

## Senile Dementia and Oskar Fischer's Presbyophrenia: The Forgotten Giant's Contributions

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### Abstract

**Background:** In Peng [1] (2016), I point out that the eponym of Alzheimer's disease is a misnomer for two reasons: (1) Alzheimer did not deserve it; (2) Alzheimer's disease never existed, because it is a fiction. Such being the case, the question that needs to be raised now is: What is the organic cause of senile dementia in relation to Oskar Fischer's contributions?

**Objective:** My objective, therefore, is to focus on Oskar Fischer's contributions [2,3] (1907, 1910) to discuss three things: (1) what went wrong regarding the notion of senile dementia in the early 20th century, (2) what did Oskar Fischer contribute in 1907 and 1910 regarding the organic causes of senile dementia, and (3) the histopathological characteristics of such organic causes. This paper is, therefore, a follow-up as the second article after Peng [1] in a series of three articles, to be followed by a third one later.

**Method:** The methods undertaken were a standard literature review, with a critical view ranging from Fischer [2,3] (1907, 1910), Alzheimer [4,5] (1907, 1911), Bonfiglio [6] (1908), Perusini [7,8] (1910, 1911), Kraepelin [9] (1910), to Vedrani [10,11] (1910, 1911), and many others. The main focus, however, is on Fischer's contributions to the understanding of some aspects of the histopathology underlying (senile) dementia, which have been wrongly attributed to Alzheimer.

**Result:** I therefore propose what should be done to rectify this serious historical mistake which has been taught at every medical school throughout the world for more than a century. The reason is that the problems were further reinforced in the AAIC (Alzheimer Association's International Conference) held in Toronto in July 2016 where 5,000 experts on AD took part to debate on amyloid beta versus tau for a one-to-one cause-effect correlation to AD without any breakthrough, according to Prof. Amos Korczyn who attended the conference.

**Conclusion:** Subsequent researches have ignored Fischer's findings and, instead, attributed erroneously his findings to Alzheimer. It is time to correct this historical mistake by recognizing Fischer's findings as Fischer's Disease (FD) which he fully deserved.

**Keywords:** *Senile Dementia; Oskar Fischer's; Alzheimer's disease*

### Discussion

The notion of (senile) dementia has been in the literature for at least three centuries, with its meaning changing from one period to another. Notably, two general semantic trends can be discerned: (1) medical and (2) legal. They are of course interdependent upon each other and overlap in usage, with the first trend being more technical and the second being more common place: The medical sense focuses on whether dementia is a disease or not; if so, what it entails for a nosological classification, and if not, what the underlying organic causes must be. In contrast, the legal sense hinges on behavior in terms of varying mental states, such as different degrees of insanity.

Dementia as a medical notion in psychiatry was hotly debated in the 19<sup>th</sup> and the early 20<sup>th</sup> century, due primarily to Kraepelin's invention of dementia praecox 1896, which was to be called schizophrenia by Bleuler [12] (1911). It became a crucial issue in the early 20<sup>th</sup>

century when Fischer and Alzheimer published their articles. To wit: The establishment of the dementia praecox concept has brought clarity and order into this confusion. The Kraepelinian dementia praecox is an actual disease concept. The concept includes symptoms which occur only and always in dementia praecox. Thereby the disease group is provided with concrete delimitations [12].

Meanwhile, however, if the change from Latin to Greek is a "plus" for an actual disease concept in psychiatry, I wonder why the term becomes in the 21<sup>st</sup> century bipolar spectrum disorders. I am of the opinion that because schizophrenia carries a negative connotation, like in schizoencephalia (or schizencephalia) it was changed to a rather neutral term like bipolar spectrum disorders to avoid it. The change was probably inspired by or in response to Szasz's criticism [13] (1976).

Bleuler's statement characterized, contrary to his claim, the fundamental problem underlying the chaos in psychiatry at that time, a serious problem which surfaced in the midst of confusion, thereby leading to the erroneous eponym of AD in 1910 that has prolonged to this date. That is, Kraepelin and Alzheimer and their followers, notably Bonfiglio and Perusini, were confused on Auguste's medical conditions as to whether she had psychosis, presenile or senile dementia, atypical form of senile dementia, or even schizophrenia (dementia praecox); in other words, she was said to have no paralysis or paresis which was a form of psychosis as the manifestation of syphilis, but was diagnosed to have psychosis, and yet she had no syphilis even though she was severely demented according to Alzheimer and Kraepelin who had obtained such information from Perusini on and off from 1906 onward to 1910.

Their confusion, rather than clarity on account of dementia praecox purported by Bleuler, led Alzheimer, Bonfiglio, and Perusini to believe erroneously that they "discovered" a new disease in Auguste, which they could not classify nosologically when her symptoms were molded onto the fabric of dementia praecox. Their claim was an error that prompted Kraepelin to proclaim "This Alzheimer's disease of very severe senile dementia", thereby resulting in a chaos that has perpetuated to this date, with fabrications of the so-called "two hallmarks" of AD as may be evidenced by the publication in Science. See Peng's: Letter to the Editor of Science in 2006 which is recapitulated here to do justice to the historical facts in time and space.

The issue then was whether subdivisions were needed to delineate (senile) dementia pathologically or it was a single disorder. The reason for the issue was largely because according to Bleuler [12] (1911:278) Kraepelin somewhat narrowed down his concept, for instance, by separating senium praecox, subsuming presenile and senile dementia, from dementia praecox.

To that extent, Fischer took a strictly histopathological approach; it was more neurologically oriented, even though he was made Associate Professor of Psychiatry after Pick, in keeping with A. Pick's camp in Prague. In contrast, Alzheimer followed more or less the psychiatric tradition of progressive paralysis in terms of psychosis in line with Kraepelin's camp in Munich. The underlying cause of the issue was the claim in the Kraepelin's camp that dementia praecox was supposed to subsume all psychoses (or various clinical conditions) in constituting a single entity as stated by Bleuler above. That is, Fischer was anatomo-pathologically oriented in his approach but Alzheimer was preoccupied with the classification of differing mental states in dementia as a psychosis in clinical symptoms, because he thought he encountered a new case in 1906 which could not be classified under the existing paradigm, dementia praecox. The reason, as stated above, was that according to Perusini's description the patient, Auguste, did not have paralysis, but was severely demented; hence, a new disease was proclaimed by alluding to two unique features of Alzheimer's presentation in 1906 which have ironically become the two "hallmarks" of AD [1] (Peng, 2016). See also Peng [14,15] (2008; 2012).

However, there was a common objective; the two camps had been competing tacitly to find some organic bases to substantiate their clinical observations. As such, both camps regarded (senile) dementia as a mental disease. Nonetheless, there was a major difference: Fischer was not interested in the classification of the disease, for he took (senile) dementia as a given when he analyzed his 16 cases 12 of which were diagnosed to have (senile) dementia; Alzheimer, under the influence of Kraepelin for his ideas on classification and dementia praecox, was perplexed by what he thought was new when he heard the report of the clinical symptoms of Auguste's illness from Perusini. As a result, Alzheimer changed his diagnosis of Auguste a few times, from senile psychosis, to atypical form of senile dementia, to presenile dementia (most likely at Kraepelin's suggestion) in an attempt to conform to Kraepelin's new invention of senium praecox at that time. His

semantic confusion can be corroborated in his 1911 publication [5] regarding his second case---older than Auguste---for which he then claimed," the notion of senile dementia was never considered".

It is this general distinction of the two camps, coupled with the competition, from the late 19<sup>th</sup> century to the early 21<sup>st</sup> century, that has perpetuated to this date; such a distinction has also been gradually compounded by subsequent semantic confusions in the literature with unfounded exaggerations, misunderstandings, and unbelievable or totally unscholarly fabrications. See the details in Peng [1] (2016). The unfortunate result of the fabrications is the false claim of two hallmarks in AD and the neglect of all due credits Oskar Fischer fully deserved.

### Point of Departure

Since I have already concluded that AD is a fiction, I need to explain in advance why the fiction has perpetuated to this date, so as to give credence of support on the eponym of Fischer's Disease (FD) to replace AD. I believe that it is time to give due credits to Oskar Fischer whose contributions have been ignored, covered up, and misunderstood, or even erroneously attributed to Alzheimer.

### Fallacy of the Two Hallmarks

My main concern here is the twisting of historical facts by subsequent researchers after 1907 regarding the two hallmarks, viz., plaques and tangles, stemming from Bonfiglio's false assertion of Alzheimer's two unique findings in 1906. That is, subsequent researchers believe that Alzheimer presented two unique findings which he discovered but could not classify in accordance with Kraepelin's ruling paradigm, and that he also made histopathological illustrations of plaques and tangles in 1906, when he did nothing of that sort in 1906 for his oral presentation, which received no discussion as it was a failure, nor in his 1907 publication.

Without knowing such historical facts, let me illustrate briefly a vivid example of bold, public, and unfounded mistake which took place and I encountered and witnessed in an international congress organized by ADI, in 2013. It was encouraged by politicians, like Newt Gingrich, who naively proclaimed in writing, 2000, that "we would eliminate and cure AD by 2025".

His proclamation somehow excited two neuroscientists in 2013 for a debate in the final plenary session at the ADI Conference held in Taipei, Taiwan. One of them from Australia took the "No" first. He was followed by the other from Singapore who took the "Yes", saying that "we have only 12 years to go"; he even presented Auguste's "famous" picture in support of his histopathological illustrations.

The shocking point is that both, presumably neuroscientists specialized in the research on AD, had elaborate histopathological slides of plaques and tangles, stained in modern histological methods to show them as if Alzheimer had made them in 1906 for presentation in Tübingen and published them in a barely two page report; the truth is that his oral presentation received "Keine Diskussion" (no discussion) and his barely two-page case report has NO such illustrations. When confronted by my question of "where did you get those histopathological slides", they both had no choice but to admit that the slides were made in their own labs.

This elaboration of unscholarly debate also reminds me of the shocking publication in *Science* of 2006 accompanied by two interesting articles with stained slides of plaques and tangles also published in the same issue with Alzheimer's photo as the cover page. The purpose was to celebrate the occasion of centennial commemoration of Alzheimer's "discovery" of plaques and tangles and, erroneously, the eponym of AD in 1906.

Shocked by the publication, I wrote an open letter to the editor of *Science* at that time, requesting that it be also published to counter the utterly false impression given to thousands of readers. My request was tactfully denied. I therefore published it in my second book [15] (2012) as an Epilogue which is recapitulated below to prove that it is this kind of unscholarly and unscientific twisting of historical facts in time and space, published in *Science*, that has perpetuated the fiction of AD to this date.

### My Open Letter to Science: Does Alzheimer's Disease Really Exist?

Of the November 3, 2006 issue of *Science*, the cover page has Alzheimer's photo and two histopathologic illustrations which are accom-

panied on page 713 by a statement as follows: "Images from a state-of-the-art Bielschowsky-stained slide prepared by Alzheimer show the disease's hallmark pathological lesions – a neurofibrillary tangle at high magnification (left) and a tangle and several neuritic plaques (right)". The description for the Cover also says "On 3 November 1906, Alois Alzheimer described the pathological characteristics of the neurodegenerative disease that bears his name at the Clinic for Psychiatry at the University of Tübingen". I find both the statement and the description totally false.

I have made a thorough examination of several publications from a historical perspective: Fischer [2] (1907), Alzheimer [4] (1907), Kraepelin [9] (1910), Perusini [7,8] (1910, 1911), Bonfiglio [6] (1908), and many others. The evidence of my claims presented below is based on such an examination.

1. The two slides on the cover page are fake for the following reasons: (1) Alzheimer NEVER made or prepared any histopathological illustrations for his 1906 oral presentation or 1907 case report; (2) the two slides published by Science on the cover page were fabricated by someone, most likely in 2006 or earlier, at the Clinic for Psychiatry at the University of Tübingen, or elsewhere, to coincide with the event of the celebration, to make them look like Alzheimer had prepared them in 1906; (3) Alzheimer quit his first job in Frankfurt in June, 1902, and moved to Heidelberg for one year and then went to Munich in 1903 with Kraepelin; (4) when the patient died on April 8, 1906, Alzheimer was in Munich several hundred kilometers from Frankfurt; (5) he could not have prepared the said slides himself in 1906: (6) the quality of the two slides DOES NOT reflect the technology of the early twentieth century, because all slides published in Fischer [2] (1907), Kraepelin [9] (1910), and Perusini [7] (1910) were based on microscopic preparations or hand-drawn, and therefore did not have that kind of high quality images or resolution for photocopying; (7) the two slides CANNOT be found in all the published histopathological illustrations of Perusini's Case 1 which was Auguste D., the patient Perusini took care of and treated, because Alzheimer did not treat her nor did he observe, take notes of, and record her behavioral alterations; and (8) the two slides do not even match the three histopathologic illustrations which Kraepelin [9] (1910) plagiarized from Perusini's data, although the left slide shows a similar tangle.
2. Alzheimer NEVER had a job at the Clinic for Psychiatry at the University of Tübingen, nor was Auguste D. admitted there for treatment; she was admitted at the mental asylum in Frankfurt am Main under Perusini's care for treatment and observations; its Director was Dr. Sioli.
3. Alzheimer was trained as a medical student in Tübingen before 1888 and only presented his case report there on November 3, 1906 which according to Ballenger [16] (2006) was met with a big yawn. Ballenger's comment can be corroborated by Alzheimer's own publication [4] (1907) which says his oral presentation (Eigenbericht) received Keine Diskussion (no discussion).
4. Auguste D. did not just have the "two hallmarks". She had four brain diseases: (1) arteriosclerosis, (2) evenly atrophic brain, (3) miliary foci (or plaques), and (4) strange substance (tangles). I even suspect that in addition she had (i) untreated DM (diabetes mellitus), because she became completely blind towards the end – not psychic or psychological blindness purported by Perusini [7] (1910) – and had abnormal vascular growths in her lower limbs, and (ii) decubitus angina which caused her stupors. However, Alzheimer spent only two sentences to allude to the miliary foci Perusini had prepared for him.
5. Before 1907, Blocq and Marinesco [17] (1892) had published a case of senile plaques in senile dementia with the co-morbidity of epilepsy and Redlich [18] (1898) had also published two cases of miliary sclerosis (miliary necrosis to Fischer). Alzheimer was not aware of these publications or ignored them, although Perusini did mention Redlich in his 1911 publication [8].
6. It was Bonfiglio [6] (1908) and Perusini [8] (1910) who started the erroneous notion of two "hallmarks" in Auguste's autopsied brain; their supporting materials in their subsequent cases had other diseases like syphilis and abnormal conditions like epilepsy as well.
7. Senile plaques and neurofibrillary tangles were described in great detail by Fischer [2] (1907), who used the term "plaques" which

became known as Fischer's plaques in Vedrani [10] (1910). Perusini [8] (1911) changed his mind by following Vedrani [10] (1910) and called them Redlich's and Fischer's plaques and, in keeping with Vedrani [11] (1911), named presbyophrenia as Fischer's presbyophrenia. Even Alzheimer [5] (1911) himself had no choice but to reluctantly acknowledge Fischer's plaques while keeping "fibrillary patterns" taken from Kraepelin [9] (1910) for himself, although the three illustrations Kraepelin used to illustrate his so-called "fibrillary patterns" were not prepared by Alzheimer himself at all but by Perusini; Kraepelin simply plagiarized them from Perusini's preparations.

8. The description in *Science* made a serious mistake that gives the wrong impression that Alzheimer had described the pathological characteristics of the neurodegenerative disease with the eponym already "in the bag" at Clinic for Psychiatry at the University of Tübingen. The truth is that the eponym came out erroneously in Kraepelin's revised textbook [9] (1910), not because he saw any scientific value in Alzheimer's 1906 presentation but because he had been looking for a justification of his pet idea of "senium praecox" as a senile psychosis. To wit: In all three cases as approximately similar finding was presented by Alzheimer, a circumstance to which in addition the corresponding clinic picture speaks strongly in favour of the concept that we are dealing with a single disease process [19] (Bick, Adamucci, and Pepeu, 1987).
9. Perusini's histopathologic illustrations happened to be useful for his self-interest, thereby allowing Kraepelin to take advantage of the three illustrations mentioned above, which Perusini had prepared for his own publication [7] (1910) but could not use them, because Kraepelin had already used them [9] (1910) to proclaim "This Alzheimer's Disease of serious senile dementia".
10. The underlying motive for Kraepelin to proclaim the eponym was that he desperately wanted to down play Fischer's findings [2] (1907) in order to uphold the obscure and shaky description Alzheimer presented [4] (1907). To wit: In such cases we should at least assume a "senium praecox", if not perhaps a more or less age-independent unique disease process. The clinical pattern with this extremely serious process of dementia and far reaching speech disorders, signs of spastic attacks, differs decisively from presbyophrenia, which normally accompanies the simple age-related cortical alterations. It is possible that there exists a relation between these two diseases which previously were looked upon as presenile disease patterns [19] (Bick, Amaducci, and Pepeu, 1987).
11. However, I should mention that Kraepelin did not even attend the conference on November 3, 1906 or hear Alzheimer's oral presentation. Had Kraepelin heard it, why was there no discussion after Alzheimer's oral presentation, and why did he have to wait until 1910 to proclaim "This Alzheimer's disease" by plagiarizing Perusini's histopathologic illustrations?
12. The bottom line is that Kraepelin exploited Alzheimer by plagiarizing Perusini's histopathological illustrations to serve his political end against Pick and Fischer in order to downplay Fischer's far superior findings. His move was a political farce.

Finally, let me point out that the photo on the cover page of the November 3, 2006 issue of *Science* and the photo in the November 24, 2006 Morning Edition N P R (National Product Reports) are the SAME photo of Alzheimer. But why is one the mirror-image of the other?

Is there a resurrection in the order of the scandalous fabrication of ES cell Research committed by Dr. Hwang of South Korea, which was also published in *Science*? I am a life-member of the AAAS. Are we doing honest science or hocus-pocus fiction?

My answer to the question of "Does Alzheimer's Disease Really Exist?" is that it never existed, does not exist, and will never exist. This is not to say that neuritic plaques and neurofibrillary tangles do not cause cortical lesions to result in dementia as a behavioral consequence. The crux is that AD is a misnomer, and therefore a fiction [1] (2016). A different term must be called for, such as Dementia with Plaques and Tangles (DPT), patterned after DLB (Dementia with Lewy Bodies).

Perhaps, Fischer's Disease (FD) is better suited to replace AD, as I have now proposed in this article, hoping that the medical community will come to its senses to correct the serious mistake made in 1910 by Kraepelin [9]. The correction is more than 100 years overdue.

### It is Time to Give Oskar Fischer all Credits He Deserved

In the preceding sections, I have on and off alluded to Fischer's contributions in addition to my demonstration that the so-called AD is a fiction [1] (2016) invented by Kraepelin [9] (1910). Because there were more contributions by Fischer, which have been neglected in the literature, I believe it is appropriate that, for the good of the general public, all investigators on (senile) dementia are reminded of these important contributions.

### Oskar Fischer: The Forgotten Giant

Oskar Fischer was a German Jew, a physician at the German School of Medicine in Prague in the then Republic of Czechoslovakia. He served as an assistant to his mentor and superior, Prof. Dr. Arnold Pick. The German School of Medicine had two sections, The German Section and the Czech Section in the same building compound. When the Nazis occupied Prague, the Czech Section was closed. After the defeat of Nazi Germany, the German Section was closed and the School became what it is today: A Czech School of Medicine. However, being a German Jew, Fischer was sent to the Concentration Camp during the Nazi occupation of Prague and died of a tragic death there.

### A Brief Description of Fischer's Major Contributions

In 1907, Fischer published his important article entitled "Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz". The original German text was translated into English for me. The following is an excerpt from the English translation to point out the major and important contributions which are also extremely significant to current researches on dementia.

It is a lengthy article, originally presented at a conference as a keynote lecture of the Scientific Society of German Physicians in Prague on June 19, 1907. It was published in 1907 from the German Psychiatric Clinic in Prague by Karger in *Monatsschrift für Psychiatrie und Neurologie* (with A. Pick as its Director). But, interestingly enough, the article was considered a provisional communication (Vorläufige Mitteilung). He must have had a very high standard of his own work, or Pick must have had a very strong expectation of scholarship from his assistants, of whom Fischer was but one, because judging from the content and presentation of the article, which has twelve printed pages, it is first-rate, even by today's standard, when pitted against Alzheimer's very short paper, barely two-pages in length, also published in 1907.

There are several remarkably intriguing and scientifically very sound features of Fischer's article which describes 16 cases of his own plus 45 some others. For the full details of his contributions, see the original text.

1. He includes eight microscopic, histologic illustrations of the neuropathology, the first one of which shows a very clear plaque (Herde); he calls it miliare Nekrose (miliary necrosis) as well although he also refers it to Redlich many times for Redlich's confirmation of senile plaques in two cases and discusses them at length in spite of his disagreement with Redlich on the detailed pathogenesis regarding glial cells.
2. He also in the same illustration points out the formation of such a senile plaque from an early one (mit bereits beginnendem Hofe) which he calls focus (Hof) or halo.
3. The rest of the eight illustrations show the cause-effect relationships of senile plaques (or miliary necroses) and neurofibrillary tangles; because some of these miliary necroses were admixtures of senile plaques and neurofibrillary tangles, he calls them peculiar (or strange) growths of neurofibrills and is puzzled, thereby referring to them as presbyophrenia.
4. He separates senile plaques (or miliare Nekrosen) in three cases confirming the richness of Redlich's description of two cases, where the cortex is interspersed with foci.
5. He identifies nine cases wherein there are many plaques some of which can even be found in every serration (i.e., gyrus); only in four

cases are there none to be found in many different parts of the brain. In general, the foci are either numerous or scanty, but always of the same fabric, even though the slightly smaller foci are found generally scantier.

6. The neurofibrillary tangles (which he calls "tangled up growths of the neurofibrills") are also everywhere to be found; however, they can be found more often in the brains which are richly interspersed with plaques and where the single clubs are bulkier and bigger.
7. Where possible, he describes the cases of admixture as "peculiar" and calls them "presbyophrenia" (old man's mind), a term he also uses to refer to Alzheimer's case later.

I should emphasize that Fischer publishes four more articles after 1907 -- one in 1910, two in 1911, and one in 1912 -- all of which are quoted widely. His eight histopathologic figures in [2] 1907 are readily available in his original article with the detailed description provided in his main text; because of space limitation and copyright, they are not reproduced here.

These histopathologic illustrations in the article of [3] 1910 are the varying augmentations of the original microscopic preparations, resulting from the staining method he employed, presumably Bielschowsky, although he also used other staining methods for the purpose of comparison; he had even employed one by his own techniques to compare the results with others. These illustrations are to demonstrate that the frequency of the plaques is the cause of senile dementia which to him was a disease, and that the formations as a proliferation procedure of the neurofibrillary tangles are caused by a damage to the fibers inflicted upon by the adjacent necrotic foci.

In other words, as far as I can discern from his very sophisticated text, there are close interactions of miliary foci, senile plaques (miliary necroses), and neurofibrillary tangles; miliary foci cause damages to neurofibrils in a proliferation procedure, such that in the end of the proliferation of the damages they lead to the formations of neurofibrillary tangles; and the miliary foci then turn to miliary necroses (senile plaques) as a result.

In order to prove his point, because of the great frequency of plaques in those cases diagnosed as senile dementia which was a disease to him, he examined 45 medical cases of progressive paralysis, 10 normal brains and 10 cases of different "non-organic" psychoses, thereby showing the result of a great number of serrations from various regions of the cortex but without similar mutations therein whatsoever; only in one of the seven cases of brain atrophy, after softening foci, can a few foci be found which are identical with those found in senile dementia.

This single case of dementia with miliary foci, interestingly enough, has arteriosclerotic brain atrophy. This raises several interesting speculative questions:

1. What is the relationship of miliary foci and arteriosclerosis in brain atrophy that eventually leads to dementia?
2. Will the miliary foci become miliary necroses (plaques) in the presence of arteriosclerosis without causing damages to the neurofibrils in the brain as well, either at the same time or later, to result in neurofibrillary tangles as a proliferation procedure?
3. Is the co-morbidity of arteriosclerosis and miliary foci a sufficient ground on which to suggest that miliary foci also cause arteriosclerosis, since they are extra-cellular in addition to their also being capable of causing damages to neurofibrils which are intracellular to result in neurofibrillary tangles? If the answer to this third question is affirmative, it should indicate that miliary foci are the common cause of both neurofibrillary tangles and arteriosclerosis.
4. Are senile plaques and neurofibrillary tangles two pathologies (or diseases) to Fischer then and to subsequent investigators later or two phases of one pathology (or disease)? To Fischer, the answer to the fourth question is that they develop from one pathogenesis in two phases; namely, simple dementia (without glandular necrosis) and presbyophrenia (with glandular necrosis). This issue was hotly debated later, NOT as an issue implicitly raised in Fischer's cases, but erroneously as an issue of the two hallmarks of AD, when

Alzheimer did very little to examine and analyze them, not to mention that he devoted only two sentences to refer to senile plaques, an important point that will become clear later.

As was mentioned further above, in the 2016 AAIC held in Toronto, July 24<sup>th</sup>-28<sup>th</sup>, discussion on AD turned to tauopathy in an attempt to replace the Amyloid Beta Hypothesis for the one-to-one cause to AD. Will the proliferation of miliary foci described above by Fischer be considered tauopathy via miliary necroses (plaques) and glandular necroses (neurofibrillary tanles) or arteriosclerosis for causing dementia? If so, it is only one of many causes for dementia which is not a disease, thereby having nothing to do with AD which never existed to begin with (Peng, [1] 2016).

I should add, however, that Fischer was preoccupied with the idea of proving senile dementia as a disease the pathological evidence of which, he thought, was the presence of senile plaques; he calls them miliary necroses which come from miliary foci (early forms of plaques) that also triggers the formation of neurofibrillary tangles (or glandular growths of neurofibrils). Thus, he did not pay much attention to arteriosclerosis as a cause of dementia, nor was he aware of the strong possibility of the relationship between miliary foci and the formation of arteriosclerosis, even though miliary foci as the early forms of senile plaques (miliary necroses) are extracellular to begin with.

Not with standing, he is aware that the plaques and glandular formations of neurofibrils are co-morbid in many of his 16 cases; but he is convinced that the plaques after softening foci, found also in one of the seven brain atrophy cases, are identical with those in senile dementia, and therefore they must have been the cause of senile dementia and should not be unfamiliar. However, he is puzzled by the co-morbid admixture of plaques and glandular necroses or foci of formation as a proliferation procedure to result in the growths of clubs. Thus, he poses an interesting question: If such glandular necroses only show up in the cases of senile dementia, and only at the rate of this high percentage, how can the cases of miliary necroses in senile dementia differ clinically from those without them? He then draws the summary of the clinical symptoms of all cases, a summary that leads to a surprising result as shown below:

1. The cases without necroses are simple senile dementia with a simple decrease of all mental abilities.
2. Those with necroses are more or less downright presbyophrenia with confabulation and worse disorders of memory.
3. Indeed, especially those medical cases, which show the most numerous glandular necroses, distinguish themselves by a faster deterioration and particularly by various hallucinations.
4. Even though we do not have any specific mutations of the senile cerebral cortex, we have to acknowledge the glandular necroses as the essential pathologic-anatomical substrate.

From the above summary, it is clear that to Fischer, as to Alzheimer later [5] (1911), miliary necroses (plaques) and glandular growths (tangles) were mixed together as one pathology which had an intriguing development, as he shows in his description which will be elaborated below.

### **Fischer's Plaques and Fischer's Presbyophrenia: The Pathogenesis**

From the above description of Fischer's major contributions it must follow that there are four neuropathologies with which he was concerned, even though he was "bogged down" on the admixture of plaques and tangles as one pathology: That is, (1) miliary foci/miliary necroses (senile plaques), (2) glandular growths of the neurofibrils (neurofibrillary tangles), (3) arteriosclerosis, and (4) brain atrophy. In addition, in some of his 16 cases, he found the same richness of senile plaques as in Redlich's two cases, although he disagreed with Redlich on the pathogenesis. So, let me summarize the differences from his [2] (1907) publication.

### **Redlich's Observations**

It is of great interest to note that Redlich makes many observations of the pathology of his two cases, with which Fischer agrees; the

difference lies in the way in which the two draw their conclusions regarding the pathogenesis of the observed pathology. I shall allude to Redlich's observations first, which are followed by his conclusion.

1. He calls the pathology "miliary sclerosis" which is a peculiar change in the brain cortex to him. It is interesting that both Fischer [2] (1907) and Alzheimer [5] (1911), who much later by four years followed Fischer's observations, also call the pathologies of their cases "peculiar" or "strange".
2. The brain cortex is littered with plaques 4 - 6 times as big as a ganglionic cell, which are intensively colored by carmine, and are diffusely scattered all over. This observation is also interesting because both Fischer [3] (1907) and Alzheimer [5] (1911), much later probably by following Fischer's observations, make more or less a similar observation in their cases.
3. These plaques can be found in large quantity in the layers of small pyramids. In the center, they show a homogeneous, slightly granular texture, "while in the periphery a fine fiber-felt wisp is still traceable, which form a gradual passage to the surrounding glial substance." It is important to point out that both Fischer and Alzheimer in the said articles also mentioned the layers of pyramids (or higher layers) in their cases.
4. In the center itself there are then still, frequently, remnants of the nucleus of a protoplasm or pigment lumps. The remnants of the nucleus are also observed by Fischer, but it is how to interpret such remnants (their presence and absence) that constitute Fischer's departure from Redlich's conclusion.
5. According to Fischer, then, Redlich thinks that these plaques are proliferated glial cells and that the aforementioned remnants of the nucleus of the protoplasm are remnants of the primary glial cells. (Both Fischer and Alzheimer following Fischer also mentioned the glial involvement in their cases alluded to above)
6. Redlich also thinks, Fischer continues, that the main reason for the glial proliferation is the atrophy and the losses of several ganglionic cells, and further believes that he has seen such fading ganglionic cells in some of the foci.

### Redlich's Conclusion as Reported by Fischer

Even though Fischer agrees with Redlich that the plaques are peculiar, there are differences in the interpretation of the pathogenesis, albeit the plaques in Redlich's two cases and those in Fischer's are identical.

1. According to Fischer, Redlich understands what he described as "glial proliferations".
2. He thinks that such a plaque is caused by a peculiar proliferation of the glial cell which would lose its nucleus later.
3. Such a glial cell then occupies the place of an already dead ganglionic cell.

Fischer then points out that there are many arguments against Redlich's opinion:

1. Redlich's opinion is based in the main on the appearance of the foci in common Eosin- and van Gieson-preparations, in which these foci give the impression of a simple condensation of the basic fabrics of the brain cortex, often with a hint of subtle radial-like strips; however, at the time of staining, the whole appearance is already different, dense, subtly threaded.
2. Since Redlich appositely describes the appearance of the neuroglia as the structural quality of cotton in comparison, he must himself admit that this impression and the appearance of glial cells are so very different that not "without difficulty" can the connection with the common web-like cells be made.
3. Redlich fails to stain the glial cells; in contrast, Fischer claimed that in his successfully stained preparation of glial cells, it cannot be verified that there are even a single glial fiber or proliferated glial cells in the plaques or around them.

4. Redlich's statement that there is often a nucleus or there are remnants of a nucleus in the center of a focus is in general incorrect, especially in the idea of making such a nucleus look like the origin of these plaques.
5. The reason, Fischer continues, is precisely because nowhere in the smallest plaques as well as those in the initial stage which can be called foci is there a nucleus to be found, but only in larger plaques and also mostly in the periphery are there nuclei.
6. Fischer comments that this situation is best explained by way of the growth of gradual enclosure of nervous tissues. (I assume that "the growth of gradual enclosure of nervous tissues" is the beginning of neurofibrillary tangles ---FCCP).

#### **Fischer's Own Conclusion**

Having stated his arguments against Redlich's conclusion, Fischer then presents his conclusion; he tries to tie the difference from Redlich's conclusion to his own cases where he compares with other investigators' materials, such as Cajal, Bielschowsky, Marinesco, Nageotte, among others (see the text for his full account). The important point here is that his conclusion, though a vague notion of "necrosis" which is pitted against Redlich's "sclerosis", makes the pathological connection with neurofibrillary tangles, a connection that is totally absent in Redlich's two cases (at least in accordance with Fischer's report); his reasoning of the pathology is also interesting, despite the fact that he remains uncommitted regarding its pathogenesis.

1. According to all the available materials, it can be induced that the smallest plaques are most surely the initial phase of foci.
2. In them, an immediate small granule can be found without any connection to any fabric or blood vessel.
3. But with the application of haematoxylin it turns bluish, and yet according to Bielschowsky it was a granule colored slightly reddish.
4. Such a granule often shows a thread-like structure, similar to a bacterial colony.
5. The whole appearance leads to the conclusion that it is an unfamiliar precipitate the character of which still remains a mystery.
6. It is neither the plasma nor something neural; it does not contain lime or iron, either; nor is it a fibrin, and the bacterial staining also led to negative results.
7. The best possible way is to regard it as a peculiar necrosis, but here it must be cautioned that the perishing of neural elements – cells or fibers—at least in the smallest of the foci cannot be proven.
8. In any event, the term necrosis is probably most fitting, because the appearance of the smallest plaques is reminiscent of a necrotic area.
9. As the plaques grow bigger, the fibrils elude more and more, and those fibrils which are located in the proximity of the plaques tend to show the phenomenon of peculiar proliferations, thereby taking the shape of spindle-like distensions resembling clubs with multiple branches which tend to arrange themselves radially at the margins of the plaques with the swollen ends facing outward, so much so that the whole thing pretty much looks like an actinomyces gland/filament.
10. Therefore, the whole plaque is nothing but a necrosis resembling most likely a peculiar precipitate that cannot be precisely defined with proliferated changes near the adjacent neurofibrills.
11. See my detailed explanation Peng [14,15] (2008, 2012) of the differences between Redlich and Fischer regarding the involvement of glial cells. The differences lie in the interpretation: That is, Redlich draws his conclusion on the basis of his two cases at the end to indicate that the two cases had glial cases at the end, and therefore these two cases must have had the involvement of glial cells at the

beginning; but Fischer draws his conclusion on the basis of his many cases at the beginning of the formation of plaques without any involvement of glial cells, and therefore there must have been no involvement of glial cells at the end.

### Conclusion

#### The Potential Impact of Fischer's Disease (FD)

In view of Fischer's arguments and conclusion, in spite of his rather vague notion of necrosis, such plaques were subsequently called Fischer's plaques in the literature, even by Alzheimer himself [5] (1911). And Fischer's presbyophrenia, a term he used to denote the clinical symptoms of the admixture of plaques and tangles, also appeared later in the literature. More important, however, was his description of the connection with (or admixture of) neurofibrillary tangles. (See the Section above). I have, therefore, ventured to call the pathology he described Fischer's disease (FD). I believe that it is this connection of miliary foci (senile plaques) and glandular growths of neurofibrils (neurofibrillary tangles) – in club-shape--- which he displayed vividly in [2] (1907) in three stages and expanded in [3] (1910) to eight types by bringing cases of vascular origin---that was meant to be the potential impact upon later researches; it is an impact that subsequent investigators have unfortunately missed in as much as trying to solve the two "hallmarks of AD" independently but mistakenly through the Amyloid Beta hypothesis or later in 2016 by tauopathy for a one-to-one cause-effect correlation to AD which is a fiction.

The seeking of such a correlation is a serious mistake, a wild goose chase for a fiction, because dementia is not a disease but, rather, caused by totality of the effects of wear and tear, many-to-one, owing to aging which is the ongoing process of wear and tear.

#### The Unfinished Tasks Left by Fischer

There are several important, unfinished tasks left by Fischer in 1907 and 1910. Whether or not they were dealt with later in his subsequent publications need to be looked into by those who want to pursue the line of Fischer's inquiry. For instance, (1) the connection of plaques and tangles through proliferation as to whether they are two phases of one pathogenesis or not; (2) as well as the many-to-one pathological correlations, vascular and non-vascular, with senile dementia. These unfinished tasks left by Fischer must be pursued without using the fiction of AD as a contrast to invent new terms.

The wild goose chase must be abandoned, for senile dementia is not a disease and can be vascular or non-vascular in origin owing to wear and tear as the ongoing process. It is drastically different from Alzheimer's publication (1911) which simply followed many of Fischer's findings in [3] (1907 and [4] (1910) and is completely missing in all subsequent literature other than the creation of new terms to contrast AD.

I for one will pursue Fischer's line of insight from two angles---(1) autophagy and (2) apoptosis---when they are carefully studied from the point of view of wear and tear independent of AD which is a fiction (Peng [1] 2016). The wide implications of my conclusion are that in the absence of AD, as it is a fiction, (1) PD, PSP, Epilepsy, SCA, Pick's Disease, MS, HD and others are all bound by wear and tear, because of apoptosis, to result in dementia of one form or another. Therefore, I shall divide the unfinished tasks as outlined into two categories: (1) neuropathological and (2) behavioral.

#### Neuropathological Category

It is time to stop using AD, which is a fiction, as a contrast to claim the existence of vascular dementia (Paul, Cohen, Ott, and Salloway [20] 2005) or FTD (Frontal-Temporal Dementia/Disease) for three very important reasons:

1. Fischer already verified and presented evidence that dementia can be vascular or non-vascular in origin, as I have already amply described.
2. Auguste's dementia was of vascular and non-vascular origin (Peng [1] 2016) coupled with her internal and external hydrocephalus, and evenly atrophied brain. Note that in 1906 there was no VP shunt as a neurosurgical technique available to treat hydrocephalus.

3. The latter two ---- hydrocephali --- are now shown to cause serious behavioral alterations resulting from damage to the brain functions in a case study at the BIT 4th Annual World Congress of Geriatrics and Gerontology, 2016. And PD is shown to cause apoptosis which is bound to result in dementia, as was also reported at the same BIT World Congress, 2016. Such being the case, it makes absolutely no sense to claim that autophagy paves a way for application to cure diseases like AD and PD, as reported by many TV news announcements in 2016, when the Nobel prize in physiology (or medicine) was awarded to Dr. Ohsumi of Japan. My view is that any neurological disorders causing apoptosis or behavioral alterations, because of wear and tear, are bound to result in dementia, whether we like it or not, without bringing in fictitious AD for co-morbidity with PD to claim PD Plus, for instance.

### Behavioral Category

Although Fischer's publications mention mostly neuropathological causes at autopsy, by implications such causes were bound to have altered each patient's pre-mortal behaviors. However, he did describe some as mentioned above in his publications. I therefore venture to add that when any patient is diagnosed to have dementia, the physician usually gets the information from three sources:

1. observations of the patient's responses to questions of the present, like time, dates, and the goings-on,
2. information from the patient's family members who have observed the patient's daily life at home, and
3. the results of a test, psychological or otherwise.

Seldom does a physician have an opportunity to observe the patient's instantaneous, unprepared, or even spontaneous behaviors to the external environment in a dyadic interaction with a dyadic partner, in order to detect the evidence of behavioral alterations that indicate the symptoms of memory impairment which underlies dementia. The description, recapitulated below as an example, is a concrete observation of cases by Fischer in varying contexts of situation.

1. The cases without necroses are simple senile dementia with a simple decrease of all mental abilities.
2. Those with necroses are more or less downright presbyophrenia with confabulation and worse disorders of memory.
3. Indeed, especially those medical cases, which show the most numerous glandular necroses, distinguish themselves by a faster deterioration and particularly by various hallucinations.
4. Even though we do not have any specific mutations of the senile cerebral cortex, we have to acknowledge the glandular necroses as the essential pathologic-anatomical substrate.

To these observations, I would like to present a vivid example of a case *in vivo*, whom I encountered on Nov. 20<sup>th</sup>, 2016, at the 4<sup>th</sup> BIT World Congress during a lunch break. The following is what happened on that date, keeping in mind that the context of situation was a lunch break at an international congress, not at a restaurant.

1. A man suddenly came to my table and sat next to me, saying he appreciated my article on Alzheimer's Disease. He wanted to know the symptoms of AD.
2. He said right away, "My parents were diagnosed to have AD. My brother and sister were also said to have AD. What are the symptoms?"
3. I replied, "AD is a fiction. Did your parents have any vascular disorders, like a stroke or some other conditions?"
4. He was puzzled for several seconds but repeated a few times, "What are the symptoms?"
5. At that time, I replied, "How old are you?". He replied, "78?". I therefore replied, "I don't know what you are after. What symptoms you want to know? Dementia is caused by wear and tear"

6. As I was drinking a glass of juice, a staff-helper came to collect some empty dishes, He suddenly told the helper, "Get me also a glass of juice". She was somewhat shocked and told him "You get it yourself".
7. Realizing the awkward situation, I politely asked the staff-helper, "Kindly get him a glass of juice". She did comply and brought a glass of juice back. But he never touched it nor did he thank her for bringing the glass of juice to him.
8. At that time, someone else, probably a friend, came in to sit next to him. He then turned to the friend and engaged in a conversation probably unrelated to the subject of symptoms. Their conversation continued for quite some time, completely forgetting that he had been engaged in technical questions of AD and its symptoms with me. As I finished my lunch, I therefore stood up and left while he continued his conversation with his friend.
9. Now, here are the symptoms of his behavioral alterations, probably in line with Fischer's simple dementia in production, pertinent to his memory impairments
  - a. He could NOT make the distinction between a restaurant and a lunch hour at an international congress, when he treated the staff-helper as if she was a waitress and ordered her to bring a glass of juice.
  - b. When she told him, "You get it yourself", her rather unhappy reply did NOT dawn on him that he had made a mistake, because she was not a waitress and it was a lunch hour of the world congress he was attending.
  - c. He did not even touch the glass of juice, nor thank her, when she brought to him what he wanted. Perhaps, he forgot that he had asked for it.
  - d. When his friend came in, he turned to him with his back on me, forgetting that he had been in the midst of an "important" question-and- answer session with me regarding the symptoms of AD in relation to his parents, brother and sister, and probably to himself.
  - e. Normally, a healthy person, when an important conversation is interrupted by someone else, will most likely say to the dyadic partner "Excuse me", or something to that extent, before he turns around to engage in a completely different conversation with another dyadic partner. But he did nothing of that sort, most likely forgetting that he had asked the important questions of the symptoms of AD in the midst of a conversation with me, just like he forgot that he had requested, inappropriately, a glass of juice but did not even touch it when it became available.
10. In the evening of the same day for the farewell buffet dinner, he saw me again but never said word of the incident at lunch time. Normally, a healthy person would immediately come to me to apologize that the conversation with me was interrupted by a friend. Probably he did not even remember that the conversation with me took place.

Here, I would like to point out four clues to summarize this man's memory impairment as symptoms displayed in the production of spontaneous behaviors to the external environments. (1) He could not make the distinction between a restaurant and the lunch hour during a world congress he was attending. (2) He could not remember what he had asked a glass of juice for, because he did not even care to drink it when it became available. (3) He could not remember that he had been engaged in an important conversation with me, concerning his parents, brother and sister, and himself regarding the symptoms of AD, and switched to another conversation as if the preceding conversation with me had never taken place. (4) Finally when he saw me in the evening of the same day, he could remember me but did not remember that he had neglected me in a conversation when it was interrupted by his friend.

Of course, similar tasks described above could not have been undertaken by Fischer. But the fact remains that there is a biological and behavioral connections between senile dementia and Fischer's presbyophrenia as he described. Such connections must be pursued rigor-

ously without engaging in a wild goose chase for a fiction. The problem lies in the long-term longitudinal approach of memory impairment when patients are diagnosed to have Fischer's simple dementia, without jumping the gun to misdiagnose them as suffering from AD. If such patients have vascular disorders they can be handled fairly. But there is no animal model that can be used to mimic human memory impairment.

I must emphasize that what Alzheimer described in 1911, after Kraepelin's invention of "This Alzheimer's disease of senile dementia [9] (1910), is NOT Alzheimer's disease re-discovered, as Bick and others have claimed. Rather, Fischer had already described in great detail what Alzheimer followed later. He who describes and presents the findings first has the priority in any scientific endeavor. For this reason, Fischer's Disease (FD) must replace the fiction of AD to set the record straight in order to correct the historical mistakes which have perpetuated for more than 100 years now.

### Bibliography

1. Peng FCC. "Is Alzheimer's Disease A Fiction?" *Clinical Research and Trials* 2.1 (2016): 108-111.
2. Fischer O. "Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine Regelmässige Veränderung der Hirnrinde bei senile Demenz". *Monatsschrift Für Psychiatrie und Neurologie* 22.4 (1907): 361-372.
3. Fischer O. "Die presbyophrene Demenz, deren anatomische Grundiage und Klinische Abgrenzung". *Zeitschrift für die gesamte Neurologie und Psychiatrie*. Originalen 3 (1910): 371-471.
4. Alzheimer A. "Über eine eigenartige Erkrankung der Hirnrinde (About a Strange Disease of the Cerebral Cortex)". *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Cerichtliche Medizin* 64 (1907): 146-148.
5. Alzheimer A. "Über eigenartige Krankheitsfalle des späteren Alters". *Zeitschrift Gesamte Neurologie und Psychiatrie* 4 (1911): 356-385.
6. Bonfiglio F. "Di speciali reperti in un caso di probabile sifilide cerebrale". *Rivista Sperimentale di Freniatria* 34 (1908): 196-206.
7. Perusini G. "Über klinisch und histologisch eigenartige psychische Erkrankung des späteren Lebensalters". *Histologische und histopathologische Arbeiten über die Grosshirnrinde* 3 (1910): 297-358.
8. Perusini G. "Sul valore nosografico di alcuni reperti istopatologici caratteristici per la Senilita". *Rivista Italiana di Neuropatologia, Psichiatria ed Elettroterapia* 4 (1911): 145-213.
9. Kraepelin E. *Psychiatrie: ein Lehrbuch für Studierende und Ärzte*. Klinisch Psychiatrie. Leipzig: Barth (Volume 2) (1910).
10. Vedrani A. "Le placche di Fischer". *Il bollettino dei Manicomi Fasc 7* (Volume 7) (1910).
11. Vedrani A. "Presbiofrenia e sphaerotrichia cerebri multiplex di Fischer". *Quaderni di Psichiatria* 1 (1911): 1-15.
12. Bleuler E. *Dementia Praecox or the Group of Schizophrenia, 1911*. New York: International University Press (1950).
13. Szasz T. *Schizophrenia: The Sacred Symbol of Psychiatry*. New York: Syracuse University Press (1976).
14. Peng FCC. *Does Alzheimer's Disease Really Exist?* Ho-Chi Book Publishing Co (2008).
15. Peng FCC. *Alzheimer's Disease: What Is It After All?* Ho-Chi Book Publishing Co (2012).
16. Ballenger J. *Self, senility and Alzheimer's disease in modern America*. Baltimore: Johns Hopkins University Press (2006).

17. Blocq P and Marinesco G. "Sur les lesions et la pathogénie de l'épilepsie dite essentielle". *Semaine Medical* 12 (1892): 445-446.
18. Redlich E. "Ueber miliare Sklerose der Hirnrinde bei seniler Atrophie". *Jahrbucher für Psychiatrie und Neurologie* 17 (1898):208-216.
19. Bick KL., et al. *The Early Story of Alzheimer's Disease*. Padova: Liviana Press (1987).
20. Paul RH., et al. *Vascular Dementia: Cerebrovascular Mechanisms and Clinical Management*. New Jersey: Humana Press.

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