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The case described by Alois Alzheimer in 1911

Historical and conceptual perspectives based on the clinical record and neurohistological sections

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Abstract In 1906, Alzheimer presented the first case of the disease which was later named Alzheimer's disease by Kraeplin. While the publication on this case in 1907 is only a relatively short communication, Alzheimer published a very comprehensive paper in 1911 in which he discussed the concept of the disease in detail. This publication focusses on the report of a second patient suffering from Alzheimer's disease, the case of Johann F. The detection of neurohistopathological sections from this patient found among archives at the Institute of Neuropathology of the University of Munich enabled us to reinvestigate this case using modern methods. Neurohistopathologically, the case of Johann F. is "plaque-only" Alzheimer's disease. There is a controversy in the modern literature as to whether these "plaque-only" cases belong to the modern concept of Alzheimer's disease. A careful analysis of all pros and contras in the literature led to the conclusion that plaque-only cases are also an integrative part of the modern Alzheimer disease concept.

Key words Alzheimer's disease · Dementia · "Plaque-only" Alzheimer's disease

Introduction

In November 1901 Alzheimer documented in detail the symptoms and the progress of mental degeneration in a 51-year-old woman (Auguste D.) who was a patient at the Frankfurt Hospital. Severe cognitive disturbances, disorientation, aphasia, delusions, and unpredictable behavior were listed as the main clinical symptoms. The patient died 4.5 years later in April 1906. The pathological–anatomical examination revealed a diffuse atrophy of the entire brain and characteristic changes in its internal structures, in particular in the cortical cell clusters. In his textbook from 1910 Kraepelin suggested the term "Alzheimer's disease" for this illness (Hoff and Hippius 1989).

After the death of the patient, Alzheimer gave a report of the case at the conference of psychiatrists in Tübingen, Germany, on 3 November 1906. The title of the lecture was "On the peculiar disease process of the cerebral cortex" (*Über eine eigenartige Erkrankung der Hirnrinde*; Alzheimer 1906), a shorter version of which was later on published (Alzheimer 1907a, b).

In 1910 Perusini, Alzheimer's coworker in Munich, published a paper on "Clinically and histologically peculiar mental disorders of old age" (Perusini 1910). The first of four cases mentioned in this report is apparently identical with Alzheimer's case of A. D.

It is of interest that, although the patient A.D. never was hospitalized in the Psychiatric Hospital in Munich to our knowledge, the original record, which was discovered recently by Maurer et al. (1997), contains a short epicrisis in a format typical for the Psychiatric Hospital of the University of Munich at this time with the name of the hospital on top. It is difficult to explain why Alzheimer or one of his colleagues wrote this epicrisis. Perhaps he thought it was necessary that such a document accompany the postmortem brain preparation of the patient. This, together with the fact that Alzheimer had also been working at the Psychiatric Hospital of the University of Munich since 1904, leads to the assumption that the neuropathological and neurohistopathological analyses of this case might have been performed in Munich. Alzheimer's personal impression of the nosological relevance of what he had described in this case is of interest (Alzheimer 1906, 1907a, b). This position follows the principal nosological approach of Kraepelin.

> . . . All things considered, we are obviously concerned with a peculiar disease process. Such processes have been established in great numbers in recent years. This finding will necessarily induce us not to be content with laboriously forcing any clinically uncertain case into one of our well known nosological categories. Doubtless there are many more mental disorders than

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> are listed in our textbooks; in some of these cases histological analysis will allow the peculiarity of the case to be identified later. Then we will gradually reach the point where we will separate single cases clinically from the large nosological groups of our textbooks and define these large groups clinically in a more precise way…

Neither Alzheimer himself nor his close coworkers seem to have been fully aware at this early stage that he had "discovered" an entirely new disease (Hoff 1991). But following Kraepelin's influential suggestion, this "presenile dementia" with a diffuse atrophy of the entire brain, but especially of the cortex, together with the various changes in the inner structure of the neurons was later called "Alzheimer's disease" or "Morbus Alzheimer." In his comprehensive study of 1911, Alzheimer seems surprised when he states that "Kraepelin in the eighth edition of his textbook on psychiatry has already given a short summary of these diseases and called them Alzheimer's disease" (Alzheimer 1911). After a review of the contemporary literature (Bonfiglio, Fisher, Hübner, Myake, Perusini, Pick, Redlich, Sarteschi, Simchowicz), he discussed whether the cases he had regarded as peculiar should be separated clinically or histologically from senile dementia.

In recent years, there has been much speculation as to why in the 1910 edition of his textbook Kraepelin so readily accepted that Alzheimer's clinical and histopathological description should constitute a new and distinct disease entity (Hoff 1991). Were there mainly scientific reasons, as proposed by Beach (1987), or was Kraepelin highly motivated to add prestige to his Munich laboratory, either in order to demonstrate the superiority of his "school" over psychoanalytic concepts or – more likely – over the competing group in Prague headed by Arnold Pick (Torak 1979). Oskar Fischer, one of Pick's coworkers, had in fact published interesting histopathological findings on senile dementia in 1907 (Fischer 1907). However, from a historical point of view, none of these hypotheses about Kraepelin's motives for coining the term "Alzheimer's disease" can be regarded as being definitely proven so quickly (Berrios 1990).

Recently it has been speculated that the patient's dementia was not caused by the typical neurodegeneration of Alzheimer's disease but rather by arteriosclerosis of the brain (O'Brien 1996).

Alzheimer's first report on Auguste D. from 1906 (Alzheimer 1907a) is not a full-sized research paper, but rather an abstract summarizing the presentation he gave at the 37th meeting of the South West German Psychiatrists (*37. Versammlung Sudwestdeutscher Irrenärzte*) in Tübingen, Germany, on 3 November 1906. Therefore, Alzheimer's first report on the morphology of the disease does not contain any illustrations. Yet a number of figures, mainly drawings, which include examples of the histopathology of his first case, Auguste D., were published by Alzheimer in 1911 together with a second case report (Alzheimer 1911) – that of Johann F. Hence, this case report, which the publication from 1911 centers on, seems to be of greatest importance.

Alzheimer provided ample clinical, biographic, and neuropathological data from this patient which have enabled us to identify not only the epicrisis of this patient in the archive of the Psychiatric Hospital of the University of Munich, but also to identify histological sections found among archives at the Institute of Neuropathology of the University of Munich (Graeber et al. 1997). It is not known whether Kraepelin ever saw Auguste D. However, Kraepelin was most likely familiar with Johann F, as Kraepelin and Alzheimer worked very closely, which is gratefully acknowledged by Kraepelin in the introduction to the second volume of his textbook (Kraepelin 1910).

The case report of Johann F

According to the epicritical report (Fig. 1), the patient, a 56-year-old laborer, was admitted to the Psychiatric Hospital on 12 September 1907 (incidentally, it should be noted that this date does not correspond to the one given in Alzheimer's paper from 1911, where November is given as admission date). The report further states:

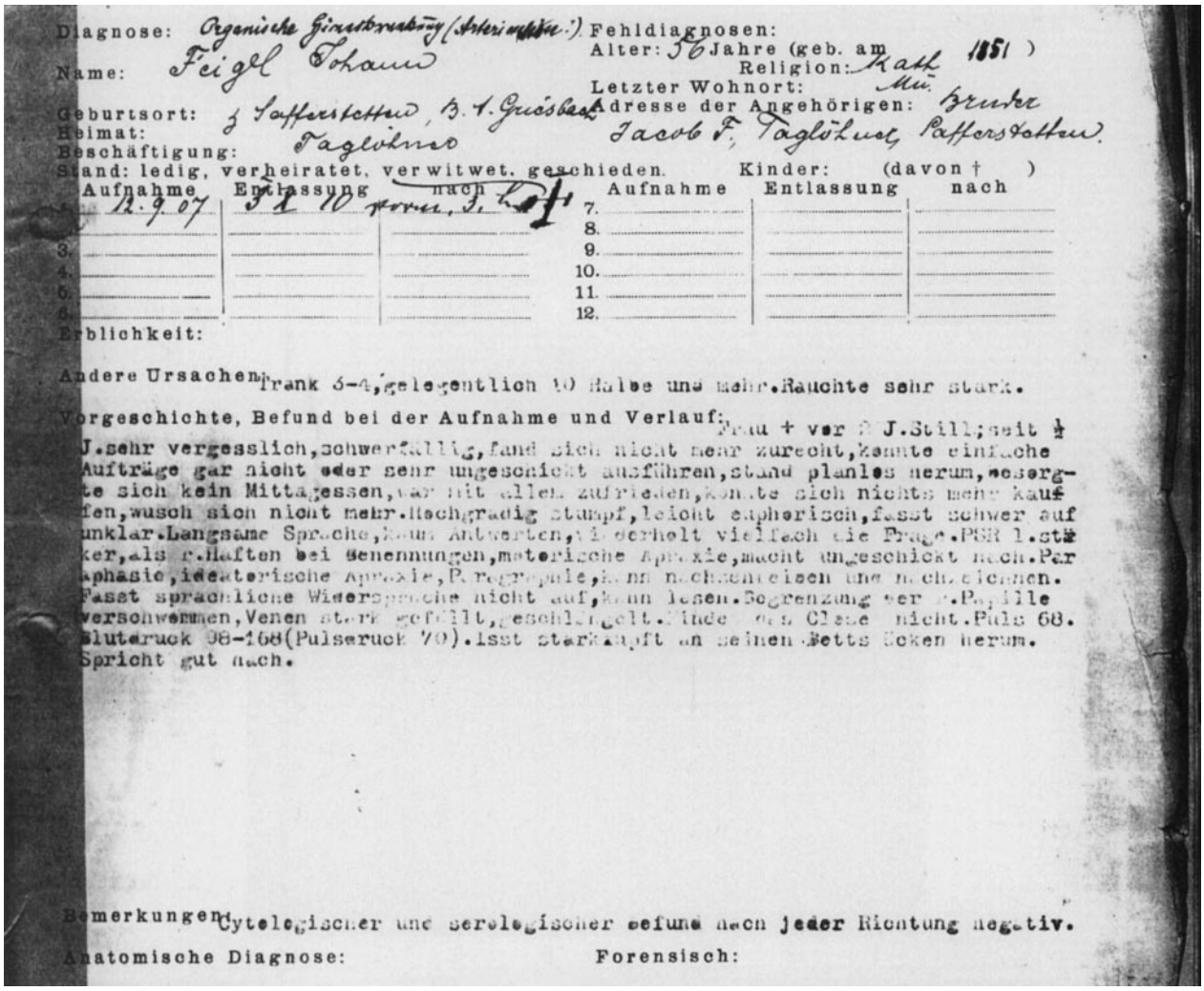
> …Wife died 2 years ago. Quiet; since $^1/_2$ year very forgetful, clumsy, could not find his way, was unable to perform simple tasks or carried these out with difficulty, stood around helplessly, did not provide himself with lunch, was content with everything, was not capable of buying anything by himself and did not wash himself. Very dull, slightly euphoric, slow in comprehension, unclear. Slowed speech, rare answers, frequent repetition of the question. PTR l. more pronounced than r. Sticking when naming things, motor apraxia, imitates in a clumsy way. Paraphasia, ideational apraxia, paragraphia, able to copy writings and drawings. Does not realise contradictions in speech, can read. Blurred demarcation of the r. optic disk, veins very filled, wavy. Does not find the toilet. Heart rate 68. Blood pressure 98–168. Eats a lot. Is tugging at his sheets. Repeats sentences without problems…

The patient died after 3 years of hospitalization on 3 October 1910 in the Psychiatric Hospital of the University of Munich due to pneumonia.

Interestingly, J.F. was admitted under the diagnosis of possible vascular dementia. The initial clinical diagnosis probably written by Alzheimer reads "organische Hirnerkrankung (Arteriosklerose?)", i.e., "organic brain disease (arteriosclerosis?)." The autopsy book states "*Alzheimersche Krankheit*" i.e., "Alzheimer's disease." The hand-writing in the autopsy book describing the patient's diagnosis apparently closely resembles that of Alzheimer (Figs. 2, 3).

In the publication from 1911 Alzheimer gave a detailed description of the clinical history of this 56-year-old patient (Alzheimer 1911, pp 358–361). Because of the special relevance of this case in the conceptualization of Alzheimer's disease, the full version of this case report is presented here to show the individual history of the case and also to demonstrate the clinical diagnostic approach of Alzheimer (translation of this and the following quotations according to Förstl and Levy 1991):

> …The 56-year-old labourer Johann F. was admitted to the psychiatric Clinic on 12 Nov. 1907. There was no history of excessive drinking. Two years before admission his wife died, since when he became quiet and dull. In the previous 6 months he had


Diagnose: Organische Einsteifung (Arteriosklerose) Fehldiagnosen:
Name: Feigl Johann Alter: 56 Jahre (geb. am 1851)
Religion: Kath.
Letzter Wohnort: Mü.
Geburtsort: Pfaffenstetten, B.A. Griesbach Adresse der Angehörigen: Bruder
Heimat: Jacob F. Taglöhner Pfaffenstetten
Beschäftigung: Taglöhner
Stand: ledig, verheiratet, verwitwet, geschieden. Kinder: (davon †)

	Aufnahme	Entlassung	nach		Aufnahme	Entlassung	nach
1.	12.9.07	24.10	Irren A. Kolb	7.			
2.				8.			
3.				9.			
4.				10.			
5.				11.			
6.				12.			

Erblichkeit:

Andere Ursachen: Trank 3-4, gelegentlich 10 Halbe und mehr. Rauchte sehr stark.

Vorgeschichte, Befund bei der Aufnahme und Verlauf: Frau + vor 2 J. Still; seit ½ J. sehr vergesslich, schwerfällig, fand sich nicht mehr zurecht, konnte einfache Aufträge gar nicht oder sehr ungeschickt ausführen, stand planlos herum, besorgte sich kein Mittagessen, war mit allem zufrieden, konnte sich nichts mehr kaufen, wusch sich nicht mehr. Hochgradig stumpf, leicht euphorisch, fasst schwer auf unklar. Langsame Sprache, kann Antworten, wiederholt vielfach die Frage. PSR l. stärker, als r. Haften bei Benennungen, motorische Aphasie, macht ungeschickt nach. Paraphasie, ideatorische Apraxie, Paragraphie, kann nachsprechen und nachahmen. Fasst sprachliche Widersprüche nicht auf, kann lesen. Begrenzung der Papille verschwommen, Venen stark gefüllt, geschlängelt. Rinde [illegible] Cl. nicht. Puls 68. Blutdruck 98-168 (Pulsdruck 70). Isst stark auf an seinen Betts Seiten herum. Spricht gut nach.

Bemerkungen: Cytologischer und serologischer Befund nach jeder Richtung negativ.

Anatomische Diagnose: Forensisch:

Fig. 1 Epicritical report of Johann F. (Archives of the Psychiatric Hospital, Munich) (Graeber et al. 1997)

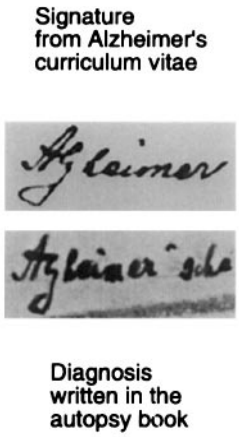


Fig. 2 Alzheimer's signature (*upper part*) taken from his curriculum vitae which was written after he had joined the Psychiatric Hospital in Munich. For comparison, the diagnosis written in the autopsy book has been enlarged (*lower part*) (Graeber et al. 1997)

become forgetful, could not find his way, could not perform simple tasks or carried these out with difficulty. He stood around, did not appear to bother about food, but ate greedily whatever was put before him. He was not capable of buying anything for himself and did not wash. He was admitted by the service for the poor.

14 Nov. 1907. Pupillary reaction normal. Patellar-reflex a little brisk. No signs of nervous palsy. Language strikingly slow, but without articulatory disturbance. Dull, slightly euphoric, impaired understanding. Echoes questions put to him frequently and repeatedly instead of giving a reply. Can only solve very simple calculations after a long delay.

When asked to point to different parts of his body, he hesitates. After having spoken about the knee-cap, he calls a key a knee-cap. Does the same with a matchbox, which he rubs against his knee-cap when asked what one would do with it. He then does the same with a piece of soap. He finally responds correctly to other commands to unlock a door or to wash his hands but only does so extraordinarily slowly and clumsily.

20 Sept. 1907. To the question, what is the colour of blood? 'red'; snow? 'white'; milk? good; soot? –

Counts correctly to 10, does the same with days of the week and months of the year. Gives half of the 'Our father' but cannot continue. $2 \times 2 = 4$, $2 \times 3 = 6$, $6 \times 6 = 6$. Reads the time correctly. Unbuttons his frock correctly. Takes a cigar in his mouth, strikes a match, lights the cigar and smokes: everything in the correct manner. Takes coins in his hands and checks each side. 'That is, that is, we have got a, here, here…'

Similarly, he cannot name a matchbox.

a

b

Fig. 3 **a** Autopsy book of the psychiatric clinic in Munich. **b** Entry no. 784 lists a male individual bearing the name "Feigl" who died on 3 October 1910 in the psychiatric hospital (*Klinik München*). The diagnosis reads "*Alzheimer'sche Krankheit*" (Alzheimer's disease) (Graeber et al. 1997)

He knows how to use a mouth organ, bell, purse, but cannot name them. When asked to do so, he selects a matchbox and a light from a number of objects but not a brush or a corkscrew. When asked to bend his knees, he makes a fist. Repetition is unimpaired.

How many legs has a calf? '4'. A man? '2'.

Where does a fish live? In the forest up on the trees? 'In the forest up on the trees.'

Lumbar puncture: No increased cell count. No alteration in complement in blood and cerebrospinal fluid.

Ophthalmoscopy: blurring of the right papilla, veins well filled, normal findings on the left.

23 Sept. 1907. Gets up and urinates by the bed.

8 Oct. 1907. When asked to write, he does not take the pencil but picks a matchbox and tried to write with it. Otherwise focal symptoms show striking changes in severity.

15 Nov. 1907. Happy, laughs a lot, eats an extraordinary amount. Sits around looking dull but moves his hands constantly, picking his blanket or his shirt. At times he tears pieces of cloth which he pushes into his mouth.

Repetition still good. He often uses objects in the wrong way, e.g. tries to brush his frock with his comb. When he is given a key and is asked to unlock the door, he approaches the door but does not know what to do. When writing his name he sticks to letters. He cannot be persuaded to write anything but his name. When he is asked to name objects, he does not respond promptly, or echoes the question without understanding it, at times repeatedly. He does not speak spontaneously. When teased, e.g. by trying to take away a cloth, which he is uncoiling, he sometimes curses. When asked to carry out a movement, he often repeats the question. When the movement is demonstrated to him, he usually looks without appearing to understand. He imitates some of the demonstrated movements with his right or left hand. When asked to touch his nose with his right hand, he holds the extended fingers to his chin. When asked to blow a kiss, he holds out his hand in a peculiar way. Then when a threatening gesture and a military salute are demonstrated to him, he puts his hand to his mouth as though blowing a kiss.

8 Dec. 1907. Obviously further deterioration. Keeps leaving his bed, fusses around with his sheets.

Wassermann's test in blood and serum negative. 1 cell per mm^3 cerebrospinal fluid.

2 March 1908. Asked to wash his hands, he starts correctly but then keeps on washing endlessly. Asked to close a tap, he holds his hands under it. Asked to seal a letter, he tries to light the candle with the seal, then he warms up the sealing-wax and applies it against the seal.

Asked to light a cigar, he strikes it against the matchbox.

4 March 1908. Restless, appears as though delirious. Keeps rolling his sheets into a bundle and wants to walk out with them. He often keeps working away for days on end without a break, his face sweating. Gets more and more reluctant. Does not obey when summoned. When given a hairbrush, he licks it. Almost no spontaneous speech.

5 May 1908. Other patients have taught him how to sing. When asked he sings: 'We sit so happily together'. He has to be prompted again and again with the words but does rather well with the tune.

12 May 1908. Physical examination does not yield any abnormal results in either of the pupils or the reflexes. Papillae look normal (right papilla shows a slightly abnormal configuration).

When asked for something, he usually answers with a 'yes' and laughs idiotically, or repeats the question without understanding. He is still quite capable of repetition and at times he keeps repeating the word several times. He generally imitates individual movements, like extension of hands, swearing correctly, but clumsily.

12 June 1908. He walks in the garden and will not let anyone stop him. Although completely soaked with sweat, he walks round and round continuously, constantly winding the long coattails of his frock round his hand which he clenches occasionally. In his bed he does the same thing with his blanket. When pricked with a needle or tickled on his soles, he does not react for a long time but finally hits the physician. Hardly utters a word.

It is striking that his gross motility appears unimpaired in spite of his profound imbecility. No ataxia or weakness of limb movements are to be seen.

14 Dec. 1908. Incontinent of faeces and urine wherever he is. Does not say anything anymore; is permanently occupied with his bed or shirt. Does still sing 'We are sitting so happily together' when others start him off.

3 Feb. 1909. Epileptiform seizure lasting a few minutes. Twitching of his face.

6 Feb. 1909. Right-sided facial palsy.

9 Feb. 1909. No obvious facial weakness anymore.

Repeat tests of blood and serum yield the same negative results as before. Very reluctant to cooperate. Always busy with his blanket or shirt. Does not speak anymore; does not obey any commands.

31 May 1910. His body-weight falls slowly and steadily. Still fidgeting with his sheets in the same manner.

28 July 1910. Epileptiform seizure of 2 minutes duration.

l Sept. l910. Temperature increased to 38.5 C. Rhonchi over his lung.

3 Oct. 1910. Death with features of pneumonia.

Thus we see a 54-year-old man who slowly and imperceptibly and with no impairment of consciousness or seizures develops a state of profound mental impairment with prominent agnostic, aphasic, and apractic disturbances. A more accurate analysis of these focal symptoms presents various problems because the impairment of recognition, language comprehension and expression, as well as praxis, the general mental impairment and reluctant behaviour, make the interpretation of individual verbal capacities and acts difficult. It is, however, certain that the language disturbances of the patients have to be considered as transcortical aphasias because of the long-preserved ability for repetition. Since there was an early impoverishment of word production which progressed to a complete loss of spontaneous language, we have to assume a mixed motor and sensory aphasia in spite of gross signs of paralysis. Of the apractic disturbances, although these were sometimes purely motor, ideational apraxia was more prominent. In contrast to the severe disturbances of language and of praxis, disturbance of motility was slight and the absence of real signs of paralysis of the extremities was striking. In the late stages of the condition and towards the end of his life, repeated epileptic attacks and a transient right-sided facial nerve paralysis occurred.

The clinical analysis of this case raises several difficulties. Senile dementia was never considered because of the onset at the age of 54 and the fact that, even on first examination, a profound mental impairment with a hint of aphasic agnostic and apractic disturbances was found. After physical examination had apparently established a right-sided papilloedema, one had to consider a tumour. Because of the lack of other signs of increased intracranial pressure and the profound general mental impairment with multiple localizing signs, one would have to postulate a diffuse tumour invading nervous tissue without occupying much space. Since repeated examination yielded only a slight abnormality of the right papilla which did not progress, this could not be considered as papilloedema and the diagnosis of a tumour was no longer supported…

Alzheimer's neuropathological findings and theoretical reflections based on the case Johann F.

In the introduction of this relatively long publication (about 30 pages) Alzheimer describes not only the clinical picture, but also the typical neuropathological characteristics of the first Alzheimer's disease case, the case of Auguste D.:

…The microscopy of Bielschowsky-stained tissue showed a strikingly peculiar degeneration of cortical nerve-cells which was essentially characterized by a clotting of fibrils which changed their staining-properties and outlived the cellular disintegration so that in the end there were bundles of fibrils lying in the tissue rolled up like coils or twisted like slings as the only remnants of the cell. In addition there were an extraordinary number of peculiar patches disseminated throughout the whole cortex… (Alzheimer 1911, p. 356, translation according to Förstl and Levy, 1991).

As already mentioned this case description was the basis for long theoretical reflections. Alzheimer states that Kraepelin, in the eighth edition of his textbook on psychiatry, has already given a short summary of this disease and called it Alzheimer's disease. He refers to the scientific findings concerning this topic since 1906 (Bonfiglio, Fisher, Hübner, Myake, Perusini, Pick, Redlich, Sarteschi, Simchowicz) and discusses whether the cases he had regarded as peculiar should be separated clinically or histologically from senile dementia:

…In almost all of the succeeding years new examples of similar cases were reported. In 1908 Bonfiglio described one, in 1909 Perusini presented a clinical and anatomical description of 4 cases. Since then 2 new cases have been seen here and examined anatomically. In the 8th edition of his *Psychiatry* Kraepelin produced a summarized account of this disease which he called Alzheimer's disease.

The patches in the cortex had in the meantime been observed in presbyophrenia by Fischer who described them in detail in a number of papers and considered them as a characteristic feature of that disorder. Redlich had also demonstrated them by different methods. I had myself already observed and described them in Dementia senilis using Nissl and Weigert staining. I had not however realized that they corresponded to the images seen in Bielschowsky-stained preparations. Perusini has pointed out that the fibrillary changes in nerve cells which I had described are also seen in severe cases of Dementia senilis and Fischer has expressed the same view. The question therefore arises as to whether the cases of disease which I considered peculiar are sufficiently different clinically or histologically to be distinguished from senile dementia or whether they should be included under that rubric.

Perusini felt that these cases represented a separate disease, partly for clinical and partly for histological reasons. The clinical differences were the early onset, and the presence and severity of focal symptoms which were not thought to be a feature of Dementia senilis, the anatomical differences being the greater severity of the histological changes although they develop at an earlier age. Kraepelin still considers that the position of these cases is unclear. Even if the anatomical findings might suggest severe mental impairment, the early onset (one would have to assume a 'senium praecox'), the profound language disturbance, spasticity and seizures are very different from those of presbyophrenia which is usually associated with purely cortical senile changes. The disease may therefore be related to one or to the other of the pre-senile conditions which he described. Fischer has written an exhaustive discussion of Perusini's cases in his paper; 'The presbyophrenic dementia, its anatomical basis and clinical differentiation'. He considered the patches as characteristic of a specific disorder and saw no objections to including in the same category cases occurring at an early age, both because of the histological changes and because the paralysis of adults and young people which represent the disease at a different age share all the essential features of later cases.

It seems to me that a simple inclusion of these cases with presbyophrenia does not take sufficient account of several interesting features, and that Perusini's and Kraepelin's reservations against this integration have not been convincingly eliminated by Fischer's arguments. After all, we are dealing with the case of a 56-year-old woman and of Perusini's 46-year-old man, in whom nobody would have made a clinical diagnosis of senile dementia… (Alzheimer 1911, p. 356–358).

After the broad description of the case history of Johann F. (see above), Alzheimer gives some differential diagnostic reflections on this individual case, excluding especially the diagnosis of a vascular brain disease:

> …An arteriosclerotic brain disease could be excluded as no specific alterations of the vessels were found. The facts that vertigo and apoplectiform seizures had been completely absent during the first years of the disease and that the profound imbecility as well as the focal symptoms had developed quite gradually and with no sudden change, argue against a pure cerebral arteriosclerosis…
>
> …Autopsy revealed only a moderate opacity and thickening of the pia over the convexity of the brain. The brain vessels only showed minor indications of arteriosclerotic degeneration. The gyri of the frontal, parietal and temporal lobes were considerably narrowed on both sides, the sulci enlarged, while the central gyri did not appear particularly atrophic. There were no softened areas in cortex or white matter nor were any other circumscribed alterations to be found anywhere. The rest of the autopsy findings were without importance. Thus although the macroscopic observation of the brain revealed a diffuse atrophic process which has been established as the cause of the disorder, it did not clarify the nature of the underlying process… (Alzheimer 1911, p. 362).

After these differential diagnostic considerations he described in a very detailed manner the neuropathological features of the case, especially the details of the amyloid plaques:

> …Microscopical investigation showed the cortex to be filled in varying degrees of Fischer's plaques. Their number in general corresponded with the macroscopically recognizable amount of brain atrophy. They were numerous in the frontal lobe, scarce in the central gyri, present in enormous numbers in the parietal and partly also in the temporal lobes and again less numerous in the occipital lobe. There were no obvious differences between left and right sides. In the striatum, lentiform nucleus and thalamus they were also present in abundance. Within the cerebellum they occurred abundantly in individual lobuli, while they were completely absent in other large parts of the brain. Single plaques were also visible in the grey matter of the pons and in different nuclei of the medulla oblongata. In the spinal cord I only saw a solitary one in the posterior horn of a slice at the thoracic level.
>
> Among the plaques in the cerebral cortex many were of an extraordinary size, such as I have never seen, even in the cornu ammonis of senile dementia. They often extended through several layers. Some evidently arose from the fusion of smaller ones since they contained several central cores but others had one exceptionally big central core and an uncommonly large halo. Very frequently it was noticeable that the numbers of plaques at the surface and centre of the gyrus was smaller than those at the sides. In places where they were particularly numerous, the plaques were very rarely located in the first cortical layer. They usually started in the region with a sudden increase of glial reticulum at the transition to the first microcellular layer. There were sometimes a few particularly small ones at the very edge of the first to the second layers. They tended to accumulate in the 2nd and 3rd layers, were rarer in deeper layers but were still fairly numerous in the white matter… (Alzheimer 1911, p. 363).

Then he reports that, apparently, fibrillary degeneration was not found in this patient:

> …Rather remarkably, numerous preparations produced from very many different areas of the brain did not show a single cell with the peculiar fibrillary degeneration which I have previously described. This form of cell change, which occurred very frequently in the other case descriptions of this peculiar disease and which is not infrequently also to be found in severe cases of senile dementia, was missing here, although the plaques were of a size and frequency never seen before in the other cases. So although one might be tempted to do so one cannot relate plaques to fibrillary changes or vice versa… (Alzheimer 1911, p. 369).

Later on he discusses the relationship of the amyloid plaques in senile and presenile dementia:

> …I believe that the results of the microscopic examination of this case allow us to address a general pathological question, which has been of interest in anatomico-pathological research, as far as it is concerned with the psychoses since Fischers's papers. It cannot be doubted that the plaques in theses specific cases do in all relevant aspects correspond to those which we find in Dementia senilis. This is evident from the description which other investigators have given about the plaques in Dementia senilis, and this is obvious from the comparisons which Perusini, Simchowicz and I myself have undertaken in quite large amounts of material… (Alzheimer 1911, p. 371).
>
> …As I have pointed out in the connection with other histological findings, Dementia senilis and arteriosclerosis of the brain are in principle different disease processes. This has been proved even more conclusively because of the presence of senile plaques (Fischer, Simchowicz).
>
> If we now return to our case, we must of course still have reservations in asserting its attribution to the senile disease process solely on the basis of the presence of particularly numerous plaques. This is because, according to our previous thoughts, we can only consider the plaques as an accompanying feature of the senile cortical alterations, and one must first establish how the other alterations which we find in this case relate to those of senile dementia. The fibrillary degeneration of the ganglion cells is absent in this case, while in the cases of such presenile diseases described up to now it was particularly common. We now know that the same cellular degeneration had been observed frequently in cases of severe senile dementia but sometimes it is absent altogether. On the other hand, up to now it has not been found in any disease of younger people. The particularly frequent occurrence in most of the presenile cases might support their relationship to senile dementia. Moreover, we see in this case an extraordinarily heavy accumulation of lipoid substances in the ganglion cells, glial cells and the walls of the vessels, and especially in the numerous fibre-forming glial cells of the cerebral cortex and indeed in the whole central nervous system.
>
> Therefore we observe that all elements are altered in the same manner and direction as in senile dementia, but in this case, as in the others described by Perusini, the alterations exceed in their severity the average to be found in Dementia senilis…
>
> …A further peculiarity of the present case was the localization of the alterations. Even if we were dealing with a diffuse disease of the cortex alone, the parietal and temporal lobes bilaterally were unmistakably especially affected and much more so than the frontal brain. In ordinary cases of senile dementia, the frontal brain is the most severely diseased, as has been found only recently by Simchowicz…
>
> …However, the differences of the localization of the disease process cannot be used as an argument against relating these forms of dementia to Dementia senilis. After all, we know that the disease process of progressive paralysis allows for the emergence of numerous cases with an atypical localization as well as the majority of cases with a typical one.
>
> Further essential facts, which support the membership of such cases to the category of senile dementia, came out of the observations in two cases, which I have investigated recently.
>
> Due to circumstances pertaining to the Munich Department it is quite exceptional for patients with advanced Dementia senilis to be examined histologically, since most of these patients are transferred to asylums in earlier stages of the disease. How-

ever, amongst the older material made available to me due to the kindness of my former Chief, Herrn Professor Sioli, I was able to find a case in which alterations had only developed in late old age. Here the number of plaques, the severity of the nerve cell alteration, and the bulk of glial growth were no less severe than in presenile cases…

…Hence there appear to be a variety of intermediate forms between these presenile diseases and the typical cases of senile dementia. As similar cases of disease obviously occur in the late old age, it is therefore not exclusively a presenile disease, and there are cases of senile dementia which do not differ from these presenile cases with respect to the severity of disease process.

There is then no tenable reason to consider these cases as caused by a specific disease process. *They are senile psychoses, atypical forms of senile dementia.* Nevertheless, they do assume a certain separate position, so that one has to know of their existence as one has to know about Lissauer's paralysis, in order to avoid misdiagnosis. It will therefore have to be the task of future research to collect a larger number of such cases, which, as the observations in this department show, should not be too rare in order to establish the symptomatology of this group even more clearly, and to substantiate their position with respect to senile dementia on an even firmer basis by proving the existence of further transitional cases… (Alzheimer 1911, pp. 376–378).

Modern histopathological and moleculargenetic analysis of this case

As mentioned above, the histological sections were found among archives at the Institute of Neuropathology of the University of Munich (Graeber et al. 1997). The histological sections belonging to this case were first studied under the light microscope, then they were used for molecular genetic analysis with recently established methods for the molecular genetic analysis of neuropathological tissues (Egensperger et al. 1995; Graeber et al. 1997; Kösel and Graeber 1993, 1994).

Light microscopic examination of the histological sections from Johann F.'s brain yielded morphological results which are in complete agreement with Alzheimer's paper (Alzheimer 1911). Although many amyloid plaques were visible in the cerebral cortex of this patient (Fig. 4), neurofibrillary tangles (NFT) could not be detected. It is interesting to note that sections of the hippocampus and the entorhinal region were not available. Silver impregnations performed over 2 days in Alzheimer's laboratory using the Bielschowsky method (Fig. 4) were found together with a number of Nissl-stained specimens. In addition, numerous sections apparently prepared according to the methods of Mann, Herxheimer, and Weigert were discovered.

Using direct, nonradioactive sequencing of polymerase chain reaction (PCR) products (Kösel and Graeber 1993; Kösel et al. 1997), mutations at codons 692, 693, 713, and 717 or at other nucleotides within exon 17 of the *APP* gene could be excluded. The apolipoprotein E genotype of the Alzheimer's patient Johann F. was determined as ε3/ε3. Furthermore, screening for mutations in the presenilin genes is planned. However, given the limited amount of tissue available, the latter study was postponed until our knowledge on the genetics of Alzheimer disease is more comprehensive.

Historical and modern perspectives

As already mentioned, there has been much speculation (Hoff 1991) as to why Kraepelin so readily accepted Alzheimer's clinical and histopathological description. One reason may have been the competition between Munich and the group in Prague headed by Arnold Pick, whose coworker Fischer had published interesting findings on amyloid plaques (Fischer 1907). However, the case of Johann F. may provide a better explanation. Alzheimer submitted his report on this patient together with a detailed description of the cellular pathology of Alzheimer's disease in January of 1911, i.e., only a few months after the autopsy. This suggests that the studies on Johann F. became part of a long-planned manuscript. It also implies that Johann F., who was admitted with a diagnosis of possible vascular dementia (Fig. 1), was observed very closely during his stay in the psychiatric clinic. Finally, publication of the new eponym "Alzheimersche Krankheit" by Kraepelin (Alzheimer 1911; Kraepelin 1910) practically forced Alzheimer to write his own name as the patient's diagnosis in the autopsy book (Figs. 2, 3), only 3 years after his first description of the disease.

The tissue sections reported on in this paper likely represent the only histological material which is left from Alzheimer's own research on the disease that was named after him. The material and the stains are well preserved and of high quality, documenting once again Alzheimer's high technical standards (Meyer 1961). Examination of the histological sections under the light microscope demonstrated many amyloid plaques, but not NFT. Hence, the results are in complete concordance with Alzheimer's results on this case.

As evident from Alzheimer's paper (Alzheimer 1911), the case of Johann F. is remarkable from a histopathological point of view: numerous plaques but no NFT are present in the cerebral cortex of this patient. A significant number of Alzheimer cases may belong to this type, and it has been suggested that "plaque dementia" may comprise a separate subgroup of the disorder (Terry et al. 1987). While it is commonly held that both neuritic plaques (NP) and NFT can be found in the neocortex of Alzheimer's disease (Terry 1985; Tomlinson and Corsellis 1984), Terry et al. (1982) have, in fact, found that NFT are absent in the neocortex in 30% of elderly patients although they are present in the hippocampal area in these cases. In addition, NFT in the neocortex have a strong negative correlation with age in this disorder (Mann et al. 1985). In the absence of neocortical NFT, the question arises as to whether this disease is the same as Alzheimer's disease or a variation of normal aging, or whether it should be assigned a different name? Terry et al. (1987) tried to determine whether cases of Alzheimer's disease in elderly patients with neocortical NP and NFT differed from similarly demented patients with only NP. Several measurable parameters other than the presence of the neocortical NFT were evaluated.

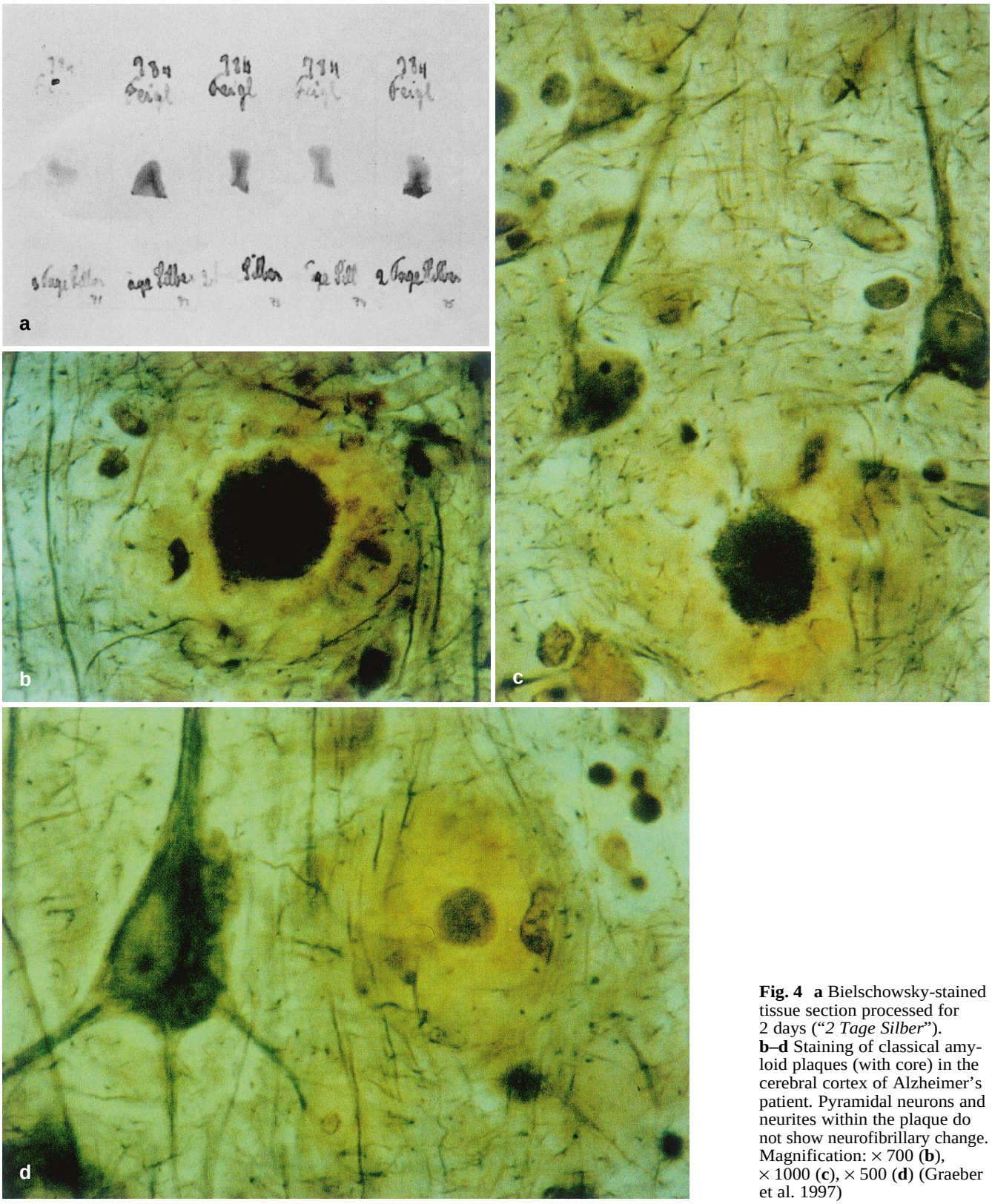


Fig. 4 **a** Bielschowsky-stained tissue section processed for 2 days ("*2 Tage Silber*"). **b–d** Staining of classical amyloid plaques (with core) in the cerebral cortex of Alzheimer's patient. Pyramidal neurons and neurites within the plaque do not show neurofibrillary change. Magnification: × 700 (**b**), × 1000 (**c**), × 500 (**d**) (Graeber et al. 1997)

Despite the absence of statistically significant differences in the measured parameters between the groups, an interesting pattern of differences was present. Almost without exception, the NP and NFT group was more abnormal than the NP only group, i.e., the former had higher cognitive dysfunction, more cortical atrophy, fewer residual neurons, lower amounts of choline acetyltransferase, and more NP. The levels of somatostatin, however, seem

to be an exception. The general pattern of greater overall severity associated with the presence of tangles is consistent with earlier reports correlating overall severity with NFT counts.

Since the hippocampus is often severely affected in senile dementia of the Alzheimer type (SDAT), Terry et al. (1987) also compared the numbers of plaques and tangles occurring there in the two groups. Tangles were present here in all cases, but no significant differences were found as to the concentration of these lesions. NP were less prevalent in the plaque-only group in two areas (midfrontal $P < 0.001$; superior temporal $P < 0.02$), but not in the inferior parietal region (Terry et al. 1987).

According to the conclusions of Terry et al. (1987) the data indicate that SDAT with neocortical NFT does not differ significantly from SDAT without them. The two types should, therefore, be considered as variants of the same disease, although the NFT, as is the case in the Alzheimer's disease versus SDAT question, are associated with a pattern of somewhat greater pathological deviation from normality. Further, since normal aging is not associated with numerous neocortical NP or NFT, the presence of both or either constitutes a disease process. It may be that SDAT of the type seen in the plaque-only group reflects an attenuated expression in the elderly of a disease with greater histopathological severity in the presenium, i.e., classical presenile Alzheimer's disease (see below!). Alternatively, the proliferation of NP only in cases of SDAT may represent an exaggeration of the same aging process that produces a few plaques in nondemented elderly patients. Alzheimer himself considered cases in which NP but not neocortical NFT were present to be the same disease. In light of the similarities in the parameters studied in this investigation, his classification should be continued.

The existence of such plaque-only or plaque-predominant Alzheimer's disease has subsequently been confirmed in other large series (Joachim et al. 1988; McKee et al. 1991; Probst et al. 1989) and seems generally well accepted by American neuropathologists. In most European laboratories, however, numerous neocortical NFT are still requisite for a neuropathological diagnosis of Alzheimer's disease, and the validity of a plaque-only Alzheimer's disease category is still questioned (Hansen et al. 1993; Tomlinson 1989).

Recently, Hansen et al.(1993) hypothesized a close relationship between the "plaque-only" Alzheimer's disease and the Lewy body variant (LB). Most cases of primary dementia in the elderly associated with LB have numerous senile plaques, but few neocortical NFT (Hansen et al. 1990, 1991). They can, therefore, be considered a subset of plaque-only Alzheimer's disease, and Hansen et al. (1993) coined the term "LB variant of Alzheimer's disease" (LBV). If, however, plaque-only Alzheimer's disease is not thought to represent a form of it, then such cases receive different nosologic designations, i.e., senile dementia of the LB type (Perry et al. 1990), diffuse LB disease, common form, with plaques and/or tangles (Kosaka 1990), or diffuse LB disease (Dickson et al. 1987). Hansen et al. (1993) have reserved the term diffuse LB disease for cases of dementia with brainstem and neocortical LB which do not have enough neocortical senile plaques to meet the National Institute on Aging diagnostic criteria for Alzheimer's disease (Hansen and Galasko 1992; Hansen et al. 1993). Given the restriction that we had to rely on the stains from Alzheimer's time, we were not able to detect any LB in the case of Johann F. The clinical picture does not seem typical of LB dementia either.

In a recently performed study Hansen et al. (1993) investigated the relationship between "plaque-only" Alzheimer disease and the LB-only variant. In a total of 147 cases (mean age 79.2) 110 were plaque and tangle Alzheimer's disease (mean age 78.6) and 37 were plaque-only Alzheimer's disease (mean age 81.0). There were 105 cases of pure Alzheimer's disease (mean age 79.1) and 42 cases of LBV (mean age 79.5). The 105 cases of pure Alzheimer's disease included 9 which were plaque-only. The 42 cases of LBV included 28 which were plaque-only Alzheimer's disease and 14 which were plaque and tangle Alzheimer's disease. Of the 110 cases of plaque and tangle Alzheimer's disease, 96 were pure Alzheimer's disease and 14 were LBV. Of the 37 cases of plaque only Alzheimer's disease, 28 were LBV and 9 were pure Alzheimer's disease. The only subgroup of Alzheimer's disease in which mean age differed significantly from the mean age for the entire 147 cases of Alzheimer's disease was the plaque-only pure Alzheimer's disease group. The mean age for these 9 cases was 85.4 compared to a mean of 79.2 for the total 147 cases ($P = 0.024$) (Hansen et al. 1993).

According to the theoretical considerations of Hansen et al. (1993), plaque-only Alzheimer's disease may simply represent a developmental stage of the condition in which neocortical tangles are destined to develop if patients survive long enough. Braak and Braak (1991) delineated an evolutionary sequence in the progression of Alzheimer's disease pathology based solely on entorhinal, hippocampal, and neocortical neurofibrillary pathology. In this scheme, neocortical plaque-only Alzheimer's disease occurs in stages 1–4 and plaque and tangle Alzheimer's disease does not appear until stages 5 and 6. Neurofibrillary pathology in the entorhinal cortex of LBV is intermediate in severity between age-matched controls and pure Alzheimer's disease (Hansen et al. 1991). Similarly, a study of hippocampal and entorhinal NFT, senile plaques, and granulovascular degeneration in senile dementia of the LB type (SDLT) found levels intermediate between those age-matched controls and those of patients with pure Alzheimer's disease (Ince et al. 1991). Such findings seem to support the contention that the plaque-only Alzheimer's disease pathology typically encountered in LBV or SDLT represents an earlier developmental stage in Alzheimer's disease, corresponding to Braak and Braak's stages 2,3, or 4.

Assuming that neocortical senile plaques do not correlate as well with dementia as do neocortical NFT (Berg et al. 1993), Hansen et al. (1993) ask why plaque-only Alzheimer's disease patients are as demented as plaque and

tangle Alzheimer's disease patients (Terry et al. 1987). In Terry's view, the results of their study imply that, for three-fourths of the neocortical plaque-only Alzheimer's disease patients, the answer might lie in the presence of concomitant LB pathology. The neuron loss which accompanies LB formation in the locus cereleus, substantia nigra, and substantia innominata may contribute a component of subcortical dementia to an evolving cortical dementia caused by early Alzheimer's disease pathology. The LB variants show greater neuron loss in the substantia innomnata than pure Alzheimer's disease and greater loss of neocortical choline acetyltransferase (Hansen et al. 1990). Neocortical LB may also contribute to the dementia. Hansen et al. (1993) also attempted to answer the question of why the few patients with plaque-only Alzheimer's disease which lack accompanying LB are as demented as patients with plaque and tangle Alzheimer's disease. Of the 147 cases of Alzheimer's disease in their study, only nine were both plaque-only Alzheimer's disease and pure Alzheimer's disease. Interestingly, this was the only subgroup which differed significantly in average age from the mean age for the total 147 cases. Specifically, the mean age of the nine plaque-only pure Alzheimer's disease patients was 85.4, while that of the total 147 Alzheimer's disease patients was 79.2 ($P = 0.024$). This may explain why these individuals were demented despite mild Alzheimer's disease pathology. The single best correlate for dementia is neocortical synapse loss (Terry et al. 1991), and normal aging is associated with synaptic decline (Masliah et al. 1993). The normal synaptic loss of aging could conceivably, therefore, lower the threshold for dementia in patients in the early stages of the neuropathological evolution of Alzheimer's disease. The result would be, as observed in these nine cases, plaque-only pure Alzheimer's disease with dementia in the very elderly, despite only a modest burden of Alzheimer's disease pathology (Hansen et al. 1993).

The finding that neuropathological tissue which has been stored for more than 80 years can be used successfully for molecular genetic analysis may be of general relevance in this context as the results of our study strongly support the concept that epidemiologically relevant data may be obtained using retrospective genotyping of archival brains (Graeber et al. 1995).

From a molecular genetic point of view it is of interest to note that Alzheimer's patient lacks the common Alzheimer's disease susceptibility allele, apolipoprotein Eε4 (Corder et al. 1993; Saunders et al. 1993). This allele represents a well-known genetic risk factor for the development of Alzheimer's disease; approximately two-thirds of all Alzheimer patients carry one or two copies of this allele. Some authors have found that presence of the ε4 allele is associated with an increased deposition of amyloid. Yet, influence of apolipoprotein E genotype on neuropathology is lacking in familial Alzheimer cases (Lippa et al. 1996). Unfortunately, pedigree data are presently unavailable in the case of Johann F., who was affected by a presenile form of the disease. While exon 17 *APP* mutations are absent, we cannot exclude mutations in the *presenilin-1*, *presenilin-2*, or other Alzheimer disease genes that may underlie the abnormal amyloid deposition in this patient (Citron et al. 1997; Levy Lahad et al. 1995; Rogaev et al. 1995; Sherrington et al. 1995). Therefore, the case of Johann F. may belong to a subgroup of Alzheimer's disease not only from a clinical and histopathological but also from a molecular genetic point of view. This is in agreement with the emerging concept of Alzheimer's disease not representing a single disease entity but a heterogeneous group of disorders (Roses 1996).

Historically, a distinction has been made between those cases of dementia arising in patients younger than 65 years and those occurring in older patients, categorized as Alzheimer's disease and SDAT, respectively (Tomlinson and Corsellis 1984). Many investigations have attempted to determine whether they constitute a single disease entity. The current consensus is that they represent the same fundamental disease process and differ principally in the severity of neuropathological alterations relative to age-matched controls (Terry 1985; Tomlinson and Corsellis 1984). In younger patients with Alzheimer's disease, a profusion of NP and NFT contrasts sharply with similarly aged normal subjects in whom such lesions are absent. Among older undemented individuals, however, small numbers of NP and even very rarely NFT may appear as a consequence of normal aging and not necessarily as early manifestations of disease. Numerous lesions in elderly patients with SDAT, at least in part, constitute a quantitative deviation from normal, while in younger patients numerous plaques and tangles seem qualitatively to differentiate diseased from unaffected control brains. Younger patients in general display a greater degree of neuropathological changes, such as cerebral atrophy (Tomlinson and Corsellis 1984) and neuronal loss (Mann et al. 1984). If Alzheimer's disease and SDAT do represent points along a continuum, an inverse relationship seems to exist between neuropathological severity and age. Pursuant to these observations, Terry et al. (1987) find, in agreement with others (Mann et al. 1984), that the concentrations of both NP and NFT in Alzheimer's disease decline with advancing age. The density of cortical NFT correlates well with many parameters of disease severity in younger patients with Alzheimer's disease. This is so despite the fact that NFT with the ultrastructural morphology of paired helical filaments are far from being specific to Alzheimer's disease. Such tangles have been reported in a variety of other conditions, including most categories of neuropathological disease (Halper et al. 1986; Wisniewski et al. 1979).

In conclusion, we quote the assessment of Förstl and Levy (1991) of Alzheimer's report of this case and its theoretical implications:

> ...Some of the problems discussed here have remained unresolved and continue to be a source of speculation to this day. These include the distinction between senile dementia and normal cerebral aging, as well as the question of whether Alzheimer's disease should be considered as a variant of senile dementia or as a separate disease. The neuropathological description includes important points

which have subsequently been "rediscovered" and are currently much debated. This applies to his detailed account of the changes in white matter to which Brun et al. (1986) have more recently drawn attention and to the lack of any close correlation between the number of plaques and those of tangles with the possibility that one might draw a distinction between predominantly "plaque dementia" such as this case and "tangle dementia" which was more of a feature of the 1907 case.

Alzheimer also devotes a great deal of space to the changes in glial cells and speculates about the possible role which these may have played in the formation of plaques. His careful distinction between the "core" and the rest of the plaque which he refers to as "halo" also strikes a notable modern note, as does his emphasis on the different variety of plaques seen both in his case and in others (Hansen et al. 1983).

Although many of these changes which he reports had previously been described both singly and collectively by others, notably Fischer, Redlich and Simchowicz, to whom Alzheimer always pays generous tribute, it is this paper which clearly establishes Alzheimer's central role and which fully justifies the attachment of his name to this intriguing disease"…

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