, Professor of Psychiatry at the University of Vienna, who was awarded the 1927 Nobel Prize in Physiology or Medicine for 'his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica' (Wagner-Jauregg, 1950; Whithrow, 1993).

Early history of the plaque

In 1892, Paul Blocq and Georges Marinesco, while working at the Salpêtrière Hospital in Paris (directed by Jean-Martin Charcot), described the presence of abundant 'amas ronds' (round heaps) in the cerebral cortex from an elderly individual with epilepsy (Blocq and Marinesco, 1892). Their study compared the histopathological changes in nine patients with idiopathic epilepsy, who had died at different ages and whose brains were stained in various ways. They found round heaps in a single brain but did not comment further on their possible significance. The round heaps were identified because they were stained more strongly than the neuropil with haematoxylin–eosin and a number of other stains. Blocq and Marinesco suggested that they corresponded to nodules of glial sclerosis. Prior to this work, Beljahow (1889) had described nerve cell degeneration in senile dementia. Although somewhat vague, several of his statements have variously been interpreted as describing plaques and tangles.

In 1898, Emil Redlich, who worked at the Second Psychiatric Clinic of the University of Vienna (directed by Wagner-Jauregg), described what he named 'miliare Sklerose' (miliary sclerosis) in two cases of senile dementia (Redlich, 1898). He also referred to these structures as 'plaques', probably the first use of the now familiar denomination. Redlich used the dye carmine red to stain the cerebral cortex of a 78-year-old woman who had died with advanced dementia. Her brain was reduced in size, with the most severe atrophy in the frontal and temporal lobes of the cerebral cortex. Redlich observed the presence of large numbers of plaques in grey matter, often in proximity to degenerating ganglion cells. They were of different sizes, contained some fibrous material and tended to have a nucleus in the centre. He referred to the smaller plaques as cotton wool-like, introducing yet another term that is still in use. Like Blocq and Marinesco, Redlich also believed that plaques corresponded to a modified type of glial cell, mostly because of the presence of fibrous material. He reflected on whether glial cell proliferation could be the primary event or whether it was secondary to nerve cell degeneration. He concluded that it was a secondary event.

In 1906, Koichi Miyake from the Psychiatric Clinic of Tokyo University, who had trained in Vienna, reported on changes in the ageing cerebral cortex (Miyake, 1906). He studied 25 brains, 4 of which were from patients with dementia. Two of these had plaques that Miyake believed to be glial in origin. Alzheimer's 1907 paper is remarkable because of the description of both plaques and tangles in the brain of Auguste Deter (Alzheimer, 1907). It did not, however, advance understanding of the plaque beyond what Redlich had reported 15 years earlier.

Fischer's 1907 paper

Fischer studied the cerebral cortex of 16 cases of senile dementia using a variety of staining techniques, including Bielschowsky silver. He described the presence of plaques in 12 cases and provided the first description of what is now known as the neuritic plaque (Fig. 2). He failed to observe plaques in the brains of 10 controls, 10 cases with psychosis and 45 cases with neurosyphilis.

Unlike Blocq, Marinesco and Redlich, Fischer did not believe in a glial origin of plaques. He described them as inclusions of unknown origin and different sizes, ranging from 10 to 120 μm in diameter. The smallest plaques had a compact appearance and were embedded in what appeared to be the normal neuropil. As the plaques grew in size, they tended to consist of a core surrounded by a corona and were associated with a large number of abnormal neurites. The overall appearance of the mature plaques reminded Fischer of the histological appearance of an actinomycosis ('Aktinomycesdruse'). Subsequently, both Fischer and others often referred to plaques as 'Drusen' or 'drusige Nekrosen'. Willibald Scholz used the term in his 'drusige Entartung der Gefäße', to describe what is now known as cerebral amyloid angiopathy (Scholz, 1938). The German 'Druse' is equivalent to the English 'geode', a cavity in a rock that has its interior surface studded with crystals. Geodes are commonly found in volcanic rocks. An 'Aktinomycesdruse' resembles a typical plaque.

Fischer considered the abnormal neurites to be an important characteristic of the plaque. He described them as club-shaped and believed that their appearance resulted from proliferative changes of what were called 'neurofibrils' at the beginning of the 20th century (Bethe, 1900). They correspond to a network of fine filaments that traverses nerve cells and resemble most

closely what we now call the neuronal cytoskeleton. The term neurofibril has survived in the expressions 'neurofibrillary tangle' and 'neurofibrillary degeneration'. The neuritic changes reminded Fischer of structures that had been described before, mostly in the developing nervous system. However, he did not go so far as to describe them as regenerative. Despite their appearance, he believed them to be degenerative. One year after Fischer, Hübner also described the presence of neuritic plaques in cases of senile dementia (Hübner, 1908).

Fischer described plaques in 12 of 16 cases with senile dementia. This led him to investigate whether the clinical symptoms distinguished the 12 cases from the other four. He found that the cases with neuritic plaques had features compatible with a clinical diagnosis of presbyophrenia, whereas the cases devoid of plaques had simple senile dementia characterized by general mental decline. Fischer concluded that the 'drusige Nekrose' was the pathoanatomical substrate of presbyophrenia. He was of the opinion that presbyophrenia and simple senile dementia were two different diseases.

Presbyophrenia refers to a subtype of dementia characterized by confabulations, disorientation, marked memory impairment for recent events, hyperactivity and elevated mood (Berrios, 1986, 1990). The term was coined by Ludwig Kahlbaum in 1838 but it did not become widespread until its reintroduction by Carl Wernicke (1906). Over the next two decades, presbyophrenia was commonly used, before it disappeared progressively with the redefinition of dementia in terms of impaired cognition.

Fischer's 1910 paper

This paper of nearly 100 pages provides a comprehensive pathological and clinical description of a large number of cases with

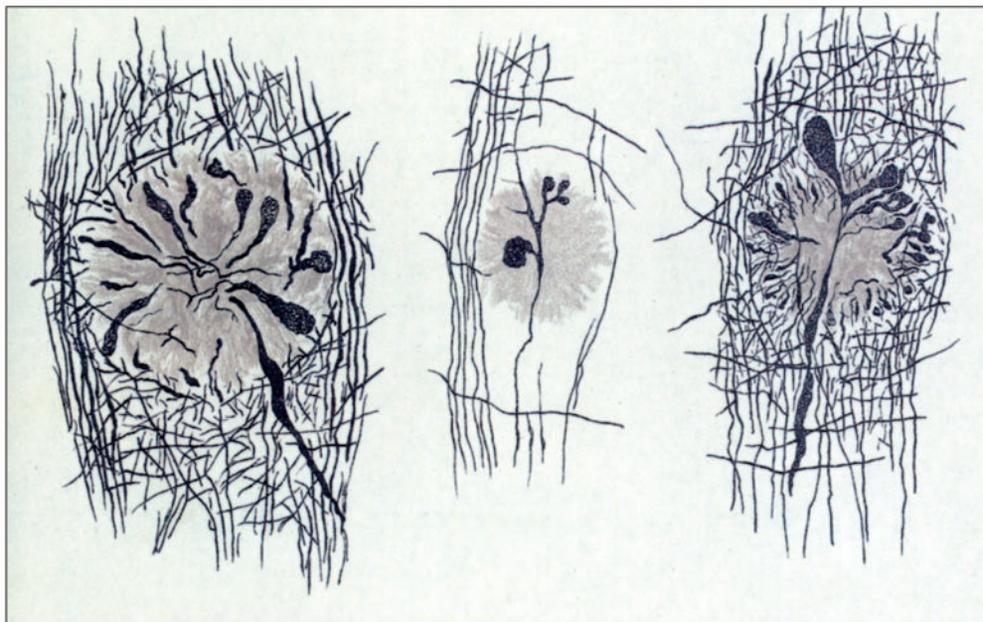


Figure 2 Drawings of three neuritic plaques from the brains of patients with senile dementia. Compiled from the illustrations of Fischer's 1907 paper. Note the abnormal, club-shaped neurites and the displacement of normal-looking fibrils in the space occupied by the plaques.

plaques. Fischer studied a total of 275 brains from cases of psychosis, neurosyphilis and controls of various ages, with 110 being over 50 years old at the time of death. He found plaques in 56 cases, all of whom were >50 years of age. He confirmed his findings of 1907 and proposed that the 'drusige Nekrose', which he now referred to as *Sphaerotrichia multiplex cerebri* (to reflect the spherical nature and filamentous organization of the plaque) was the defining pathological characteristic of presbyophrenic dementia. Of the 56 cases with plaques, 42 exhibited a clinical picture of presbyophrenia, as defined by Wernicke. The remaining 14 cases were more varied but exhibited at least some presbyophrenic features. Of the 275 cases examined, only 2 fell outside the proposed classification, in that they had plaques with a clinical picture of simple dementia. Fischer did note, however, that the abundance of plaques in these 2 cases was much lower than in the 56 cases with presbyophrenic dementia and that their brains showed no signs of atrophy. Solomon Carter Fuller reported similar observations the following year (Fuller, 1911). Fischer speculated that, had these individuals lived longer, they would have gone on to develop abundant plaques and the clinical symptoms of presbyophrenia. In addition to his previous observations, Fischer now also described neurofibrillary tangles in a subset (17%) of cases with plaques (Fig. 3).

Besides the sheer number of cases studied in great clinical and neuropathological detail, this paper is remarkable for its comprehensive and insightful description of the plaques. Fischer found them to be concentrated in cortical grey matter, with the heaviest load in frontal cortex, followed by temporal cortex. He observed smaller numbers of plaques in thalamus, striatum and cerebellum but not in brainstem or spinal cord. Based on morphological

criteria, Fischer distinguished eight types of plaques (Fig. 4). Stage I consisted of little star-like fibrous structures embedded in the normal neuropil. Over time, several of these structures, Fischer referred to them as 'Morgensterne' (morning stars), merged (stage II) and displaced normal-looking neurites that bent around them. Stage III was characterized by an increase in plaque size and the presence of abnormal material outside the star-like structures, giving rise to a spoke-like appearance. The plaques of stage IV looked like wheels, with a star-like core linked to a fibrous sphere through several spokes. The largest plaques made up stage V; they had a homogeneous appearance and were made of thick fibrous material.

Stage VI referred specifically to the association of plaques with blood vessels. Fischer described examples of perivascular deposits and of blood vessel walls infiltrated by what appeared to be the same abnormal material, resulting in the destruction of the vessel wall. The vascular abnormalities associated with senile dementia were first described by Gustav Oppenheim from the University of Freiburg (Germany) in 1909. He found 'drusige Nekrosen' next to hyalinized blood vessels in about half of the autopsied brains of individuals with senile dementia and speculated that the material deposited in the capillaries was the same as that in the 'Drusen' (Oppenheim, 1909). Fischer's description of 1910 was more comprehensive than Oppenheim's and provided the first illustration of what is now known as 'cerebral amyloid angiopathy'. Neither Oppenheim nor Fischer made the connection between cerebral amyloid angiopathy and intracerebral haemorrhage. It was only established many years later (Neumann, 1960). Stage VII was characterized by the presence of fine fibrous material inside the plaque that Fischer interpreted as a sign of destruction. Finally,

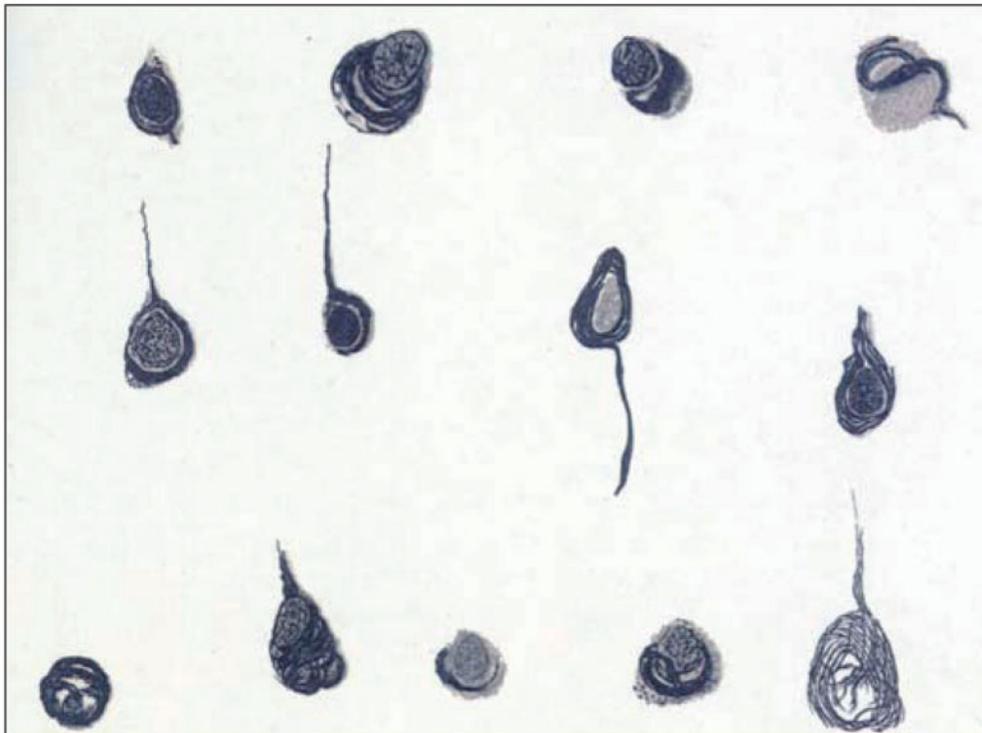


Figure 3 Drawings of neurofibrillary tangles from the brains of patients with senile dementia. Reproduced from Fischer's 1910 paper.

Stage VIII was quite distinct, in that it consisted of a massive, diffuse infiltration of cortical grey matter by what looked like the same fibrous material found at the periphery of the more mature plaques. Ganglion cells located within these infiltrations appeared to be degenerating.

Fischer believed that plaque stages I–V formed a continuum extending from early to late clinical stages. He observed a close relationship between disease duration and plaque stage. The longer the duration of disease, the older the plaques appeared. Plaque stages I–III were associated with an average disease duration of 6 months, stages III and IV with an average duration of 19.5 months and stages IV and V with an average duration of 37 months. Fischer was not sure where stages VI and VII fitted in but tended towards classifying them as late stages. Stage VIII, by contrast, was considered to be an early stage in brain tissue that was unusually susceptible to the deposition of fibrous material. Club-shaped abnormal neurites were associated with approximately 50% of plaques. Most of these were at stage V, with some stage IV and a few stage III plaques also being affected. Stages I and II were not associated with club-shaped neurites.

Fischer concluded that *Sphaerotrichia cerebri multiplex* was a specific brain disease in the clinical and pathological-anatomical sense. Unlike most of his contemporaries who focused on clinical classification, he used a characteristic pathological change to delineate a clinical condition that he believed to be identical with presbyophrenic dementia.

Fischer's 1912 paper

The third and final paper brings the number cases with a pathology of *Sphaerotrichia multiplex cerebri* and a clinical picture of presbyophrenic dementia identified by Fischer to 72. Of these, 21% also exhibited tangles, which Fischer referred to as 'grobfaserige Fibrillenwucherung der Ganglienzellen' (coarse-fibred proliferation of ganglion cell fibrils). There were no cases with tangles without plaques but Fischer drew attention to such a case that had been reported by Schnitzler. It was probably a case of Pick's disease (Schnitzler, 1911). Although the link between the presence of abundant 'Drusen' and presbyophrenic dementia was strong, Fischer also observed presbyophrenic symptoms in a subset of patients with arteriosclerotic dementia (10 out of 44 cases), in the absence of plaques. He called this condition 'arteriosclerotic pseudopresbyophrenia' and concluded that distinct disease processes could give rise to a similar clinical picture. Fischer reported 42 additional cases with senile psychosis, who lacked plaques and did not suffer from presbyophrenic dementia.

He was aware of the fact that the frequent occurrence of abundant plaques in old people without mental impairment could fatally undermine his view that the plaque represents the morphological substrate of presbyophrenic dementia. He therefore investigated the brains of 35 normal individuals aged 60–93 years and found plaques in only 2 cases, which he believed to be indicative of presymptomatic disease. These individuals showed no signs of brain atrophy. It therefore seemed unlikely that plaques were the remnants of degenerated nerve cells. Following a lengthy discussion about possible plaque constituents based on their staining

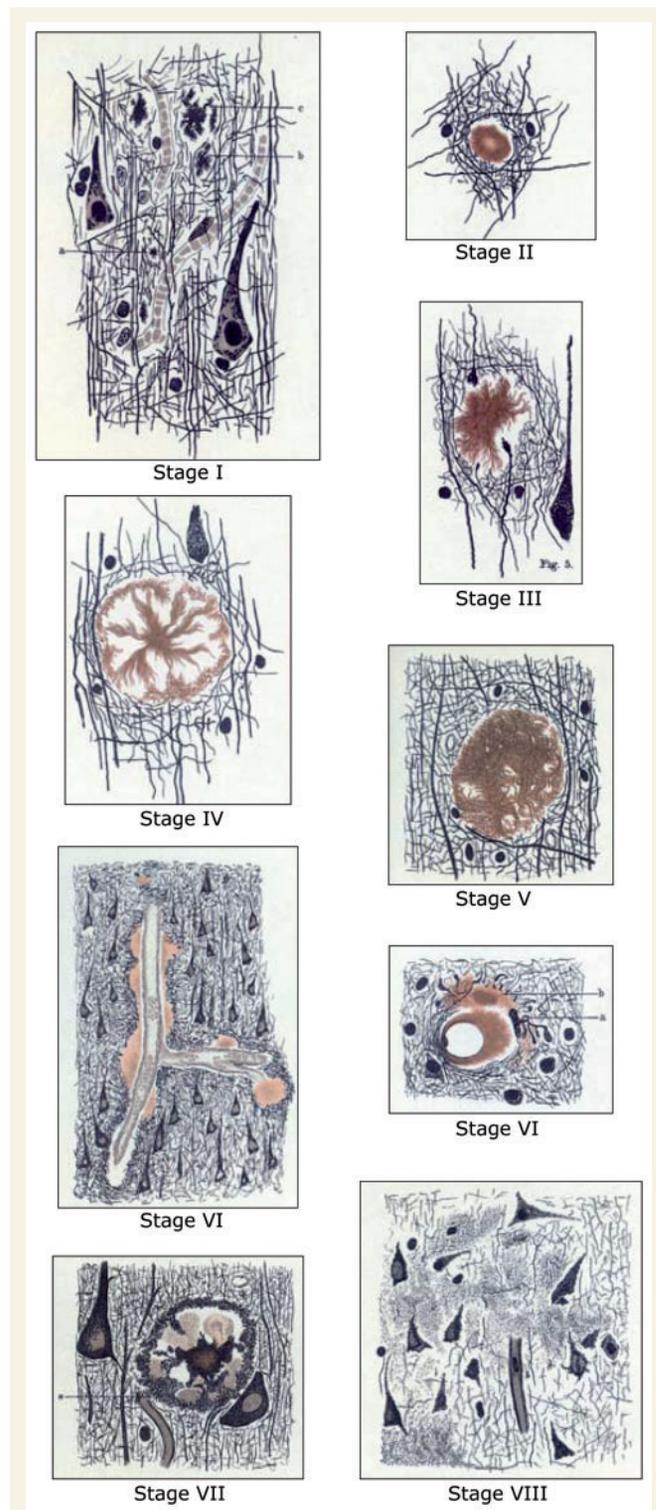


Figure 4 Drawings of plaque stages I–VIII from the brains of patients with senile dementia. Compiled from the illustrations of Fischer's 1910 paper. Fischer believed that plaque stages I–V formed a continuum. Abnormal, club-shaped neurites were frequently found in association with plaque stages III–V but not with stages I or II.

characteristics, Fischer concluded that plaques were made of a proteinaceous metabolic brain product.

In this paper, Fischer also responded to criticisms on his 1907 and 1910 papers. They centred mainly on the link between presbyophrenic dementia and the presence of 'Drusen'. Teophil Simchowicz and Walther Spielmeyer, while acknowledging Fischer's contributions, were of the opinion that the 'Drusen' were characteristic of senile dementia (Simchowicz, 1911). Simchowicz was the first to use the term 'senile plaque'. What he identified as senile dementia was most similar to simple dementia, a condition Fischer believed to be devoid of plaques. Spielmeyer considered plaques to be a manifestation of normal ageing, whereas Fischer saw them as pathological, even when present in small numbers in an otherwise asymptomatic patient. Fischer's views were remarkably modern. He separated dementia from normal ageing and considered clinical signs not to be decisive by themselves for diagnosis. Instead, he considered the presence in abundance of an identifiable morphological substrate—the 'Druse'—as the defining criterion.

Fischer and Alzheimer

When viewed together, Fischer and Alzheimer described neuritic plaques and neurofibrillary tangles. What gave them the edge over others was their use of the Bielschowsky silver staining technique in cases of dementia. In 1907, Alzheimer described the co-occurrence of plaques and tangles, whereas Fischer described neuritic plaques. This renders their respective contributions complementary, more so because it is now known that paired helical and straight tau filaments are major components of both tangles and abnormal neurites (Goedert and Spillantini, 2006). It is surprising that it was Alzheimer who went on to discover what was later called the 'Pick body' in two cases of Pick's disease (Alzheimer, 1911), whereas Fischer, who worked in the Department directed by Pick from 1903 to 1919, does not appear to have examined cases of frontotemporal dementia histologically.

Alzheimer's paper of 1911 and Fischer's papers of 1910 and 1912 show two scientific rivals at the height of their powers. Like others, Alzheimer took issue with Fischer's insistence on a link between presbyophrenic dementia and plaques. Although he agreed that plaques were particularly abundant in cases of presbyophrenic dementia, he did not believe them to be pathognomonic for this condition. He considered plaques to be a histological hallmark of senile dementia that did not, however, cause the disease. Alzheimer credited Fischer with having drawn attention to the relevance of plaques for the diagnosis of senile dementia. He considered his own cases of presenile dementia (Alzheimer's disease) and Fischer's cases of presbyophrenic dementia to be atypical cases of senile dementia. In his 1911 paper, Alzheimer confirmed Fischer's 1907 discovery of the neuritic plaque.

Fischer stood by his distinction between presbyophrenic dementia and simple senile dementia. In the 1912 paper, he also presented and discussed four cases of the entity Kraepelin had named after Alzheimer (only three of these had a presenile age of onset). Fischer did not believe in the existence of a separate Alzheimer's

disease and classified these cases as atypical forms of presbyophrenic dementia.

Fischer and Alzheimer also disagreed on the origin of the tangle. Fischer thought that the coarse-fibred fibril proliferation formed *de novo* and that the constituent material was unrelated to neurofibrils. Alzheimer, by contrast, believed tangles to consist of chemically modified neurofibrils. Fischer considered tangles to be a particularly severe abnormality of ganglion cells that was causing their demise. However, since he found them in only 21% of cases, he did not believe that they were diagnostic of presbyophrenic dementia. Alzheimer believed in the central importance of tangles, even though his second case (Johann Feigl) appears to have lacked them in cerebral cortex. Neither Fischer nor Alzheimer suspected an association between tangles and neuritic changes. It was Bielschowsky who proposed such a link in his paper on a case of Alzheimer's disease published in 1911. He concluded that the changes at the level of cell bodies, axons and dendrites were caused by the deposition of the same unknown substance. (Bielschowsky, 1911). Like Fischer before him, Bielschowsky identified up to eight different plaque stages.

Fischer's interest in extrasensory perception

During a visit to Vienna in 1916, Fischer met Raphael Schermann, the well-known graphologist and psychic (Hayek, 1921). Over the next 2 years, Fischer and Schermann met in Vienna and Prague on 27 separate occasions. At each meeting, Fischer put Schermann to the test by asking him to describe in detail the character, physical appearance and life story of individuals unknown to him, based on a sample of their handwriting or on Fischer picturing them in his own mind. At the time, Fischer was working at the Barracks Hospital in Pardubice. This explains why his meetings with Schermann were clustered, often taking place daily for periods of 7–10 days, with lengthy intervals in-between. Fischer published the results of these investigations in his 1924 book entitled 'Experimente mit Raphael Schermann. Ein Beitrag zu den Problemen der Graphologie, Telepathie und des Hellsehens' (Experiments with Raphael Schermann. A contribution to the study of graphology, telepathy and clairvoyance) (Fischer, 1924). This unusual book purports to study the paranormal in a rigorous and empirical manner. As a by-product, several of the reported case studies throw light on Fischer's own life and personality.

The book describes in detail the 27 sessions, during which Fischer tested Schermann in a total of 280 separate experiments. For each experiment, Fischer decided on whether the outcome was a success, a failure or neither. The overall success rate was 65%, with 27% failures and 8% uncertain responses. Fischer concluded that extrasensory perception was a real phenomenon that could be studied scientifically. This was the time when invisible rays (radium and X-rays) entered public consciousness. Accordingly, Fischer postulated the existence of an unknown energy which, when released from cortical ganglion cells of one individual, was able to influence the equivalent nerve cells in the cerebral cortex of a second individual, resulting in the transfer of

psychic phenomena. Fischer wished to continue his study of Schermann's psychic powers after 1918 but this was rendered impossible by Schermann's unwillingness to cooperate any further.

In the memorandum of 1921 entitled 'Psychoanalysis and telepathy', written for his inner circle and published posthumously, Sigmund Freud discussed Schermann's psychic powers (Freud, 1941). Freud was less impressed by Schermann than Fischer and bemoaned that the analysis of telepathic phenomena tended to concentrate on successes, while ignoring the many failures. On the subject as a whole, Freud nonetheless admitted to a 'favourable prejudice in favour of telepathy', but he believed it to be irrelevant for psychoanalysis.

In the ensuing years, Fischer became a well-known expert in graphology and extrasensory perception whose advice was frequently sought after. He was a member of the Editorial Board of the 'Zeitschrift für Parapsychologie' and was called as an expert witness for the prosecution in the trial 'Hanussen—a case of precognition or fraud?', which was held in Litoměřice (Leitmeritz) in northwestern Bohemia in 1929. Erik Jan Hanussen (alias Herschmann Steinschneider) was one of the best-known magicians and clairvoyants of the time (Gorden, 2001; for a fictional account of Hanussen's life, see Feuchtwanger, 1944). Although he claimed to be descended from Danish nobility, he was of Jewish extraction and grew up in Moravia. Hanussen stood accused of duping citizens of Czechoslovakia through superstition and other deceptive means. Despite the prosecution's efforts to expose him as a fraud, Hanussen was acquitted following a demonstration of his psychic powers to the court. He then moved to Berlin, which he took by storm. In March 1932, Hanussen predicted that within a year the National Socialist party would be in power and that Adolf Hitler would be Reichschancellor. Later that year he is said to have given Hitler elocution lessons. The following year, Hanussen was accused of being implicated in the plot that led to the burning of the Reichstag. He was arrested by the SA and executed in March 1933.

World War I and its immediate aftermath were marked by a revival of spiritualism in many countries. Fischer's own interest in extrasensory perception seems to have stemmed from his desire to understand more about the brain–mind conundrum. Since Fischer's time, the study of the paranormal has moved firmly to the outer fringes of the scientific discourse because of a lack of evidence for the existence of genuine paranormal phenomena (Randi, 1982; Macknik *et al.*, 2008).

The sanatorium at Veleslavín

In 1908, with his cousin Leo Kosák, Fischer bought an estate in Veleslavín, on the outskirts of Prague, that they transformed into a sanatorium for the mentally ill. They ran it together until 1939, when the sanatorium was confiscated by the German occupant. In 1942, Kosák was taken to the ghetto of Terezín, from where he was deported to Auschwitz in October 1944, in what was the last transport leaving Terezín for the East.

For >30 years, Fischer and Kosák were in charge of the sanatorium; Fischer also lived on its grounds for some of this time. In 1917, Milena Jesenská, the future journalist, translator and friend

of Kafka (Kafka, 1952), then 20 years old, was committed to the Veleslavín sanatorium for nine months at the behest of her father, who was Professor of Oral Surgery at the Czech University in Prague, because of 'a pathological lack of moral concepts and feelings' (Stach, 2008). When aged 21 years, Jesenská discharged herself, married Ernst Pollak, the man her father loathed, left Prague and moved to Vienna. The sanatorium at Veleslavín entered national consciousness in December 1918, when Tomáš Masaryk returned from exile as the first President of an independent Czechoslovakia (Zeman, 1990). Charlotte, Masaryk's American wife, who had stayed in Prague during World War I with three of their four children, suffered from bouts of depression requiring hospitalisation. In 1918, she was a patient at Veleslavín. On the day of his inauguration, Masaryk visited her at the sanatorium, where he was greeted by Fischer and Kosák. Until her death in 1923, Charlotte Garrigue Masaryk spent much time at the sanatorium in Veleslavín, where her husband was a frequent visitor.

Prague and Munich

Why do we speak today of Alzheimer's disease and not of Alzheimer-Fischer's disease or of Fischer's disease? It is interesting to speculate why Alzheimer's work is remembered so much better than Fischer's. This was not always the case. Early on, plaques were often referred to as 'Fischer's plaques' or 'Redlich-Fischer's' plaques (see for instance Schröder, 1911; Uyematsu, 1923; Divry, 1927). Alzheimer also mentioned Fischer's plaques in his 1911 paper. Presbyophrenic dementia and Alzheimer's disease were used interchangeably for many years (see for instance Stoddard, 1913). In successive editions of Bleuler's standard textbook of Psychiatry in German, including the eighth published in 1949, the relevant heading read 'Alzheimer's disease (and the presbyophrenia of O. Fischer)' (Bleuler, 1949). However, by the ninth edition published in 1955, it had been shortened to 'Alzheimer's disease' (Bleuler, 1955). Fischer's work was now discussed under this heading and the concept of presbyophrenia was said to be obsolete. The progressive disuse of presbyophrenic dementia will no doubt have contributed to the neglect Fischer's work has suffered.

When it comes to his scientific legacy, Fischer was not helped by either the time and place he lived in. He left his research position at the German University in 1919 and his right to teach there was forcibly removed in 1939. He died tragically in 1942 as one of the millions of innocent victims of the National Socialist regime. The German University ceased to exist in 1945, following a long history of German nationalism, anti-Semitism and, in its final years, collaboration with the German occupant (Rothkirchen, 2005). Following the Prague coup of February 1948, Czechoslovakia came under Communist rule until the Velvet Revolution of November 1989. Given all this, it is not difficult to see how Fischer's contributions came to be forgotten. He does not appear to have had any students who could have continued his work and there never was a Prague school of neuropathology. The German and Czech Universities were at odds throughout their parallel existence and it is therefore hardly surprising that after 1945

there was no great desire in Czechoslovakia to keep the memory of the German University alive.

Contrast this with Alzheimer. He worked at the Clinic whose head, Kraepelin, had not only named the disease after him, but was also one of the most influential psychiatrists of the time. The tradition of the Munich Institute continued for many years, even if the Institute itself underwent several changes in the process. Alzheimer was one of the founders of what became known as the Munich school of neuropathology. When he left Munich for Breslau in 1912, Spielmeyer, one of the pre-eminent histopathologists of the time, succeeded him. When Spielmeyer died in 1935, Scholz became his successor. Following a rather inglorious period in the late 1930s and early 1940s under the directorship of Ernst Rüdin (Weber, 1996), the Munich Institute was reconstituted after World War II as the Max-Planck-Institute of Psychiatry located in Munich's Kraepelinstrasse. The memory of Alzheimer's contributions was kept alive through all these years.

Kraepelin defined Alzheimer's disease as a rare form of presenile dementia. It was only in the 1970s that it became widely accepted that most patients with clinically defined senile dementia (onset of disease after 65 years) have very similar pathological changes in their brains as patients in their presenium with Alzheimer's disease (Ballenger, 2006). As a result, rather than change the name of the disease, the concept of Alzheimer's disease was widened significantly (Katzman, 1976; Katzman and Bick, 2000). This redefinition, more than anything, turned Alzheimer into a household name, synonymous with the most common form of severe, age-related memory loss.

Acknowledgements

I am most grateful to Mrs Hana Fischerová for Figure 1, original documents and information on her father-in-law, Professor Oskar Fischer. I thank Dr Miloš Pojar, Dr Dagmar Hájková and Dr Eva Kosáková for crucial insights. Dr Kosáková also kindly provided the family memoir written by Dr Viktor Kosák, the son of Dr Leo Kosák. I am indebted to Prof. Jiří Raboch and Dr Lucie Nawková for their hospitality in Prague and for organizing my visit to the Archives of the Charles University. I am grateful to Dr Nawková for her translations from Czech into English. Special thanks go to Mr Ian Walker, Mrs Wanda Bullock and Mrs Nathalie Cornée from the Library of the MRC Laboratory of Molecular Biology for tracking down dozens of articles from times past and to Mrs Mary-Ann Starkey from the Neurobiology Division for her help with the manuscript.

Funding

Funding for open access charge: MetLife Foundation.

References

- Adler HG. Theresienstadt 1941-1945. Das Antlitz einer Zwangsgemeinschaft. Göttingen: Wallstein; 1960.
- Alzheimer A. Histologische Studien zur Differentialdiagnose der progressiven Paralyse. Nissl-Alzheimers Histol Histopathol Arb Hirnr 1904; 1: 1–297.
- Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. Allg Z Psychiat 1907; 64: 146–8.
- Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. Z ges Neurol Psychiat 1911; 4: 356–85.
- Amaducci LA, Rocca WA, Schoenberg BS. Origin of the distinction between Alzheimer's disease and senile dementia. Neurology 1986; 36: 1497–9.
- Ballenger JF. Self, senility, and Alzheimer's disease in modern America. Baltimore: Johns Hopkins University Press; 2006.
- Beljahow S. Pathological modifications in the brains of demented patients. J Ment Sci 1889; 35: 261–2.
- Berrios GE. Presbyophrenia: the rise and fall of a concept. Psychol Med 1986; 16: 267–75.
- Berrios GE. Alzheimer's disease: a conceptual history. Int J Geriatr Psychiat 1990; 5: 355–65.
- Bethe A. Über die Neurofibrillen in den Ganglienzellen von Wirbeltieren und ihre Beziehungen zu Golginetzen. Arch mikr Anat 1900; 55: 513–58.
- Bielschowsky M. Die Silberimprägnation der Achsenzylinder. Neurol Centralbl 1902; 21: 578–84.
- Bielschowsky M. Die Silberimprägnation der Neurofibrillen. Neurol Centralbl 1903; 22: 997–1006.
- Bielschowsky M. Zur Kenntnis der Alzheimerschen Krankheit (präsenilen Demenz mit Herdsymptomen). J Psychol Neurol 1911; 18: 1–20.
- Bleuler E. Lehrbuch der Psychiatrie. Achte Auflage. Berlin: Springer; 1949.
- Bleuler E. Lehrbuch der Psychiatrie. Neunte Auflage. Springer: Berlin; 1955.
- Bloccq P, Marinesco G. Sur les lésions et la pathogénie de l'épilepsie dite essentielle. Sem Méd 1892; 12: 445–6.
- Bonfiglio F. Di speciali reperti in uno caso di probabile sifilide cerebrale. Rev Sper Freniatr 1908; 34: 196–206.
- Dahm R. Alzheimer's discovery. Curr Biol 2006; 16: R906–10.
- Divry P. Etude histo-chimique des plaques séniles. J Belge Neurol Psychiat 1927; 27: 643–57.
- Eissler KR. Freud und Wagner-Jauregg vor der Kommission zur Erhebung militärischer Pflichtverletzungen. Wien: Löcker; 1979.
- Feuchtwanger L. Die Brüder Lautensack. London: Hamish Hamilton; 1944.
- Fischer O. Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz. Monatsschr Psychiat Neurol 1907; 22: 361–72.
- Fischer O. Die presbyophrene Demenz, deren anatomische Grundlage und klinische Abgrenzung. Z ges Neurol Psychiat 1910; 3: 371–471.
- Fischer O. Der spongiöse Rindenschwund, ein besonderer Destruktionsprozess der Hirnrinde. Z ges Neurol Psychiat 1911; 7: 1–33.
- Fischer O. Ein weiterer Beitrag zur Klinik und Pathologie der presbyophrenen Demenz. Z ges Neurol Psychiat 1912; 12: 99–135.
- Fischer O. Bemerkungen zur phlogetischen (Leukozytose)-Therapie und über ein neues Mittel für die Therapie der Metalues. Med Klinik 1922; 28: 1–11.
- Fischer O. Experimente mit Raphael Schermann. Ein Beitrag zu den Problemen der Graphologie. Telepathie und des Hellsehens. Berlin: Urban & Schwarzenberg; 1924.
- Freud S. Psychoanalyse und Telepathie. Gesammelte Werke. Siebzehter Band. Schriften aus dem Nachlass. London: Imago Publishing Co; 1941. p. 25–48.
- Fuller SC. A study of the miliary plaques found in brains of the aged. Am J Insan 1911; 58: 147–219.
- Goedert M, Ghetti B. Alois Alzheimer: his life and times. Brain Pathol 2007; 17: 57–62.
- Goedert M, Spillantini MG. A century of Alzheimer's disease. Science 2006; 314: 777–81.
- Gorden M. Erik Jan Hanussen. Los Angeles: Feral House; 2001.

- Graeber MB. No man alone: the rediscovery of Alois Alzheimer's original cases. *Brain Pathol* 1999; 9: 237–40.
- Graeber MB. Alois Alzheimer. <http://www.ibro.info>.
- Graeber MB, Kösel S, Egensperger R, Banati RB, Müller U, Bise K, et al. Rediscovery of the case described by Alois Alzheimer in 1911: historical, histological and molecular genetic analysis. *Neurogenetics* 1997; 1: 73–80.
- Hayek M. *Der Schriftendeuter Rafael Schermann*. Leipzig: EP Tal & Co; 1921.
- Hlaváčková L, Svobodný P. *Biographisches Lexikon der deutschen medizinischen Fakultät in Prag 1883-1945*. Praha: Karolinum; 1998.
- Hübner AH. Zur Histopathologie der senilen Hirnrinde. *Arch Psychiat Neurol* 1908; 46: 598–609.
- Huppert J, Dori H. *Theresienstadt*. Prague: Vitalis; 2005.
- Jellinger KA. Alzheimer 100 – highlights in the history of Alzheimer research. *J Neural Transm* 2006; 113: 1603–23.
- Jucker M, Beyreuther K, Haass C, Nitsch R, Christen Y, editors. *Alzheimer: 100 Years and Beyond*. Heidelberg: Springer; 2006.
- Jürgs M. *Alzheimer. Spurensuche im Niemandsland*. München: List; 1999.
- Kafka F. *Briefe an Milena*. Frankfurt-am-Main: S. Fischer; 1952.
- Katzman R. The prevalence and malignancy of Alzheimer disease. *Arch Neurol* 1976; 33: 217–8.
- Katzman R, Bick KL. The rediscovery of Alzheimer disease during the 1960s and 1970s. In: Whitehouse PJ, Maurer K, Ballenger JF, editors. *Concepts of Alzheimer disease*. Baltimore: Johns Hopkins University Press; 2000. p. 104–14.
- Kaufmann F. Die planmäßige Heilung komplizierter psychogener Bewegungsstörungen bei Soldaten in einer Sitzung. *Münchener Med Wochenschr* 1916; 63: 802–4.
- Kertesz A, Kalvach P. Arnold Pick and German neuropsychiatry in Prague. *Arch Neurol* 1996; 53: 935–8.
- Klünemann HH, Fronhöfer W, Werner-Füchtenbusch J, Grasbon-Frodol E, Kloiber S, Wurster HW, et al. Characterization of the kindred of Alois Alzheimer's patient with plaque-only dementia. *Alzheimer Dis Assoc Disord* 2006; 20: 291–4.
- Kraepelin E. *Psychiatrie. Ein Lehrbuch für Studierende und Ärzte*, 8. Auflage, Band II: *Klinische Psychiatrie*. Leipzig: Barth; 1910.
- Lerner P. *Hysterical Men. War, Psychiatry and the Politics of Trauma in Germany, 1890-1930*. Ithaca, NY: Cornell University Press; 2003.
- Macknik SL, King M, Randi J, Robbins A, Teller, Thompson J, et al. Attention and awareness in stage magic: turning tricks into research. *Nat Rev Neurosci* 2008; 9: 871–879.
- Maurer K, Maurer U. *Alois Alzheimer. Das Leben eines Arztes und die Karriere einer Krankheit*. München: Piper; 1998.
- Maurer K, Volk S, Gerbaldo H, Auguste D. and Alzheimer's disease. *Lancet* 1997; 349: 1546–9.
- Míšková A. Die deutsche (Karls)-Universität vom Münchener Abkommen bis zum Ende des zweiten Weltkrieges. Praha: Karolinum; 2007.
- Miyake K. Beiträge zur Kenntnis der Altersveränderungen der menschlichen Hirnrinde. *Obersteiner's Arb* 1906; 13: 212–59.
- Neumann MA. Combined amyloid vascular changes and argyrophilic plaques in the central nervous system. *J Neuropathol Exp Neurol* 1960; 19: 370–82.
- Oppenheim G. Über "drusige Nekrosen" in der Grosshirnrinde. *Neurol Centralbl* 1909; 28: 410–13.
- Pick A. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prager med Wochenschr* 1892; 17: 165–7.
- Pick A. Über einen weiteren Symptomenkomplex im Rahmen der Dementia senilis, bedingt durch umschriebene stärkere Hirnatrophie (gemischte Apraxie). *Monatsschr Psychiat Neurol* 1906; 24: 97–108.
- Perry G, Avila J, Kinoshita J, Smith MA, editors. *A century of scientific and clinical research*. Amsterdam: IOS Press; 2006.
- Perusini G. Über klinisch und histologisch eigenartige psychische Erkrankungen des späteren Lebensalters. *Nissl-Alzheimers Histol Histopathol Arb Hirnr* 1909; 3: 297–351.
- Randi J. *Flim-Flam! Psychics, ESP, Unicorns and Other Delusions*. Amherst, New York: Prometheus Books; 1982.
- Redlich E. Über miliare Sklerose der Hirnrinde bei seniler Atrophie. *Jahrb Psychiat Neurol* 1898; 17: 208–16.
- Rothkirchen L. *The Jews of Bohemia and Moravia*. Jerusalem: Yad Vashem; 2005.
- Sarteschi U. Contributo all'istologia patologica della presbifrenia. *Riv Sper Freniatr* 1909; 35: 464–84.
- Schnitzler JG. Zur Abgrenzung der sogenannten Alzheimerschen Erkrankung. *Z ges Neurol Psychiat* 1911; 7: 34–57.
- Scholz W. Studien zur Pathologie der Hirngefäße II. Die drusige Entartung der Hirnarterien und -capillaren. *Z ges Neurol Psychiat* 1938; 162: 694–715.
- Schröder GE. Beitrag zur Kenntnis der Fischerschen Plaques im Gehirn und ihrer klinischen Bedeutung. *Z ges Neurol Psychiat* 1911; 5: 16–22.
- Simchowicz T. Histologische Studien über die senile Demenz. *Nissl-Alzheimers Histol Histopathol Arb Hirnr* 1911; 4: 267–444.
- Spector S. *Prague Territories. National Conflict and Cultural Innovation in Franz Kafka's fin de siècle*. Los Angeles: University of California Press; 2000.
- Stach R. *Franz Kafka. Die Jahre der Erkenntnis*. Frankfurt-am-Main: S. Fischer; 2008.
- Stoddard WHB. Case of presbyophrenia (Alzheimer's disease). *Proc R Soc Med* 1913; 6: 13–14.
- Uyematsu S. On the pathology of senile psychosis. The differential diagnostic significance of Redlich-Fischer's miliary plaques. *J Nerv Ment Dis* 1923; 57: 1–24; 131–56; 237–60.
- Vondráček V. *Lékař dále vzpomíná*. Praha: Avicenum; 1977.
- Wagenbach K. *Kafkas Prag. Ein Reiselesebuch*. Berlin: Wagenbach; 1993.
- Wagner-Jauregg J. *Lebenserinnerungen*. Schönbauer L, Jantsch M, editors. Wien: Springer; 1950.
- Weber MM. Ernst Rüdin, 1874-1952: a German psychiatrist and geneticist. *Am J Med Genet* 1996; 67: 323–31.
- Wernicke C. *Grundriss der Psychiatrie*. Leipzig: Thieme; 1906.
- Whitrow M. *Julius Wagner-Jauregg (1867-1940)*. London: Smith-Gordon; 1993.
- Zeman Z. *The Masaryks*. London: Tauris & Co; 1990.