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Archives of Medical Research ■ (2012) ■

Archives of Medical Research

REVIEW ARTICLE

Alzheimer's Disease: Critical Notes on the History of A Medical Concept

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Received for publication October 15, 2012; accepted October 22, 2012 (ARCMED-D-12-00585).

It is generally accepted that Alois Alzheimer, the German neuropathologist and clinician, discovered the disease that carries his name, after the clinicopathological study of a 51-year-old woman named Auguste D. who presented a dementia syndrome. The pathological study of the brain revealed the presence of neurofibrillary tangles and senile plaques. Emil Kraepelin coined the eponym Alzheimer's disease in the 8th edition of his textbook Clinical Psychiatry. However, several critical aspects of this history have been pointed out by historians of psychiatry. This article provides a narrative of the best-known facts leading to the formation of the original concept but also presents an informed discussion of the main critical points: 1. The descriptions of senile plaques and neurofibrillary tangles in the context of dementia before Alzheimer's report. 2. The presence or absence of arteriosclerotic changes in the brain of Auguste D. 3. The presence of noncognitive symptoms in August D. 4. The influence of social, political and economic issues in the formation and selection of medical concepts.

Key Words: Alzheimer, Nissl, Kraepelin, Dementia, Neuropsychiatry.

The Foundational Narrative of Alzheimer's Disease

It is generally accepted that Alois Alzheimer, the German neuropathologist and clinician, discovered the disease that carries his name. The official story we have heard and read many times tells us the following facts.

Background

Alois Alzheimer was born in Marktbreit, Bavaria in 1864, the same year in which the king of Bavaria, Maximilian II died early and left the throne to his 18-year-old son, Ludwig II, who is well remembered because of his forensic psychiatric story and his mysterious death. Ludwig II proposed that the Prussian King Wilhelm I should be proclaimed *Kaiser* (German Emperor) after the Franco-Prussian War. As known, the German Empire was the designation for the unified Germany from 1871−1918 when it became a Federal Republic after World War I. Interestingly, Ludwig II, King of Bavaria, was declared insane after an extravagant period dedicated to building castles when the war was resolved. The neuropsychiatrist and neuropathologist Bernhard von Gudden (chief of the Munich Asylum and one of the most important teachers of Emil Kraepelin and Franz Nissl and hence an important influence of Alzheimer's work) was involved in the writing of a report according to which Ludwig II suffered from paranoia and thus should undergo a deposition from his tasks as King of Bavaria. He was isolated in his own castle and Dr. von Gudden remained with him. On June 13, 1886 at approximately 6:00 pm, they both left the castle to walk along the shore of the Lake Starnberg; they never returned. At 11:00 pm they were found dead in the lake, probably due to drowning. The king's watch stopped at 6:54 pm. (1,2).

Scientific Formation

Alois Alzheimer decided to study medicine at the University of Wurzbürg in Lower Franconia. There he learned staining techniques and was very much interested in forensic psychiatry. His thesis was devoted to the earwax glands, and he obtained his medical degree in 1887. After a 5-month period in which he traveled as a personal physician of a mentally ill woman, he was hired (being 24 years old) in the Municipal Asylum for the Insane and Epileptic in Frankfurt. There he became a close friend of Franz Nissl (Figure 2) who had also been hired in the Municipal Asylum. Nissl taught him a staining technique used to

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http://dx.doi.org/10.1016/j.arcmed.2012.11.008

Figure 1. Neurofibrillary tangles as drawn by Alois Alzheimer according to the following reference (22): Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. *Zeitschrift für die Gesamte Neurologie und Psychiatrie* 1911; 4:356–85.

observe neuronal cell bodies (currently known as the Nissl stain). Although frequently regarded as a neuropathologist, is it well known that Alzheimer had particular skills and interests in clinical interviews and in the application of the nonrestraint principle by means of gaining the trust of patients through conversation. As a researcher, his interests varied from senile dementia and epilepsy to psychosis and criminology. His thesis was dedicated to general paresis, and this topic somehow decided important aspects of his personal life: in 1892 he was requested to assess a patient suffering from general paresis in North Africa. Alzheimer traveled there and decided to bring the patient to Germany, but the patient died before arriving. Later, he had a close relationship with the widow who eventually became his wife (after converting from the Jewish religion to Catholicism, Alzheimer's faith). Franz Nissl was the godfather of the first son before he moved to Heidelberg to work along with Emil Kraepelin. After Nissl's departure, Alzheimer was promoted to senior physician and assisted the hospital's administrators to open a new branch of the hospital with full implementation of the nonrestraint principle (3).

Auguste Deter

Two important facts related to women occurred in 1901: Alzheimer's wife, Cecile, died and left him with three children. They were cared for by Alois' sister, Elizabeth. The second fact refers to the admission of Auguste Deter (commonly known as Auguste D.) in the Municipal Asylum

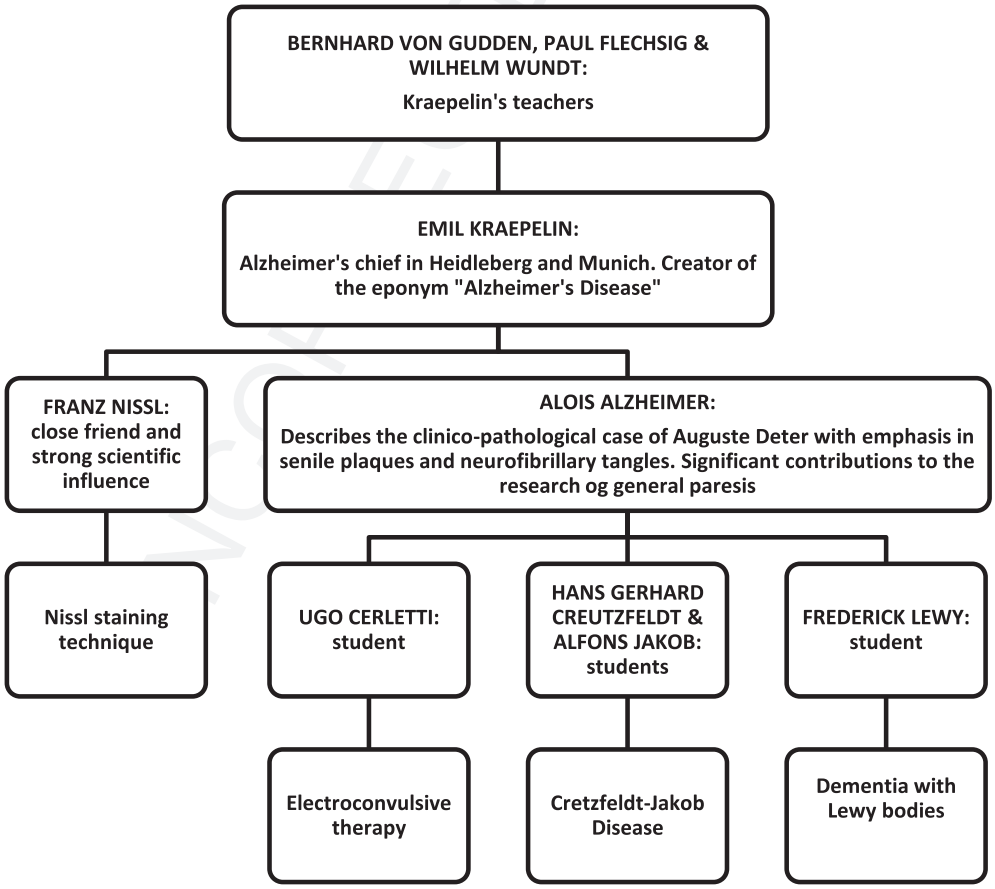

Figure 2. Highlights in the scientific genealogy of Alois Alzheimer.

of Frankfurt. She was described as a 51-year-old delusional, forgetful, disoriented, anxious, suspicious, unruly and disruptive woman (3). Her husband stated that in a 1-year period she had changed drastically: she became increasingly jealous, could not carry out her homemaking duties, and constantly expressed fears of being persecuted and bothered by the neighbors. She also described auditory hallucinatory experiences. According to Alzheimer's words in a 1907 paper, *she showed rapidly increasing memory impairments; she was disoriented carrying objects to and fro in her flat and hid them. Sometimes she felt that someone wanted to kill her and began to scream loudly* (4).

Cognitive Features of the Case

On November 25, Alzheimer registered several cognitive features of the case including language comprehension issues and perseverative discourse. For instance, when the doctor asked her first name, she answered 'Auguste', but she answered the same when he asked the second name, and the same answer came when he asked the husband's name. Alzheimer also described what he called an amnesic writing disorder (when the doctor asked her to write the number '8' she wrote: Auguste. When he asked her to write the number '5′, she wrote: A woman). Probably she also had nomination failures and/or semantic paraphasias because when the doctor asked her to tell him what she was eating (while eating meat) she would say spinach, and when he insisted she answered potatoes and horseradish. A small fragment from the August D. file, written by Alois Alzheimer himself (4), should be clear enough regarding the cognitive failures of this patient: … *If you buy 6 eggs, at 7 dimes each, how much is it? Differently. On what street do you live? I can tell you, I must wait a bit. What did I ask you? Well, this is Frankfurt am Main. On what street do you live? Waldemar street, not, no…. When did you marry? I don't know at present. The woman lives on the same floor. Which woman? The woman where we are living. The patient calls Mrs. G, Mrs. G, here a step deeper, she lives…. I show her a key, a pencil and a book and she names them correctly. What did I show you? I don't know, I don't know. It's difficult isn't it? So anxious, so anxious. I show her 3 fingers; how many fingers? 3. Are you still anxious? Yes. How many fingers did I show you? Well this is Frankfurt am Main.*

Alzheimer and Emil Kraepelin

Alzheimer moved to Heidelberg in 1903 where he worked with Nissl under the direction of Emil Kraepelin who was named director of the Royal Psychiatric Clinic and the District Mental Asylum in Munich. Alzheimer followed him and joined the medical faculty of the Ludwig-Maximilian University in 1904. In the new Munich clinic he created an anatomic laboratory where some of the finest neuropsychiatrist and neuropathologists of the early XX century were trained, including Ugo Cerletti, Hans Gerhard Creutzfeldt, Alfons Jakob and Frederick Lewy. In 1906, he was named chief physician. The same year, August D. died. Alzheimer's notes give credit to the fact that he periodically received updates about her health condition, for instance, a late note that described the following (4): *Tendency to develop a decubitus since the beginning of 1906. Ulcerations at the sacral and left trochanteric area with a size of about 5 cm. Very weak, high fever up to 40°C within the last days. Pneumonia in both inferior lobes*. Finally, Alzheimer received her brain and spinal cord tissues after death.

The First Reports

In 1906, Alzheimer attended a meeting in Tubingen where he presented a lecture entitled: *Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde* (*On a Peculiar Severe Disease Process of the Cerebral Cortex*), although this material was not published until 1907 in the paper entitled Über eine eigenartige Erkrankung der Hirnrinde and published in the journal *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin.* He described the neurofibrillary tangles, as shown in Figure 1. According to Alzheimer's words: *In the centre of an otherwise almost normal cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability.* Regarding the senile plaques, he wrote: *Numerous small miliary foci are found in the superior layers. They are determined by the storage of a peculiar material in the cortex* (4). Although Alzheimer's reports were not extensively commented by his colleagues, his student G. Perusini, and F. Bonfiglio, replicated the findings (5,6).

The Eponym

As known, it was Emil Kraepelin who coined the eponym Alzheimer's Disease by including it in the 1910 edition (8th edition) of his famous textbook on Clinical Psychiatry (7).

Later Work and Death of Alzheimer

What happened to Alois Alzheimer after the immortalization of his name? He resigned his post as chief physician in order to make several trips in regard to research devoted to epilepsy. He collaborated with Emil Kraepelin as coeditor of the *Journal of Complete Neurology and Psychiatry.* He worked as professor of psychiatry in the Silesian Friedrich-Wilhelm University of Breslau and he died in 1915 as a result of a heart and kidney condition (3).

Critical Notes on the History of Alzheimer's Disease

Although Alzheimer's discovery of a new disease has been widely accepted and reproduced in scientific and clinical domains (4,8,9), there are alternative views (7,10−13) that point to some facts that are not frequently included in the official history of the disease.

Regarding Neurofibrillary Tangles and Senile Plaques

Supposedly, the main achievement of Alois Alzheimer was to discover new pathological markers for a very old concept of dementia. These markers are the neurofibrillary tangles (NFTs) and senile plaques (SP). However, according to the critical views, this fact is difficult to accept because by the time Alzheimer published his first clinicopathological description of Auguste D. (1907): a) neurofibrillary structures were already known (14), b) these had been already linked to senile dementia (15), for instance, in a paper by the American researcher Fuller (16) who published it 5 months before Alzheimer; c) the relationship between plaques and dementia had also been reported in 1887 (17) and confirmed by Redlich and Leri before Alzheimer's paper (18). SPs and their relationship to dementia were extensively discussed by Fisher in 1907 in a study of 12 clinicopathological cases (19). In fact, SPs were referred to as Fisher plaques for some time in the scientific literature (13).

Regarding Arteriosclerosis

The debate regarding the presence of arteriosclerotic changes in the brain of Auguste D. is still alive. German Berrios (12) offers the Alzheimer 1907 paper itself as bibliographic proof in order to insist that these changes were part of the original pathological picture. He also points to the fact that in his famous announcement of the eponym, Emil Kraepelin omitted the mention of these vascular changes that possibly would change the whole direction of the discovery and thus would complicate the validation of a new disease. On the other hand, Maurer (4) sustains that there were no significant vascular changes in this case as follows: *At Alzheimer's suggestion, Perusini restudied the brain of Auguste D. and found "that the large cerebral vessels, the arterial circle of Willis and the Sylvian arteries showed no significant signs of arteriosclerosis"; only "some regressive alterations of the arterial wall" were noted.* It is easy to see that this debate, centered around the case of Auguste Deter, could be developed at many levels in many patients cared for nowadays but also raises questions regarding the conceptualization of diseases as separate nosological entities (a categorical perspective) against a view of diseases as dimensional processes (continuity vs. discontinuity hypotheses regarding the relationship between vascular dementia and neurodegenerative dementia). It is likely that Kraepelin preferred to avoid that debate in his announcement of a new disease—it would have weakened the validity of the new concept.

Regarding Noncognitive Symptoms

German Berrios (7) also questioned why Emil Kraepelin omitted the mention of noncognitive symptoms such as hallucinations and delusions in his announcement of the new disease. It is possible that the creation of a new paradigm centered on cognitive failures was likely to be more efficient by excluding the noncognitive symptoms. During the nineteenth century, the cognitive paradigm of dementia was established by a gradual process and became stereotyped in terms of an irreversible disorder of intellectual functions (11). This cognitive paradigm, as Berrios calls it, still remains but has been attenuated by the increasing interest in noncognitive features of dementia such as delusions and hallucinations, which are not easily modeled by means of the neuroanatomic perspective centered on localization and topography—a perspective that clearly influenced the stabilization of the Alzheimer's disease concept as an objective, neurological disorder that could be understood along with other neurological disorders that fit well within the topographic-localizationist perspective that emerged from the nineteenth and early twentieth centuries.

Regarding Some Social, Political and Economic Issues in the History of Medical Ideas

According to the official story of Alzheimer's disease, there is no doubt that Alois Alzheimer made an authentic discovery that changed the clinicopathological paradigm of dementias. In that case, Emil Kraepelin made a valuable recognition of such a work and an unquestionable contribution to scientific medicine by stabilizing the paradigm of a cognitive-degenerative disease without vascular disturbances. However, we should be aware of an alternative historical hypothesis, according to which the formation and stabilization of such a paradigm is not purely related to scientific discovery but also to social, political and economic factors, for instance: a) the personal opinion of Emil Kraepelin, his widespread reputation and authority may have contributed to create a dogma difficult to change (10); b) the economic pressure over Kraepelin's department may have influenced the decision to baptize in such a hurry a new disease based on a single case study, going so far as to omit relevant features of the case, for instance, the noncognitive symptoms and the possible vascular abnormalities, which would have complicated the validity of the new concept (7); c) the rivalry between Kraepelin's department and the department of Arnold Pick in Prague (the location where Fisher worked) as well as the desire for prestige for his school of neuropathology and neuropsychiatry (4) may have also influenced Emil Kraepelin to coin the eponym as if the works of other previous or contemporary clinicians and pathologists were not crucial: for instance, the works of Fisher in Prague or Fuller in the U.S. but also the works by Perusini, Bonfiglio, Bianchi, Beljahow, Redlich and Leri.

Final Remarks

Both histories of Alzheimer's disease (the official and the critical ones) are highly instructive regarding the complexities involved in the formation of medical concepts. Without a doubt, the patience and careful observations of Alois Alzheimer along with his passion for neuropathology and staining

techniques (with the strong influence of Franz Nissl and the decades of a young European neuropathology tradition) were crucial in the new understanding of dementia coming from German neuropsychiatry. On the other hand, this knowledge is only possible with the original observations of Beljahow, Redlich and Leri, Bianchi, Fisher, Fuller, Perusini, Bonfiglio.

The figure of Emil Kraepelin stands as the figure of a great scientific leader and as the realm of a man with his own relevant sociopolitical and economic pressures. Most probably, as German Berrios has formulated it, he is responsible for the formation of a scientific stereotype that is difficult to integrate with the increasing reports that provide account of the genetic, molecular, pathological and clinical heterogeneity of the phenomenon under study. However, it is difficult to deny that only a strong leader could be able to put together in the same place the talents of Franz Nissl, Alois Alzheimer, and Korbinan Brodmann, just to mention three powerful names, and also be capable of integrating cognitive research, descriptive psychopathology, neuropathology, genetics, neuropsychopharmacology, and public health—his working paradigm has not yet been surpassed (20). Finally, while discussing the genesis of Alzheimer's disease concept, we should not forget the importance of the epistemology of Emil Kraepelin, based on the notion of separate natural nosological entities (21) that could be discovered as his brother (Karl Matthias Friedrich Magnus Kraepelin, the naturalist) separated species of plants like the *Physocypria kraepelini* (an ostracod), the *Clavatula kraepelini* (a sea-snail), the *Tetramorium kraepelini* (an ant), and the *Iurus kraepelini* (a scorpion).

Beyond the enthusiast or critical anecdotes, the formation of the Alzheimer's disease concept is a great opportunity to explore the multiple, interrelated influences that operate in the history of medical ideas: the progression of facts and observations made possible by developments in clinical techniques and technological devices; the accumulation of knowledge provided by a vast tradition, scattered in space and time; the epistemological horizons of the scientists and authors of each time, which are also modeled by historical processes and philosophical intermediations and which will have a decisive influence in the observation and analytical methods. Finally, we cannot rule out the effects of political, social and economic forces, which make a complex interplay in the selection of medical ideas that will survive while others (as interesting as the triumphant ones) will be forgotten. A detailed narrative of Alois Alzheimer's contributions to medical science and a critical perspective can give us a rich picture that does not reduce to stereotypes or authoritative dogmas, but that will recognize the work of many clinicians and scientists struggling with the confusing realm of patients like Auguste Deter.

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