Is alzheimer’s disease a fiction?

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Abstract
Alzheimer’s Disease (AD) is said to have two “hallmarks”, plaques and tangles, which were allegedly discovered by Alzheimer in 1906. A thorough review of the literature reveals seven historical facts:

1. Plaques and tangles were not discovered by Alzheimer; they had been known in the literature before 1906.
2. Perusini was the attending physician of Auguste from 1901 to 1906 when she died, not Alzheimer.
3. She had four vascular disorders; diabetes mellitus, decubitus angina, arteriosclerosis, and stupor which altogether caused widespread atrophy of her brain resulting in severe dementia with pronounced language disorders.
4. She also had internal and external hydrocephalus.
5. Kraepelin did not include plaques in his pronouncement of the eponym, referred only to fibrillary patterns which were later identified as the products of Pick’s disease.
6. Alzheimer in 1911 counted the same patient twice, reported by Bonfiglio in 1908 and Perusini in 1910, added Auguste as another new case published by Perusini in 1910, and reported his second case with a history of epilepsy.
7. Alzheimer attributed in 1911 Plaques as Fischer’s Plaques.

There are no two hallmarks of AD which is a fiction. Plaques and Tangles should be attributed to Fischer as Fischer’s Disease (FD). Dementia is not caused by atrophy of the hippocampus alone. It results from any atrophy in the brain, which can spread from cortical to subcortical structure, including the cerebellum, and may be of vascular or non-vascular in origin.

Subsequent researchers coined “new” terms like (1) Mild Cognitive Impairment (MCI), a poor reinvention of Fischer’s dichotomy of Simple Dementia and Presbyophrenic Dementia; (2) Fronto-Temporal Dimentia/Disease (FTD) and (3) Vascular Dementia (VaD), overlooking the fact that dementia is “Totality of the Effects of Wear and Tear”. It is time to get on real research of dementia as an important part of aging which is an on-going process of wear and tear.

Introduction
Plaques and tangles are known as the two “hallmarks” of Alzheimer’s Disease (AD). Later, Amyloid Beta hypothesis is added, shifting the cause of AD to the atrophy of the hippocampus; dementia is then regarded as a disease synonymous with AD by many. This tradition of regarding plaques and tangles as the two “hallmarks” of AD is in error which is herewith challenged. My purpose is manifold to: (1) prove that AD is a fiction, as Alzheimer did NOT discover a new disease, though it has subsequently been purported that he did; (2) set the records straight that Auguste’s dementia was caused by widespread brain atrophy of vascular origin; diabetes mellitus, decubitus angina, arteriosclerosis, and stupor; (3) reveal that she was also found at autopsy to have internal and external hydrocephalus; (4) give due credit to Oskar Fischer for his insight that “there were no cases with tangles without plaques”; and (5) stop the erred assumptions and return to the real research on dementia of differing origins so as to help clinical practice for the benefit of millions of patients with dementia and restore the confidence and credibility in neurosciences.

Discussion
Historical facts in time and space
When Kraepelin proclaimed “This Alzheimer’s Disease of the most serious form of senile dementia” [1], he had only fibrillary patterns in three microscopic illustrations with evidence taken from Perusini’s preparations, as if Alzheimer had made them. Alzheimer did nothing of that sort after Auguste’s death; her autopsy was done by Perusini in Frankfurt, and her brain was used up by Perusini in Munich for microscopic analysis; Alzheimer simply used Perusini’s information from the autopsied materials for his 1906 oral presentation in Tübingen, which was a failure.

Alzheimer accepted the proclamation [2] which thus restored his self-confidence from the setback he suffered in 1906. But his self-confidence led to his dishonesty [2] of claiming several cases as new cases in support of his 1906 failure. Two of them were actually duplicate cases of the same patient reported by Bonfiglio in 1908 [3] and by Perusini in 1910 [4]. That patient was inflicted with syphilis, gornorrhoea, a disease of the spinal cord, Romberg sign, high grade of ataxia, marked euphoria, subpial hemorrhages, and Korsakoff’s as he had been a heavy drinker for 30 years. Auguste had none of these. Worse, one of the “new cases” was in fact Auguste, re-reported extensively by Perusini [4]; Alzheimer counted it as another “new” case [2].

Subsequent researchers, unaware of such historical facts, believe that Alzheimer treated Auguste from 1901, when she was admitted to an Asylum in Frankfurt, to 1906, where she died of decubitus angina [5]. The truth is that he had already left Frankfurt in 1902 for Heidelberg and moved to Munich with Kraepelin in 1903. There was no way in...
which Alzheimer could have treated Auguste or observed her medical conditions in Frankfurt. When she died, Perusini took her brain in a crate to Munich for microscopic analysis from which Kraepelin’s three microscopic illustrations were obtained. But Perusini had treated her only for about seven months (Nov. 25, 1901 to June 1902) [5,6].

Such historical facts suggest that Alzheimer had no idea of Auguste’s medical condition after he left Frankfurt in 1902, except for the fact that she had been admitted to the Asylum in 1901 and assigned by its Director, Emil Sioli, to Perusini for psychiatric care. Even so, after June 1902, Perusini lost interest on treating Auguste because there was a blank period of more than two years. His observation of her medical conditions was strangely resumed in February 1904 till her death on April 8, 1906; during that period, however, no data were recorded, except for one visit in February 1902 plus three visits after November 1904 to her ward. It was in these visits that her decubitus angina appeared, which unfortunately escaped Perusini’s detection and all subsequent researchers’ awareness. To wit:

1. February 1902, “She lies in bed in a strange way”
2. November 1904, “She lies mainly curled up in bed”
3. October 1905, “She lies in bed without moving. Her legs are drawn up to her chest. She does not speak but continues to mutter”.
4. December 1905, “She mainly lies with her legs pulled up to her chest. She again screams a lot. Refuses to be examined.”

It is from Perusini’s reported data coupled with the materials from her autopsy, which he published in 1910 [4] that I was able to reconstruct Auguste’s pathology of the four vascular disorders [5]. I concluded that the direct cause of her death was her decubitus angina.

**Evidence of Auguste’s vascular disorders**

1. Her diabetes mellitus made her completely blind owing to the leaking of blood in her two retinas. But Perusini mistakenly thought that her blindness was psychic. In the early 1900’s nobody knew anything about diabetes. Today a diabetic, untreated or poorly treated, will have the two feet or even lower limbs amputated besides being completely blind, becoming demented as a result. In her case, she had abnormal growths of veins in her lower extremities at autopsy, in addition to her complete blindness. I suspect that her diabetes mellitus must have started long before her admission to the Asylum in 1901.

2. Her decubitus angina was evidenced by her strange posture in bed; Perusini could not figure out why she pulled her two legs to her chest. Decubitus angina causes periodic cardiac pain due to cardiovascular disorders. However, it is interesting to note that her residual brain function of cognition enabled her to pull her legs up, a behavior that would raise the stomach to push the diaphragm against the heart, thereby somewhat reducing the cardiac pain as a result. But I suspect that she continued to mutter and scream, because she could no longer utter sensible words to convey that she was in her pain, for her residual brain function of memory and cognition was not strong enough to enable her to do so. She refused to be examined, because she was still aware that her cardiac pain could not be reduced by such an examination.

3. The autopsy showed an eventually atrophic brain which could be observed by naked eyes, according to Perusini, suggesting that her brain atrophy was not confined to a small region such as the hippocampus. Why was her brain eventually atrophic? He added that the major brain vessels were arterioscleroti- 

any explanation. Arteriosclerosis means the hardening of arteries, of which atherosclerosis is a common form. I may add that the arteriosclerotic changes, since they affected her major brain arteries, included not only anterior cerebral artery (ACA) and middle cerebral artery (MCA) but also posterior cerebral artery (PCA) and vertebral artery for the brain, and that the aorta and subclavian artery, extending bilaterally to the internal and external carotids, as well as the arteries of the heart, may have been affected too. There is no doubt that her cerebrovascular arteriosclerosis caused her eventually atrophic brain and her cardiovascular arteriosclerosis caused her decubitus angina and stupor.

But no subsequent researchers have paid any serious attention to the autopsied materials which have been available in the literature. Instead, they prefer to assign the cause of AD to the atrophy of the hippocampus, by insisting on the two “hallmarks”, raising a different issue of amyloid beta, or using animal models to mimic AD in order to justify their investigations. The efforts have been misdirected in subsequent literature, because Oskar Fischer’s insightful account of plaques and tangles were completely forgotten [5,6]; he should have been duly credited for his contributions. Do they dare claim that their specially engineered mice for the models would suffer from the mice’s language disorders and had a family history of dementia as seen in human patients of dementia in keeping with the guidelines of DSM IV, which a priori indicate the elimination of any vascular disorder for the diagnosis of AD?

While her arteriosclerosis has been forgotten, it is strange for de la Torre to claim in 2002 that AD is “a vascular disorder with neurodegenerative consequence, rather than a neurodegenerative disorder with vascular consequence [7,8]. His claim is strange because to him AD exists as a disease, a notion that cannot be substantiated by the historical facts in time and space [5,6]. However, he was predated by psychiatrists and many neurologists working on dementia, who then have asserted that there is a separate form of dementia called vascular dementia (VaD) which is said to be distinct from AD. The distinction is an error, because Auguste had the four vascular disorders. To recapitulate: (1) arteriosclerosis, (2) diabetes mellitus, and (3) decubitus angina which caused (4) her worsening stupor. Thus, if Auguste’s dementia is to be included in VaD, then AD no longer exists, for plaques and tangles were not Alzheimer’s discovery either. Recall that the diagnosis in current clinical practice is the elimination of any vascular disorder to come up with AD.

But mention must be made that dementia is not synonymous with AD nor is it a disease [7]. It is a mistake to use AD as a control to contrast with other types of dementia, e.g., VaD and, recently, frontal-temporal dementia/disease (FTD or Pick Complex). Researchers who do so completely forget or ignore that Auguste’s brain atrophy at autopsy included not only the frontal lobe but also the temporal lobe and all other regions, including the cerebellum and the brain stem. MCA supplies the lateral cortex and ACA supplies the medial cortex of the anterior portion while PCA supplies the posterior portion of each hemisphere; the rest of the arterioscleroti- 

changed brain arteries supply the remaining regions of the brain. If such mice in the animal models may become demented due to damage of their brains as a result of the injection of polymers, why should their dementia (impairment of the brain functions of memory) be called a mimicry of AD?

4. Stupor as a medical term has many forms. In general, it may be regarded as unconsciousness, partial or nearly complete. But, in psychiatry, it is regarded as a disorder expressed through reduced
behavioral responsiveness. It also has a form of dementia such that the patient is seen to be quiet, listless and nonresistant. It is then called anergic stupor. When the patient’s dementia becomes acute or worse, it is regarded as stuporous psychosis.

Perusini was a psychiatrist in residence at the Asylum in Frankfurt. Although he reported in his lengthy publication on Auguste [4] the manifestation of her stupor, I suspect that he had stuporous psychosis in mind, because Alzheimer erroneously changed his diagnosis of Auguste after 1907 several times one of which was senile psychosis, and another one of which was atypical form of senile dementia. Attention should be paid to the fact that all subsequent researchers since then have ignored this important historical fact. Instead, some have come up with the term Mild Cognitive Impairment (MCI) which is then claimed to be the early form of AD, eventually leading to AD by using the late President Ronald Reagan as an example [5,6]. The truth is that he had simple dementia while in office but did not have AD before his death; instead, he had Fischer’s presbyophrenia. That is, MCI is simply a poor reinvention of Fischer’s dichotomy of simple dementia and presbyophrenia [9]. It is hoped that researchers on dementia will stop this false assumption as a result of my challenge.

Conclusions

Five conclusions are therefore drawn from the above discussions of historical facts to stress Auguste’s medical conditions vis-à-vis her behavioral alterations as dementia resulting from her evenly atrophic brain.

1. Auguste’s overall brain atrophy was the cause of her dementia

Two of the four vascular disorders, diabetes and arteriosclerosis, led to her evenly atrophic brain which thus affected extensively her brain functions of memory as a consequence. It is wrong to assume that her severe dementia was due to the atrophy of the two hippocampi. One of the two, arteriosclerosis, was also the cause of her decubitus angina which in turn led to her worsening stupor over time. Even so, she had some residual brain function of cognition as may be evidenced by her strange posture in bed to somewhat reduce the periodic cardiac pains, but not enough to enable her to utter sensible words; that is, she had severe language disorders before her death.

However, it is important to note that her decubitus angina was the direct cause of her death, as may be evidenced by the sequence of her strange postures in bed from 1902 for more than two years: (1) November 1904 “She lies mainly curled up in bed”; (2) October 1905 “Her legs are drawn up to her chest”; (3) December 1905 “She mainly lies with her legs pulled up to her chest”; (4) April 8, 1906 “This morning she died” Put differently, without the arteriosclerosis which resulted in her evenly atrophic brain (and the subsequent decubitus angina with disorders of stupor as well), she would have lived a little longer. But, before her death, she was severely demented with language disorders.

2. Dementia is not a disease

Dementia is neither a disease nor equivalent to AD which is a fiction invented by Kraepelin. In English there are four terms: ailment, disease, illness, and sickness. However, in many other languages, German included, there is only one term. Thus, there is no linguistic problem that Demenz in German, which is regarded as Krankheit, is translated into English as dementia, both being of Latin origin. Notwithstanding, it is a linguistic mistake to also translate Krankheit as disease, because Krankheit includes all semantic fields of the four English terms. In other words, the pair Demenz and Krankheit in German are not semantically equal to the pair dementia and disease; to do so is a serious linguistic mistake with absurd consequences in clinical practice. That is, why for this reason many clinical practitioners and researchers are confused. Rather, the pair in English should be dementia and illness. Dementia may therefore be defined as totality of the effects of wear and tear owing to aging which is an ongoing process of wear and tear.

3. Are plaques and tangles two phases of one pathogenesis?

Any injury to the nervous system, central or peripheral, be it vascular or not (such as by a scalpel), will induce the formation of plaques extracellularly in the bed of neuropils; once formed, they will grow in number and bigger, and then eventually invade axons and dendrites intracellularly, resulting first in apoptosis and then glandular necrosis. That is, the patient’s dementia starts from simple dementia to reach the terminal stage of presbyophrenic dementia. This was the conclusion Fischer reached from his extensive cases [9,10]. This conclusion [10] may imply that plaques and tangles are actually two phases of one pathogenesis, a hypothesis stemming from Fischer’s findings that “there were no cases with tangles without plaques”. Put differently, plaques are not at all caused by amyloid beta nor is dementia caused by atrophy of the brain tissues limited only in one or both hippocampi, because the brain function of memory is not manipulated by the hippocampus alone, as commonly so believed in neurosciences, but by synapses resulting from presynaptic sodium potassium exchange for action potentials through neurotransmitters, all or nothing, in the nervous system.

His insight was based on: (i) his own data of dozens of cases the pathologies of which were of vascular or non-vascular origin, and (ii) research results of others before his own works [10]. However, the hypothesis is true if and only if the pathology of plaques, be it vascular or nonvascular in origin, starts extracellularly, in the bed of neuropils, which then leads to the invasion of neurofibrils in the axons and dendrites of neurons, resulting eventually in glandular necrosis which is the organic cause of presbyophrenia. The contingent reason of my argument is that the pathology of Pick’s disease starts intracellularly, with Pick bodies, and produces tangles without plaques, thereby leading to brain atrophy just the same with the consequence of dementia [5,6].

4. Oskar Fischer deserves the eponym of fischer’s disease

Given the above inference, plaques and tangles should therefore be credited to Oskar Fischer as Fischer’s Disease (FD). Even Alzheimer called plaques Fischer’s plaques [2] in keeping with Vedran’s proposals [11,12], and tangles had been reported by Pick [13,14] long before 1907, although the term tangles came out in Fischer’s 1910 publication [10].

5. There are no two hallmarks of AD because it is a fiction

In view of the evidence presented, Auguste’s four vascular disorders, coupled with her internal and external hydrocephalus, should be taken seriously when treating patients with dementia in clinical practice, without erroneously perpetuating the two hallmarks of AD. Such being the case, clinicians or researchers dealing with dementia should abandon the notion of MCI, without using AD as a contrast for other forms of dementia, be they vascular or non-vascular in origin, or as the end point. The reason is simple. Fischer’s dichotomy of simple dementia as the early form, leading eventually to presbyophrenic dementia as the end point, is far superior and more insightful as a realistic clinical notion. The late President Ronald Reagan did not have MCI or AD. He had simple dementia while in office and then presbyophrenic dementia before his death; no autopsy was performed to reveal the causes of his
dementia, however. Moreover, Fischer’s dichotomy can account for
dementia in patients with Progressive Supranuclear Palsy, Parkinson’s
Disease, Huntington’s Disease, Spinal Cerebellar Ataxia, or any other
forms of dementia of vascular or non-vascular origin.

It is hoped that my challenge will urge all researchers to take
seriously the real research on dementia as an important part of aging
in geriatrics and gerontology for the sake of millions of patients with
dementia, who have been or are being misdiagnosed to have AD. The
reason is simple: Alzheimer’s disease is a fiction.

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