EIGHT

A labyrinth of tangles: Alzheimer's disease

In the photographs taken of her in 1902, Auguste Deter looks older than her 52 years. Her husband has brought her to the psychiatric clinic in Frankfurt am Main, because he is no longer able to care for her at home. Auguste is confused and restless. She suffers from paranoia and is convinced that her husband is carrying on with the woman next door. At times she doesn't even recognize him as her husband. The family doctor notes in his referral that her memory is seriously affected, and that she suffers from insomnia. His diagnosis is 'paralysis of the brain'. On 26 November 1901, the day after her admission, Alois Alzheimer has a conversation with his new patient.[1] The first sentence in the dossier reads: 'Sitting up in bed, expression distraught'. He asks her what her name is. 'Auguste'. Last name? 'Auguste'. What is your husband's name? 'I think it's Auguste'. Are you married? 'To Auguste'. When Alzheimer asks her how long she has been there, she says 'three weeks'. He shows her various objects: a pencil, a pen, a key, a cigar. She is able to identify them, but shortly

[1] K. Maurer and U. Maurer, *Alzheimer. Das Leben eines Arztes und die Karriere einer Krankheit* (Munich, 1998). The opening chapter contains extensive quotations from the notes which Alzheimer made in the dossier.

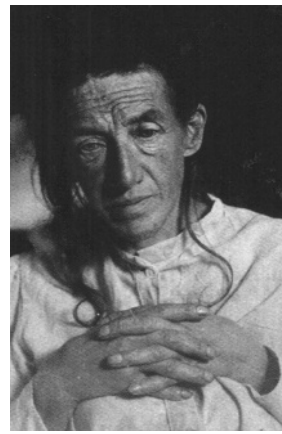

Figure 8.1: Auguste Deter (52), the 'first Alzheimer's patient'

afterwards when Alzheimer asks her to name the objects without showing them to her, she has forgotten everything. When the noon meal (cauliflower and pork) is served, he asks her what she is eating. 'Spinach'. He asks her to write down 'Mrs Auguste Deter', but after 'Mrs' she's forgotten what she was supposed to write. Two days later, Alzheimer notes on her chart: 'Constantly distraught, anxious', and a day later 'distraught, resists everything'. He asks her where she thinks she is now, when she was born, what her name is. She is unable to answer any of the questions. Auguste would ultimately spend almost five years in the clinic. Towards the end she lay in bed, dazed and incontinent, her legs drawn up, in a condition which Alzheimer described as 'total feeble-mindedness'.

In 1995, Auguste Deter's file was rediscovered in the archives of the Frankfurt clinic, where it had been filed under the wrong year. Two years later, five photographs were also found.[2] The desperation which had made such an impression on Alzheimer is written all over her face. Auguste died in the spring of 1906. In the sections which

[2] On the dossier and the photos: K. Maurer, S. Volk and H. Gerbaldo, 'Auguste D. and Alzheimer's disease', *The Lancet*, 349 (1997), 1546–9.

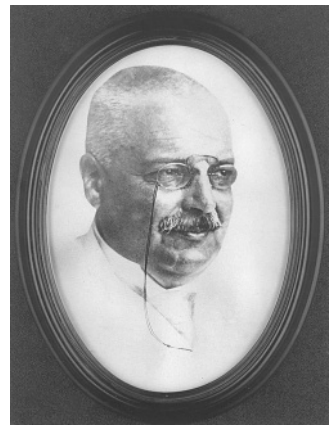

Figure 8.2: Alois Alzheimer (1864–1915)

Alzheimer took from her brain he found the tissue abnormalities characteristic of what is today known as Alzheimer's disease.

Alzheimer, neuropathologist

Alois Alzheimer (baptised Aloysius) was born in 1864 as the son of a notary in the town of Marktbreit, near Würzburg, Germany.[3] After finishing secondary school, he decided to study medicine. He had already opted for Würzburg, as it was close to home and his half-brother Karl was already at the university there. But his father was more ambitious than Alois himself (indeed, his entire life he would be surrounded by people with more ambition than he had), and he sent his son to Berlin, then the Mecca of medicine. This was the institute where, in 1882, Robert Koch had discovered the tuberculosis bacillus and then, in 1883, the year that Alzheimer began his studies, the pathogen responsible for cholera. But, after one semester, Alois

[3] J.-E. Meyer, 'Alois Alzheimer (1864–1915)' in K. Kolle (ed.), *Grosse Nervenärzte* (Stuttgart, 1959), vol. II, pp. 30–8. For a biography which combines Alzheimer's life with information on Alzheimer's disease, see M. Jürgs, *Alzheimer. Spurensuche im Niemandsland* (Munich, 1999).

packed his bags and headed for Würzburg. The extracurricular activities offered by the Corps Franconia left little time for study, and during a sabre duel, he incurred a scar that ran from his left eye to his chin. It was not until the 1884–1885 winter semester that Alzheimer began to take his medical studies seriously. He was drawn to forensic psychiatry and microscopic tissue study and from then on there was no stopping him. In 1887, he completed a dissertation devoted to the glands that produce ear wax. Alzheimer was an excellent draughtsman and, as in his later work, he used stunning drawings of tissue sections to illustrate his dissertation. The following year he took the last of his medical exams. He was then 23 years old and ready for the next step in his career.

In late 1888, he applied for the position of assistant physician at the Asylum for Lunatics and Epileptics in Frankfurt. He already had some psychiatric experience, having recently returned from a five-month journey as private physician to a mentally ill woman. He also made mention of the lectures and laboratory sessions in microscopic pathology which he had attended. The director of the institution, Emil Sioli, sent him a telegram to inform him that the job was his. The salary was 1,200 marks a year, including room and board. Alzheimer found in Sioli a kindred spirit. Both men endorsed the principle of non-restraint. Like Korsakoff, who that same year (1888) took over as head of a psychiatric clinic in Moscow, they strived to introduce a type of nursing devoid of any form of coercion, such as isolation cells and straitjackets. The premises lent themselves to this striving. The institution was set amid spacious parks and gardens, and the various pavilions reflected the psychiatric classifications then in use: calm lunatics, agitated lunatics, the feeble-minded and epileptics. Sioli also saw to it that the dissection lab cum mortuary (a cramped and malodorous hall in the centre of the building) was replaced by a free-standing, well-lit dissection laboratory.

During the day, Alzheimer made the rounds of the various wards, and yet he saw himself primarily as a neuropathologist. Indeed, he

rendered his greatest service to his patients after their death: in the evenings he would sit down at his microscope to examine the nerve tissue collected during post mortem examinations. A few months after Alzheimer joined the staff, a second promising neuropathologist arrived in Frankfurt: Franz Nissl. His departure from Munich, where he worked in the laboratory of Bernhard von Gudden, was prompted by a drama that took place in the summer of 1886.[4]

Von Gudden, together with three prominent psychiatrists, had been asked to draw up a declaration of insanity for Ludwig II of Bavaria. The king suffered from a persecution complex combined with delusions of grandeur, and the plan was to temporarily depose him, so that he could be treated. Von Gudden had Berg Castle on Lake Starnberg made ready, and late in the afternoon of 13 June, Von Gudden and his patient took a stroll through the adjacent park, followed at a distance by two male nurses. They saw Ludwig whisper something in Von Gudden's ear, after which the physician motioned to them to retreat. Several hours later the bodies of the king and the doctor were found floating in Lake Starnberg. The circumstances surrounding the deaths have never been fully clarified. The most probable scenario is that Ludwig, who the day before had just barely been prevented from committing suicide, ran into the lake, followed by Von Gudden. Traces found in the mud of the lake floor seemed to indicate that at some distance from the shore, Von Gudden had succeeded in grabbing the king by his collar, after which a struggle ensued. It is conceivable that Ludwig (41 years old, muscular and weighing in at 120 kilos) held the 62-year-old physician under water and then drowned himself. The bodies were found close together.

The tragedy had a devastating effect on Nissl's personal life. As a medical student, he had won a competition organized by Von Gudden which focused on pathological changes in brain cells. His

[4] E. Grünthal, 'Bernhard von Gudden' in Kolle (ed.), *Grosse Nervenärzte*, vol. I, pp. 126–34.

Figure 8.3: Von Gudden's microtome. The brain to be sliced was lowered into the cylinder (a). Using the setscrew (c), the anatomist could slide the brain upwards, micrometre by micrometre, in the direction of the knife, which was drawn across the surface (b). To ensure that the specimen did not adhere to the knife, the procedure was carried out under water, and the membrane floating in the water was scooped up in a saucer. Von Gudden reported that he had taken some 810 specimens from a monkey's brain measuring 4.5 cm in diameter, which would mean that they were only around 0.055 mm thick. It is clear from the design of the microtome that the Biedermeier style (1815–1848) had even found its way into anatomical laboratories, albeit somewhat belatedly

entry described a method of impregnating nerve cells with magenta red in order to make their structure visible. Later he would use methylene blue to that same end, a technique which is still known as the Nissl stain. Immediately after graduation, Von Gudden took him on as assistant physician. Von Gudden had himself given his name to a neurological innovation. Because the brain is made up of very soft tissue, it is extremely difficult to slice it into sections. In 1875, Von Gudden designed a device called a microtome, which made it possible to cut sections over the full length of the brain.[5]

The sudden death of Von Gudden knocked Nissl totally off-balance. His research stagnated and his health began to suffer, and after a stay in a spa, he decided to apply for the position of second physician

[5] B. von Gudden, 'Über ein neues Microtom', *Archiv für Psychiatrie*, 5 (1875), 229–31.

in the Asylum for Lunatics and Epileptics in Frankfurt. He and Alzheimer became good friends and respected colleagues, working together for many years. In 1894, Nissl was a witness at Alzheimer's wedding. The circumstances of this marriage were no less tumultuous than those surrounding Nissl's arrival in Frankfurt.

The Heidelberg physician, Wilhelm Erb, had a patient suffering from syphilis, a certain Otto Geisenheimer. He was originally from Frankfurt, but at the age of 20 he had gone to New York, where he made a fortune in the gem trade. When he was 38, he returned to Frankfurt intent on finding a wife, and in 1883 he married Cecilia Wallerstein (23), likewise from a well-to-do Jewish family. Geisenheimer was suffering from what was then called 'softening of the brain'. In 1892, Erb accompanied the Geisenheimers on a scientific expedition through North Africa, serving as their personal physician. They had just arrived in Algeria when Geisenheimer's condition worsened. Erb sent a telegram to Alzheimer, who had specialized in the study of syphilis and had experience as a private physician, requesting him to come as quickly as possible and to accompany the couple home. Despite excellent care, Geisenheimer died shortly after the group reached Nice. It may have been on the trip home, or perhaps somewhat later, but Alois and Cecilia fell in love and were married in April 1894. The marriage made Alzheimer financially independent.

In Frankfurt, the couple lived well. Every day, Cecilia went into town by coach, to buy the artwork and antiques which gradually filled their home. Eight maids saw to the housekeeping, and there were frequent dinners and receptions. Cecilia, who had lived in New York for a time and travelled extensively with Geisenheimer, brought with her a sophistication to which Alois was not born, but which fitted him like a glove. As Kraepelin later recalled, 'Alzheimer appreciated comfort and smoked a great deal'.[6] This is reflected in photographs: there are few if any pictures of Alzheimer *without* a cigar, and in his

[6] Quoted in Jürgs, *Alzheimer*, p. 95.

mid-thirties he already had an embonpoint which betrayed a talent for living the good life. Two daughters and a son were born to the couple in quick succession.

In February 1901, the death of Cecilia brought to an end what Nissl described as 'an extremely happy marriage'.[7] At 36, Alzheimer was now a widower with three young children. His sister Elisabeth, eight years his junior, moved in with him and helped to raise the children. Alzheimer's conversations with Auguste took place during what must have been the most miserable year in his life.

A trail of cigarette butts

In the autumn of 1903, Alzheimer moved to Munich, together with his children and Elisabeth. Emil Kraepelin, director of the Royal Psychiatric Clinic, had asked him to head the Anatomical Laboratory. It was not possible to offer him a salary, but then Alzheimer had no need of one. On the third floor there was a large, well-lit room fully equipped for pathological research. Underneath the windows were rows of microscopes on long tables and a *camera lucida*, which was used to draw microscopic sections. The laboratory had a microtome as well as cameras to photograph sections, at the time a new technique. There were two telephones on the wall for phoning in results. The laboratory was visited by students and guest researchers from all over the world: indeed, the visitors' list reads like a compendium of eponyms. There was Friedrich Heinrich Levy, who later moved to the United States and changed his name to Frederic Lewy. He is remembered for the Lewy bodies which he discovered in 1912 in the brains of Parkinson patients, and which consist of protein deposits.[8] Two other guest researchers were

[7] F. Nissl, 'Zum Andenken A. Alzheimers', *Allgemeine Zeitschrift für Psychiatrie*, 73 (1917), 96–107 (107).

[8] B. Holdorff, 'Friedrich Heinrich Lewy (1885–1950) – Initiator der Erforschung der Parkinson-Krankheit' in G. Nissen and F. Badura (eds.), *Schriftenreihe der Deutschen Gesellschaft für Geschichte der Nervenheilkunde* (Würzburg, 2001), pp. 67–79.

Hans-Gerhard Creutzfeldt and Alfons Jakob, who independently of one another described the deadly virus disease which bears their name. Every morning and every afternoon, Alzheimer did the rounds of twenty workplaces, invariably with a cigar. He pulled up a stool, took as long as necessary to explain what was to be seen, and then moved on, leaving behind a trail of cigar stubs. Not only did he work for nothing, he also bore the cost of employing draughtsmen and photographers, and financed the purchase of the necessary equipment.

Alzheimer himself set up a research programme focusing on the possible relationship between abnormalities of the nervous system and such conditions as epilepsy, schizophrenia, Huntington's chorea and multiple sclerosis. But his speciality was 'progressive paralysis', also known as 'dementia paralytica', a syndrome which in the larger cities accounted for 30 to 40 per cent of admissions to psychiatric hospitals. As is now known, and was then suspected, progressive paralysis is caused by a syphilis infection. It affected two to three times as many men as women, more soldiers than clergymen, and bachelors more often than married men. From 1888, just after his arrival in Frankfurt, until his departure in 1903, Alzheimer studied no fewer than 320 cases.[9] As he had done with Auguste, he held long talks with his patients, during which he casually introduced short exercises designed to test memory, concentration and powers of abstraction. After the death of a patient, he carried out a post mortem examination of the brain and spinal cord. Progressive paralysis, popularly known as 'softening of the brain', is the result of severe but diffuse damage to the nervous system. It manifests itself in a wide variety of symptoms. Alzheimer: 'Memory and judgement, emotion and will are the first to be affected. The patient becomes increasingly cut off from the outside world, since he finds it more and

[9] A. Alzheimer, *Histologische Studien zur Differentialdiagnose der progressiven Paralyse* (Jena, 1904).

more difficult to process the impressions which reach him from his surroundings, and to relate the few things which do register with him to his own personality. Soon he also loses all self-awareness and judgement.'[10] What Alzheimer wrote about the final stage could also have been written about a patient in the early stages of dementia: 'His powers of observation become blunted, his old memories and experiences no longer resonate, his interests intermingle and ultimately fade away. Nothing remains of his earlier personality.'[11] In the end, the patient is overcome by agitation, delusions, memory loss and paralysis. Alzheimer submitted this account as *Habilitationschrift*, earning him the coveted 'venia legendi', which qualified him to teach at the university. It was awarded in the summer of 1904, a few months after Gilles de la Tourette died in a Swiss asylum from the effects of syphilis.

On Christmas Day 1904, Alzheimer surprised his children by announcing that they were all going to Wessling am See, where they had spent their summer vacation that year. They were astonished: Now? In the middle of winter? Hans Alzheimer would later recount how his father and the rest of the family boarded the steam train to Wessling, how the children tramped through the snow that covered the frozen lake, and finally arrived at a large door set in a wall. Father tried the door handle: locked. Then he reached into his pocket and pulled out a huge key: 'Shall we see if this fits?'.[12] The children stared open-mouthed as the door swung open with a grating sound, revealing a staircase covered in moss. At the top of the stairs, in the dazzling winter light, they saw what their father had bought: an enormous white villa, complete with gardens, outbuildings and a boathouse. The Alzheimer family would spend many weekends and vacations there, often together with aunts and uncles and their offspring, who were given a warm welcome. To this day, the house is still in the family.

[10] Cited in Maurer and Maurer, *Alzheimer*, p. 152. [11] *Ibid.* [12] *Ibid.* p. 156.

Plaques and tangles

In April 1906, Alzheimer received a telephone call from Frankfurt: Auguste Deter was dead. He asked the caller to send not only her brain, but also her medical dossier. It consisted of some thirty pages. Re-reading his own notes, Alzheimer reconstructed a course which even today is characteristic of patients with this disease. At home, her memory began to fail and she wandered restlessly around the house, hiding things and then forgetting where. As for cooking a meal, she no longer knew where to begin. After her admission, she became even more disoriented. She thought she was living in Kassel (where she was born), and that Alzheimer was a guest in her house ('My husband will be home soon!'), and she had no idea what year it was or how long she had been in the institution. She told him she had a daughter of 52 but a little later mentioned that she herself was 56, without noticing the inconsequence. It is clear from the verbatim accounts of these interviews that many automatisms remain intact for some time. Auguste could recite the months of the year without a hitch, except that she was unable to name the eleventh month. When asked 'how much is nine times seven?', she answered '63', but when the question was 'If you buy six eggs at seven pfennig apiece, how much do you have to pay?', the answer was 'Poached'. Often she felt around her as if she were blind, running her hands over the faces of her fellow patients. Towards evening she would become quite anxious and restless, wandering through the wards with her bedclothes draped around her. Sometimes there was no other solution but an isolation cell, despite the non-restraint policy. No doubt Alzheimer realized early on how important the case of Auguste was. In addition to the extensive documentation and the photos, the dossier contained correspondence recording Sioli's opposition to plans to transfer her to another institution. Before his departure, Alzheimer made him promise to follow developments closely. He didn't want to run the risk of her being buried before he received word of her death. A few sketchy notes documented her final

days: 'Evening of April 6: is very groggy; whimpers from time to time, perspiring heavily. April 7: very groggy all day, temperature 41 in the afternoon, in the evening 40. April 8: died at quarter to five in the morning. Cause of death: blood poisoning as a result of bedsores.'

In his letter to Sioli, in which he thanked him for sending the brain and the dossier, Alzheimer mentioned that he intended to give a lecture on Auguste's case in Tübingen in November 1906, at a regional meeting of psychiatrists and neurologists. He did indeed give the lecture, but it proved to be a great disappointment.

According to the text of the lecture, which appeared in the *Allgemeine Zeitschrift für Psychiatrie* in 1907, Alzheimer first presented the clinical picture as he himself had recorded it in Frankfurt:[13]

> In the institution her whole manner betrays total despair. She is completely disoriented in both time and place. From time to time she makes a remark about not understanding what is going on or not being able to remember something. Sometimes she greets the doctor as if he is a guest and apologizes for not having finished her work, and the next time she screams at him, accusing him of wanting to cut her with a knife, or indignantly orders him to leave in terms that suggest she fears for her virtue. From time to time she is completely delirious, she lugs parts of her bedclothes around with her, calls for her husband and her daughter, and appears to suffer from auditory hallucinations. Often she has frightful screaming fits that go on for hours at a time.[14]

The autopsy revealed that large portions of the cerebral cortex had atrophied. Alzheimer displayed slides of various sections, pointing out the irregularities he had found in the nerve tissue: strange tangles and albumin deposits. He had also done drawings of several of those tangles. In Alzheimer's view, these abnormalities did not fit any of the known categories of disease. Everything pointed in the direction of a previously unknown condition, and he expressed the hope

[13] A. Alzheimer, 'Über eine eigenartige Erkrankung der Hirnrinde', *Allgemeine Zeitschrift für Psychiatrie*, 64 (1907), 146–8.

[14] Alzheimer, 'Erkrankung', 146.

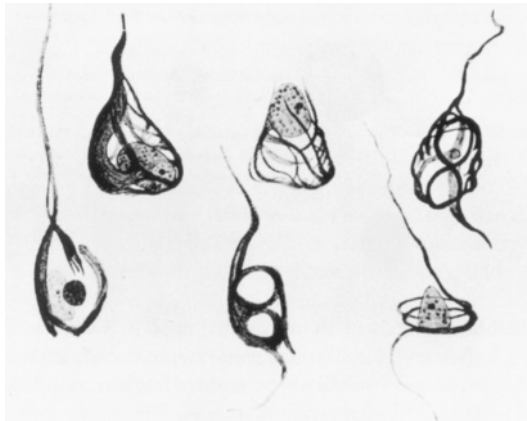

Figure 8.4: Alzheimer's drawing of the 'tangles' which he had found in the brain of Auguste D

that continuing neuropathological research would help to define the boundaries of the disease.

Thus it was in Tübingen that an audience consisting of his peers got their first glimpse of the malformations referred to as 'tangles' and 'plaques', which to this day point to a diagnosis of Alzheimer's disease. But this historic moment passed unnoticed. When Alzheimer finished speaking, the chairman opened the floor for discussion. No one in the audience felt the urge to speak, nor had the chairman prepared any questions. Alzheimer sat down again. The next speaker was then introduced, whose subject was 'the analysis of psychotraumatic symptoms'. For the remainder of the afternoon those present (including Carl Gustav Jung, who had come all the way from Zurich) engaged in a heated debate on the scientific value of psychoanalysis. The following day, the local newspaper published a detailed account of the impassioned arguments which had been voiced for and against Freud. A single line was devoted to a 'remarkable and grave pathological process which, over a period of four and a half years, led to a sharp decline in the number of nerve cells'.[15]

[15] Cited in Maurer and Maurer, *Alzheimer*, p. 211.

'We sit here so happy together'

What, then, was the state of affairs in 1907? There was a clinical description based on a single female patient, a neuropathological analysis of her brain, and one publication in a scientific journal. Alzheimer was aware that this was a slender basis on which to identify a new disease. One of his guest researchers, the Italian Gaetano Perusini, was asked to search for similar cases. He found three patients, all of whom had died shortly after admission and whose remains were available for neuropathological examination. One of them, a basket-maker who spent his days pacing back and forth in his room, anxious and disoriented, and immediately forgot everything, was even younger than Auguste – only 45 years old. The other two were 63 and 65 respectively. Perusini also reanalysed the case of Auguste, and in 1908 he presented a detailed account of his findings.[16] On the basis of Auguste's dossier, he sketched the details which, in a thousand unhappy variations, are today regarded as characteristic of the contact with Alzheimer patients: '27 November 1901. When the doctor comes over to her bed, she says (with a worried expression), "You don't have a very good opinion of me, do you?" "Why?" "I don't know. We've never been in debt or anything like that. It's just that I'm confused. Don't be angry with me."'[17] The brains of all four patients were subjected to a detailed pathological examination. The energetic Italian researcher studied sections taken from all parts of the brain, from the frontal lobe to the cerebellum and from the top to the brainstem, using twenty different colouring methods. In each case, he found the plaques and tangles which Alzheimer had described.

[16] This account would not appear until 1909: G. Perusini, 'Über klinisch und histologisch eigenartige psychische Erkrankungen des späteren Lebensalters', in F. Nissl and A. Alzheimer (eds.), *Histologische und histopathologische Arbeiten*, 3 (1909), 297–351.

[17] Perusini, 'Klinisch', p. 297.

Meanwhile, Alzheimer himself continued his research. In November 1907, a patient was admitted to his clinic with the same clinical symptoms displayed by Auguste. He followed the man, a 56-year-old day labourer named Johann Feigl, until his death.[18] In this patient, too, a number of automatisms initially remained intact: he managed to get half-way through the 'Our Father'. He could button his coat and, at Alzheimer's request, he was able to strike a match and light up a cigar. But less than six months later, when the same request was made, he rubbed the cigar helplessly against a matchbox. Alzheimer's notes read: '5 May 1908: Other patients have taught him to sing. When asked to, he will launch into the folk song "*Wir sitzen so fröhlich beisammen*" ("We sit here so happy together"). He needs constant prompting for the words, but usually manages to get the melody right.' '12 June 1908. Out in the garden he walks very quickly, stopping for no one. If he is not interrupted, he does the same lap over and over, bathed in sweat; all the while he holds the long panels of his coat wrapped around his hand, clutching them tightly. In bed, he does the same thing with the blanket.' '14 December 1908. He urinates and defecates wherever he happens to be. He no longer speaks and is constantly fussing with his bedclothes or his coat. When prompted by others, he still sings *Wir sitzen so frohlich beisammen*.' '3 October 1910. Dies of pneumonia.'[19] Alzheimer carried out the post mortem himself. The convolutions of the frontal lobe and the temporal lobes were considerably narrowed: 'The grooves were wide open.'[20] The dissection book contains (in Alzheimer's handwriting) the diagnosis of the unfortunate day labourer: '*Alzheimer'sche Krankheit*'. It was to Kraepelin that he owed the eponym. He regarded it as a questionable honour.

[18] The details of Feigl's illness appear in A. Alzheimer, 'Über eigenartige Krankheitsfälle des späteren Alters', *Zeitschrift für die gesamte Neurologie und Psychiatrie*, 4 (1911), 356–84.

[19] Alzheimer, 'Krankheitsfälle', 360–1. [20] *Ibid.* 360–2.

The Linnaeus of psychiatry

As far as his academic career was concerned, Alzheimer went through life in a state of sovereign nonchalance. Having published his dissertation at the age of 23, he seemed to be on his way, and yet he didn't get around to writing his *Habilitationsschrift* until after he turned 40. That was a good ten years too late. He does not appear to have been interested in prestigious positions outside the university, and this betrayed a somewhat laconic philosophy of life. He could afford to be nonchalant, given his financial independence, but it was also an attitude which was inherent in his character. This is reflected in the unusually generous praise which he bestowed on others in his articles, even when he could have claimed the honour for himself: praise for Perusini, who had carried out such solid pathological research, for Nissl, who had developed such brilliant colouring methods, for Bonfiglio who in 1908 had described a comparable case, for Fischer who in 1907 discovered deviant hearths in the cerebral cortex, and for Redlich who (as Alzheimer later learned) had discovered plaques in the brain of senile patients as far back as 1898. The moment tributes appeared to be heading his way, he immediately deflected them in the direction of colleagues, assistants and predecessors. The fact that he was able to do the work he did, at the scientific heart of neurology, and that his research received the visibility it deserved, was not to the credit of Alzheimer himself. It was thanks to the man who was the driving force behind a great many German careers.

Mention a trait which is typical of Alzheimer, and Kraepelin represents the opposite.[21] To begin with, Emil Kraepelin, eight years older than Alzheimer, resolved while he was still a student that he would receive a professorship by the time he turned 30, and he did. Alzheimer did not become a professor until he was 48. Kraepelin did

[21] Kurt Kolle is the author of a splendid biographical portrait: 'Emil Kraepelin (1856–1926)' in Kolle (ed.), *Grosse Nervenärtze*, vol. I, pp. 175–86.

not marry money; on the contrary, in 1883, at the age of 27, he wrote a psychiatric handbook in the hope that the proceeds would allow him to marry the girl he had been engaged to since he was 15. Every few years he revised his handbook, which expanded with each new edition, until it encompassed four hefty volumes. In 1926, three days before his death, he dictated the foreword to the ninth edition. It contained the latest categorization of psychiatric disorders which he had drawn up and which had earned him the eponym 'the Kraepelin classification' and the nickname 'the Linnaeus of psychiatry'. A lesser-known eponym was 'Kraepelin sekt', an insipid lemonade which the dour teetotaller introduced after he was appointed director of the clinic, together with a total ban on alcohol. Their enjoyment of stimulants was just one more area in which Kraepelin and Alzheimer had different tastes. But perhaps the greatest contrast was the fact that, in the republic of letters, Alzheimer felt himself surrounded by colleagues, Kraepelin by rivals. From the Royal Psychiatric Clinic in Munich, Kraepelin kept a keen eye out for openings, not because he had ambitions to fill them himself, but in order to ensure the appointment of kindred spirits. That demanded influence, wielded from a position on the editorial board of journals and the executive committee of neuropsychiatric societies. He had no affinity with Alzheimer's favourite activity, looking down a microscope. While he had attracted promising pathologists and put them to work in a superbly equipped laboratory, he himself was never seen anywhere near a microscope. Once in a great while he would make an appearance on the third floor. 'He strode through the vast halls', one of his assistants later recalled, 'taking everything in with great interest. Before he left the lab, everyone looked at him in expectation. "Well, well, well. I see that the anatomical mills grind slowly!" said the man whose word was law in German psychiatry.'[22]

[22] Cited in Maurer and Maurer, *Alzheimer*, p. 167.

While Alzheimer felt perfectly at home in the microworld of brain tissue, Kraepelin delighted in traversing the wider world of conferences, guest lectures and study tours. This meant that someone had to be appointed to serve as deputy director in his absence. In Kraepelin's view, there was no more suitable candidate than Alzheimer. The man himself disagreed. He hated anything that took him away from his work, and for some time he resisted Kraepelin's repeated urgings. When he finally allowed himself to be persuaded, he agreed only on condition that immediate steps would be taken to find a deputy for the deputy. Not surprisingly, for the first few years that search proved fruitless. According to his biographers, in 1908 alone Alzheimer had to substitute for Kraepelin for almost five months.

In the early spring of that year, Kraepelin left for Switzerland, where he remained for six weeks, preparing the eighth edition of his handbook. He was also in the process of revising the section on 'senile dementia'.[23] Toward the end of that section, he recorded the fact that Alzheimer had discovered a characteristic group of cases which displayed marked cell changes. First, he presented an overview of the major symptoms, together with Alzheimer's neuropathological findings. This was followed by the attribution of the eponym, albeit formulated with a certain reserve:

> At present, the clinical significance of Alzheimer's disease is still unclear. While on the basis of anatomical findings, one would be inclined to believe that what we see here is an exceptionally severe form of senile dementia, that finding is in a sense contradicted by the fact that the disease often begins around the age of 50. In such cases, one might be more inclined to lean towards a diagnosis of 'senium praecox', while in fact it is probably only a curious clinical picture which presents more or less independently of age.[24]

[23] E. Kraepelin, 'Das Seniele Irresein' in *Psychiatrie, ein Lehrbuch für Studierende und Ärzte* (8th edn, Leipzig, 1910), vol. II, pp. 594–630.

[24] Kraepelin, 'Seniele', pp. 625–6.

Here, Kraepelin concurred with the argument put forward by Alzheimer in Tübingen in 1906. In a clinical and neurological sense, the symptoms resemble senile dementia, also known as *Altersblödsinn* or *Greisenblödsinn*, but Auguste was only around 50 when she fell ill. Perhaps there was such a thing as '*pre*-senile dementia'. But, if so, was this a *different* disease from senile dementia, or an atypically early onset of the same disease?

Alzheimer revisited this issue in 1911. By then, he had at his disposal Perusini's three new cases, the Feigl case, and another patient who did not begin to display the clinical signs of senile dementia 'until he was in his late sixties'.[25] The ages of the patients now ranged from 45 (Perusini's basket-maker), 51 (Auguste), 56 (Feigl), 63 and 65 (Perusini), to the 'late sixties' (Alzheimer). 'Thus,' Alzheimer concluded, 'there appears to be no valid reason to regard these cases as caused by an exceptional course of the disease. They are senile psychoses, atypical forms of senile dementia.'[26] The irony of the case is that Alzheimer's disease is now universally regarded as an age-related disease, while in 1906 Alzheimer himself believed that he had discovered a new disease because his patient was relatively young. Today, many people are surprised to hear that someone in his early fifties, or even younger, can fall prey to Alzheimer's disease.

What prompted Kraepelin to bestow an eponym the clinical significance of which was 'still unclear'? This question has given rise to a number of speculations.[27] Did he seize the first opportunity that presented itself to reward his faithful deputy? Was he trying to emphasize the productivity of his Munich laboratory? Did he hope to beat his Prague colleague Arnold Pick to the mark, whose associate Oskar Fischer authored publications on neuropathological

[25] Alzheimer, 'Krankheitsfälle', 383. [26] *Ibid.* 384.

[27] M. M. Weber, 'Aloys Alzheimer, a coworker of Emil Kraepelin' in *Journal of Psychiatric Research*, 31 (1997) 6, 635–43.

abnormalities in senile dementia in the same year as Alzheimer?[28] We will never know exactly what Kraepelin's motives were, since he did not discuss the subject. As the pope of German psychiatry, he was simply in a position to bestow this kind of honorary prize and he took advantage of that fact. By the time the eighth edition of his handbook appeared in the summer of 1910, Alzheimer's name had been firmly attached to the disease.

War and nerves

In 1912, Alzheimer was called to assume a post in Breslau, as professor and director of the psychiatric clinic at Friedrich-Wilhelm University. He would be taking over the chair which for close to twenty years had been occupied by Carl Wernicke, the man who gave his name to Wernicke's aphasia and Wernicke's disease (later in part incorporated into the Korsakoff syndrome). The appointment was a source of 'great satisfaction' to Alzheimer, Kraepelin later wrote, 'since although he was fully aware of his inner worth, he suffered from the fact that his position was not commensurate with his importance'.[29] We do not know whether this is what led Alzheimer to accept the new position: there is something decidedly Kraepelinian about the presumed motive. And in the same breath, Kraepelin noted that Alzheimer's departure meant that 'the high point of his scientific career lay behind him'.[30] This may have been a reference to the administrative tasks which awaited him in Breslau, or the transition from Munich to a provincial town; or perhaps he was aggrieved because Alzheimer was leaving his laboratory. We know that he had previously sabotaged

[28] O. Fischer, 'Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz', *Monatschrift für Psychiatrie und Neurologie*, 22 (1907), 361–72.

[29] E. Kraepelin, 'Lebensschicksale deutscher Forscher (Alzheimer, Brodmann, Nissl)', *Münchener Medizinische Wochenschrift*, 67 (1920), 75–8 (76).

[30] Kraepelin, 'Lebensschicksale', 76.

applications by both Nissl and Alzheimer, because he wanted them to remain in his own laboratory. Be that as it may, his prediction came true. From the start, things went badly for Alzheimer. He fell ill on the train trip from Munich to Breslau (angina, complicated by a kidney infection) and upon arrival he had to be admitted to a sanatorium. Recovery was slow in coming, and when Kraepelin and Nissl first saw him again, at a conference in Breslau the following year, they were shocked by his condition. Kraepelin: 'Although outwardly calm, he seemed despondent, and contemplated the future with apprehension.'[31] Nissl persuaded him to go to Wiesbaden to take the waters, but this failed to bring about the desired improvement.

In 1914, the First World War brought new cares and concerns. His son Hans volunteered for service at the front (which was a source of pride to his father) and was sent to Flanders. Alzheimer himself had to take over for doctors called up for military service. At this time, he appears to have been caught up in the fiercely Prussian-nationalistic atmosphere which prevailed in Breslau. In a lecture on 'Krieg und Nerven', he predicted that the war would result in a great many nervous afflictions, but that in the end this might have a fortifying effect, ultimately producing a 'more energetic, courageous, and intrepid generation. With nerves of steel, the German people will undertake to address the exigencies of peace. In so doing, they will also conquer many of the phenomena which proliferated during the long period of peace, and which some over-anxious citizens now regard as proof of the spiritual degeneration of our people.'[32] Up until then, Alzheimer's observation of nerves had been limited to those he examined under a microscope. Now, having escaped from the narrow confines of the objective prism, he spouts opinions which introduce readers

[31] E. Kraepelin, *Lebenserinnerungen* (Berlin, 1983), p. 172.

[32] A. Alzheimer, *Krieg und Nerven* (Breslau, 1915). Cited in Maurer and Maurer, *Alzheimer*, p. 257.

to a conceptual world which had become so common within the psychiatry of the day that it is not surprising that Alzheimer – even Alzheimer – endorsed them. In that same speech, he referred to a malady known as 'benefit neurosis'. This is a disturbance whereby:

> a minor injury such as a glancing pistol shot, or a fall from a horse or wagon, results in a series of subjective symptoms for which no cause can be found, and which are disproportionate to the minor nature of the injury. The phenomenon is regularly seen in peacetime as well, among those suffering from a work-related injury, or passengers involved in a train accident. It is referred to as traumatic hysteria, and occasionally as benefit neurosis, since the public may rightly believe that the prospect of receiving benefits is the psychological factor which perpetuates the symptoms.[33]

This early reference to what we know as 'secondary gain' soon gave rise to a now familiar – but in the Germany of 1915 ominous – attitude attributed to people with a congenital susceptibility to this disturbance, namely the 'so-called degenerates, psychopaths or mentally deficient. Often these are the children of the mentally disturbed, epileptics, criminals or alcoholics.'[34] In other articles, however, Alzheimer took a more moderate view of the concept of degeneration: the designation 'so-called' was there for a reason. But his summary of the classic elements in the category of degeneration suggests that he was part of a long tradition. And he would not be the last.

The speech on 'Krieg und Nerven' marked the end of Alzheimer's scientific work. In December 1915, while Hans was in Breslau on Christmas leave, Alzheimer's condition rapidly deteriorated. The lining of the heart became inflamed and Alzheimer breathed his last. He was 51 years of age. Nissl attended the funeral. 'The ceremony proceeded as quietly and simply as his life had ebbed away. He had requested that there be no funeral orations. On 23 December we

[33] Maurer and Maurer, *Alzheimer*, p. 256. [34] *Ibid.*

accompanied our unforgettable friend to his final resting place. In keeping with his wishes, he was buried in the Frankfurt cemetery, alongside his wife, who had preceded him many years before, and with whom he was so briefly united in a very happy marriage.'[35]

Alzheimer's diseases

After reading the third or fourth 'In Memoriam', something begins to jar. *Whatever happened to Alzheimer's disease?* In most of the necrologies there is no mention at all of his articles on Auguste and Feigl, and even the *Zum Andenken* of his faithful friend Nissl does not refer to the eponym. Looking back, a strange reversal seems to have taken place in the posthumous reputation of Alzheimer. In his own day, he was honoured mainly as an expert on the consequences of syphilis infections. That expertise was of vital importance for psychiatric institutions deluged by patients with symptoms of progressive paralysis. Alzheimer's disease, by contrast, was actually quite rare in an age when no more than five people in a hundred reached the age of 65. Auguste, Johann Feigl, and Perusini's three patients were simply lost among the masses of patients suffering the late consequences of syphilis. In any case, the fact that of the entire neuropathological oeuvre published by Alzheimer, precisely the two articles dealing with 'pre-senile dementia' have been highlighted is a reflection of the rapid increase in the number of Alzheimer patients in our day. Alzheimer died as an expert on syphilis and was resurrected as the discoverer of Alzheimer's disease.

But perhaps there was another reason why in 1915 he was not remembered as the man who discovered Alzheimer's disease. Many contemporaries shared the reservations which Alzheimer himself had: was it actually a separate disease, a clearly defined entity? In the brain of Auguste he had found two sorts of deviant cells: tangles

[35] Nissl, 'Zum Andenken', 107.

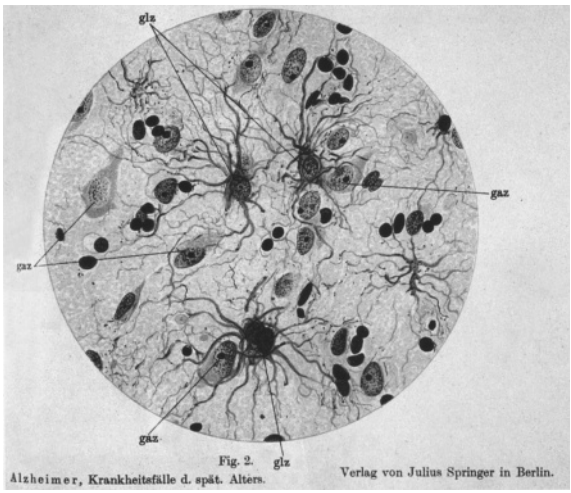

Figure 8.5: Photomicrography of a section from the brain of Johann Feigl

and plaques. The clinical picture of Feigl was an exact match to that of Auguste, but Alzheimer had discovered no tangles in his brain. That finding would be confirmed by later research. The brain of Johann Feigl, in the form of 150 preparations, is still in the archives of the Institute for Neuropathology in Munich. In 1992, when they were rediscovered, those sections were re-examined.[36] Techniques not available in Alzheimer's day confirmed the absence of tangles. Like true neuroarcheologists, the researchers then left a portion of the material untouched, awaiting new techniques or new insights into the genetic background of Alzheimer's disease.[37] In 1997, it was discovered that those same archives housed the brain of Auguste: the

[36] M. B. Graeber *et al.*, 'Rediscovery of the case described by Alois Alzheimer in 1911: historical, histological and molecular genetic analysis', *Neurogenetics*, 1 (1997), 73–80.

[37] H.-J. Möller and M. B. Graeber, 'The case described by Alois Alzheimer in 1911: historical and conceptual perspectives based on the clinical record and neurohistological sections', *European Archive of Psychiatry and Clinical Neuroscience*, 248 (1998), 111–22.

270 colourful sections, each one-tenth of a millimetre thick, had survived two world wars.[38]

After the death of Feigl, Alzheimer recorded a diagnosis of '*Alzheimer'sche Krankheit*'. But once he had examined the brain of this patient under his beloved Zeiss microscope, doubts must have arisen. It would appear that Alzheimer's disease was not the same thing as 'tangles plus plaques'. But without tangles, was he looking at a different disease or a variant of the same disease? Alzheimer himself made no pronouncement on this issue, but later generations of neurologists opted for the latter conclusion: Johann F was suffering from the 'plaques-only' variant of Alzheimer's disease.[39]

And then there is Gaetano Perusini. When in the spring of 1908, Kraepelin attributed the eponym, he did not have at his disposal the findings of Perusini, whose account was not completed until December of that year. He recorded the details of three new cases, as well as a histopathological study which was much more detailed than that of Alzheimer. Not too long ago, Italian physicians suggested that the name be changed to 'Alzheimer-Perusini disease'.[40] That manoeuvre was doomed to failure: once an eponym has gained acceptance, it is cast in stone. But it would have been a fitting tribute to a pathologist whose promising career ended at the age of 36, when he was killed in the First World War, ten days before the death of Alzheimer.

Alzheimer and Perusini were pathologists, and in all their writings, there is not a single word about treatment or therapy. Kraepelin, director of an institute, did address the subject, but his recommendations are limited to a single brief and somewhat bland paragraph: give due attention to personal hygiene; combat insomnia with baths; treat

[38] M. B. Graeber *et al.*, 'Histopathology and APOE genotype of the first Alzheimer disease patient, Auguste D.', *Neurogenetics*, 1 (1998), 223–8.

[39] Möller and Graeber, 'Case', 111.

[40] G. Macchi, C. Brahe and M. Pomponi, 'Alois Alzheimer and Gaetano Perusini: should man divide what fate united?', *European Journal of Neurology*, 4 (1997), 210–13.

'delirious states of agitation' by adding sedatives to the diet; and allay anxiety by administering small quantities of opium.[41] We do not know whether Alzheimer was optimistic or pessimistic about the likelihood of finding a cure for 'his' disease. At that juncture in history, many physicians would have found it difficult not to be optimistic, when pathogens responsible for various dreaded epidemic diseases were regularly being discovered: gangrene (1881), tuberculosis (1882), cholera (1883), rabies (1885), diphtheria (1890), tetanus (1892), dysentery (1898). There had been revolutionary developments in Alzheimer's specialism as well. In 1905, one year after the appearance of his own research into 'progressive paralysis', two German zoologists discovered the cause of syphilis, and a year later Wassermann developed the test which made it possible to establish the presence of a syphilis infection in a living being. In 1910, Ehrlich launched the remedy 'Salvarsan', putting an end to the dangerous mercury cures which had been employed up until then. Thus, within twenty years it had become possible to treat, cure or prevent a whole series of diseases. However, these were all infectious diseases, and up to then there was no indication that Alzheimer's disease fell into that category.

But if Alzheimer was indeed optimistic about the possibility of finding a remedy, he must have been just about the last person on the planet to hold that view. Ageing occurs in those parts of the world where there is money to be made from disease, and despite enormous investments in pharmaceutical research, the medication that can cure or prevent Alzheimer's is still beyond the horizon. Remedies capable of slowing the course of the disease have minor (barely measurable) effects, while the side-effects which accompany them often place a greater burden on the sufferer and his loved ones than the confusion and forgetfulness. A great deal of expertise has been accumulated with respect to the biochemical course of the catastrophe, the composition

[41] Kraepelin, 'Seniele', p. 630.

of the plaques, the formation of the tangles, the nature of the genes on chromosomes 1, 14, 19 and 21 (which appear to play a specific role in the susceptibility to the disease), the sections of the brain which are initially and most severely affected, and the order in which the clinical symptoms present themselves. And yet all this knowledge has not created a single opening in the direction of treatment. In the history of Alzheimer's research, a whole list of risk factors pertaining to nutrition, environmental influences and lifestyle have been put forward and subsequently refuted or retracted. And even when taken together, they are as nothing in comparison with that single risk factor over which we have so little control: ageing. Given the long trajectory of aspirant medicines during the test phase, any medication scheduled to become available in the next three or four years would have to have been discovered several years ago. It is unlikely that one fine day someone will take a key out of his pocket and, murmuring under his breath 'Shall we see if this fits?', take the first step leading to the eradication of Alzheimer's disease. Where this malady is concerned, what Kraepelin announced to the waiting pathologists as he left Alzheimer's lab – about the slow grinding of the anatomical mills – has proved to be a sombre but accurate prediction.

When in 1906 Alzheimer referred to 'future research', he was hoping that it would one day be possible to classify the disease more accurately by means of histopathological research. That has not proved to be the case. A hundred years later, the borders of 'Alzheimer's disease' are more ragged than ever. Since the mid-1990s, many researchers have preferred the term 'Alzheimer's diseases', a category which encompasses a spectrum of variants, types and subtypes.[42] One mysterious detail is the fact that tangles and plaques are sometimes found in the brains of people who did not display the clinical picture of Alzheimer's. The border with a form of dementia caused by the above-mentioned Lewy bodies is likewise

[42] A. D. Roses, 'The Alzheimer diseases', *Current Opinion in Biology*, 6 (1996), 644–50.

unclear. In one out of four Alzheimer patients, the brain contains Lewy bodies, and in the case of the plaques-only variant, that proportion is much higher. Often the symptoms bear such a close resemblance to those of both Alzheimer's disease (confusion and memory loss) and Parkinson's (rigidity, tremor, shuffling gait) that it has been suggested that Lewy bodies dementia should be classified as a variant of one of these two diseases. One out of three Parkinson patients ultimately develops Alzheimer's, while the Alzheimer's diseases are themselves part of a spectrum of dementias. Although Alzheimer's accounts for about three-quarters of all cases of dementia, the condition can also develop as a result of damage to the blood vessels in the brain (multi-infarct or vascular dementia).

If a committee of today's neurologists, geneticists and molecular biologists were asked to suggest a name for what we know today as 'Alzheimer's disease', they would not have opted for this particular eponym. The clinical significance of Alzheimer's disease, which in 1908 was characterized by Kraepelin as 'still unclear', is today no less than a medical arena. To some extent, the conflicts and controversies arise because the borderlines in one discipline are totally natural and practical (in terms of neuropathological findings, say), while in another discipline they appear quite artificial. It might be more correct to say that the Alzheimer diseases exist in the same way that Scorpio and the other signs of the zodiac exist: no one would deny the existence of the various stars which make up the signs of the zodiac, but it is also undeniable that they could just as well have been arranged in different constellations.

Since Alzheimer's day, the life expectancy of human beings has doubled, while the percentage of elderly people has tripled. There has also been a rapid increase in the number of patients with Alzheimer's disease. And not only will there be more Alzheimer's patients in the future, they will also suffer from the disease longer. In the Western world, there is a generation emerging which consists of people who have carefully monitored their nutrition and lifestyle, and are

therefore in relatively good health as they approach old age. Many of these fit and healthy bodies will be the abode of a confused mind for a longer and longer period. Sooner or later, the patient with early symptoms of Alzheimer will visit his GP or a memory psychologist, who will patiently ask the questions that Alzheimer asked. What is your name? What day is it today? How old are you, what are the names of your children, what year is it? Can you tell me what time it is? The knowledge – still intact – that these are things that a normal individual ought to know gives rise to shame, frustration and an embarrassing series of excuses. The patient knows that he is being subjected to the simplest exam that he has ever had to take, and that he will be unable to pass. Between the first visit to the family doctor and the death of the patient lies a period of some five years.

In the past, people suffering from the symptoms of Alzheimer's disease were said to be 'in their second childhood'. That comparison is far too romantic: the harsh reality has nothing whatsoever to do with that care-free period in our lives and the expectations normally associated with childhood – not for the patient, and not for those around him. In the course of the disease, many skills disappear in reverse order, beginning with the higher processes such as judgement, memory and concentration, and later on the motor skills. Ultimately that regression of functions also applies to reflexes. Newborn babies spread their toes upwards when you touch the soles of their feet, the Babinski reflex. After about six months, that reflex disappears and babies spread their toes downwards when touched, in the direction of the stimulus. In the very last stages of Alzheimer's, the Babinski reflex returns, together with other reflexes characteristic of newborn babies, such as sucking and grasping. It is the last stop on the return voyage. Like Auguste, the patient will curl up into the foetal position and die. Even today, the most common causes of death among Alzheimer patients are the same as for Auguste and Feigl: bedsores and pneumonia.

In the asylum in Frankfurt, Auguste dragged her bedclothes around with her, and in Munich Feigl did the rounds of the garden, at top speed and bathed in perspiration, gripping the tails of his coat. Today the architecture of most nursing homes is designed around that restlessness. Modern Augustes and Feigls are mercifully steered into an Escher-like labyrinth of tangles with no beginning and no end. Though they have long since lost their way, they will not go astray.