

Alois Alzheimer's 1888 Inaugural Dissertation about Ceruminal Glands: *An Early Otological Work of the Great Neurologist*

*Wolf Lübbbers, Wolfgang Pirsig and Albert Mudry**

Abstract :

In 1888, Alois Alzheimer presented an inaugural dissertation about ceruminal glands at the Medical Faculty of Würzburg, certainly the first on this topic. The aim of this study is to recall this dissertation. It is completed by a historical review of the scientific literature on this subject available during Alzheimer's time. It is a very good example of a well conducted acrobic research. After a historical introduction, allowing for an overview of the subject and the preceding research, Alzheimer raised a clear histological question concerning the position of the opening of the secretory canal of the ceruminal gland, which is different in children and adults. The abilities acquired during this research certainly played a major role in his further aptitude to study neuropathological histological sections of the brain and finally describe his eponymous disease. Even if it concerns only a peculiar anatomical detail of the ear, Alzheimer's inaugural dissertation can be considered as a key work in his career, which was the first milestone on the way to becoming one of the fathers of neuropathology, and the founder of the German school of neuropathology.

"I prefer cancer to Alzheimer's disease". This statement shows the whole tragedy and the fear of this difficult and severe disease, still without an effective treatment to present day. Interestingly, the famous and highly esteemed neurologist and psychiatrist Alois Alzheimer (1864-1915) has scientifically started on a peculiar level to investigate an anatomical otological detail, before describing this primary degenerative dementia in 1906. Since 1910 this illness bears his name as a well-known eponym on the suggestion of one of his mentors Emil Kraepelin (1856-1926) ⁽¹⁾.

The aim of this study is to recall Alzheimer's dissertation about ceruminous glands (CG) presented in 1888 at the Medical Faculty of Würzburg. It is completed by an historical review of the scientific literature on this subject available during Alzheimer's time. Before Alzheimer, no other dissertation on this subject was found in the usual university libraries. The importance of this 20-page with two plates work, is not only that it was the first of its kind but also by the quality of the expertly executed histological figures, all of which being hand-drawn by Alzheimer himself ⁽²⁾. This early ability and precision of observation certainly laid the foundations for Alzheimer's future works in neuropathology, conducting him to describe his eponymous disease.

Abraham Kaau-Boerhaave (1715-1758) appears to be the first to use the term glandulae ceruminosae in 1738 ⁽³⁾. Usually also named ceruminous glands, CG of the external auditory canal (EAC) are modified apocrine glands, mostly found along the entire circumference of the cartilaginous section of the EAC. Their number is between 1000 and 2000 ⁽⁴⁾. They lie in the middle and lower third of the dermis and range in size from 0.5 to 2 mm. Like the sebaceous glands, they

*

Wolf Lübbbers, MD
Ringelnatzweg 2
30419 Hannover
Germany
w.luebbbers@dr-luebbbers.de

Wolfgang Pirsig, MD
University of Ulm
Mozartstrasse 22/1
89075 Ulm
Germany

Albert Mudry, MD, PhD
Department of Otolaryngology, Head & Neck Surgery
Stanford University School of Medicine
801, Welch Road
Stanford, CA 94305-5739

form a local outgrowth from the outer root sheath of the hair follicles, named the apopilo-sebaceous unit ⁽⁵⁾. CG secret is a part of the chemical compounds found in the cerumen.

Born on June 14, 1864, Alois Alzheimer was the son of a Royal Bavarian notary in the small Bavarian town of Marktbreit am Main, Germany, 30 km away from the Franconian city of Würzburg. After starting at the local school in his place of birth, he attended the catholic Royal Humanistic Gymnasium in Aschaffenburg from 1874. In 1883, at the request of his father, he then went to Berlin to study medicine. He notably followed lectures in anatomy with the anatomist and pathologist Heinrich Wilhelm Gottfried von Waldeyer Hartz (1836-1921), better known for his description of the “tonsillar ring” or “lymphatic throat ring” in 1884 ⁽⁶⁾, later eponymously known as Waldeyer’s ring. After only one semester, he moved to Würzburg to follow his studies, where his older brother was already studying. Engaged in the student community, he became a member of Corps Franconia, a color-bearing and fencing student association. During a student fencing bout (Mensur), he got a “threw”, which reached from the left eyelid over the whole cheek to the chin (Figure 1). Supposedly, Alzheimer



Fig. 1 Alzheimer’s portrait as student (from Maurer, 1998)

has since mostly being photographed from the right ⁽⁷⁾. During the winter of 1886-1887, he spent a semester in the Swabian town of Tübingen. Back again to Würzburg to finish his studies, he began his doctorate at the Anatomical Institute under Rudolf Albert von Kölliker (1817-1905), professor of physiology, microscopic and comparative anatomy. Working in Würzburg since 1847, Kölliker had been particularly concerned with the introduction of microscopic investigations in anatomy, and supported numerous doctoral dissertations on anatomical-histological questions. Alfonso Corti (1822-1876), who eponymously gave his name to the receptor area of the inner ear, was also one of Kölliker’s assistants. Before being able to receive a medical state-degree, it was necessary to defend an inaugural dissertation, thus explaining why the dissertation’s work was conducted during the medical studies and presented before the final examination, that Alzheimer passed with ease on June 4th 1888, at the age of 24. The inaugural dissertation presented bears the title of Über die Ohrenschmalzdrüsen (About ceruminous glands) (Figure 2) ⁽⁸⁾. The necessary histological examinations were carried out by Alzheimer at the Institute of Microscopic Anatomy at Würzburg, whereby the transfer of the topic and the actual supervision of the dissertation were carried out by Philipp Stöhr (1849-1911), Professor of anatomy and head of the Anatomical Department since 1882. His well-known textbook of histology was continued until 1965 in the 30th edition. Alzheimer’s thesis was also published separately in the Transactions of the Physical and Medical Society at Würzburg ⁽⁹⁾. This other printing in a reputed journal supported the importance of Alzheimer’s dissertation for general science at that time.

The first two pages of Alzheimer’s dissertation deal with the history of the preceding descriptions of CG. They give a good idea of the research, precision and new details described by Alzheimer. These two pages are studied here in more detail and enlarged with new documents. Even if cerumen was known from time immemorial, its clear origin was not defined. For some anatomists, such as Jacopo Berengario da Carpi (1460-1530) ⁽¹⁰⁾ or Guilio Casserio (1561-1616) ⁽¹¹⁾, it was the result of a depuration of the brain, such as all the various secretions of the ear found in pathological cases, concept already mentioned

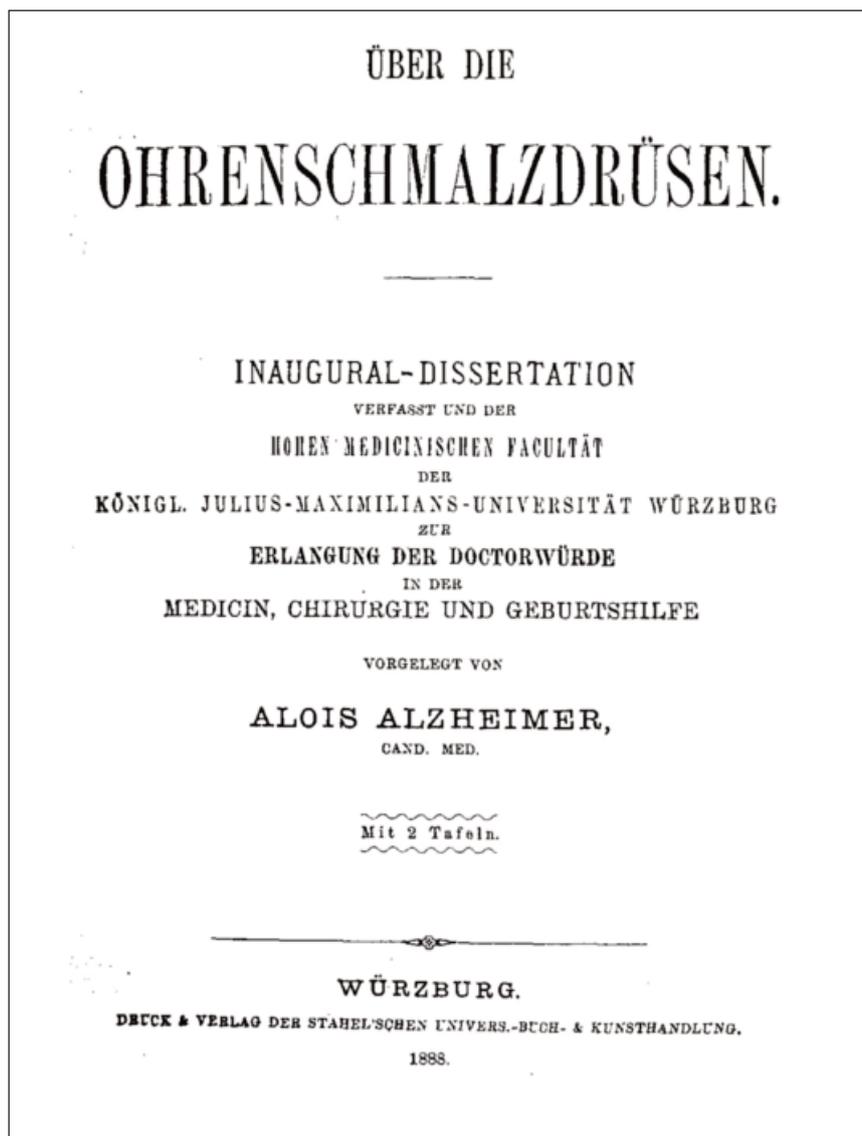


Fig. 2 Alzheimer's inaugural dissertation title

by the Hippocratic school in the 5-4th centuries BC⁽¹²⁾. It is only in 1661, that Niels Stenson (1638-1682), also known as Steno, mentioned for the first time the presence of glands in the EAC, being not sure if the cerumen originated from them. One year later, he described them with much more detail. He emphasized that demonstration of these glands was not easy. They were to be found between the cartilage and skin of the EAC: "Concerning the glandulous flesh present in the EAC, between the cartilage and the skin, this is not so obvious; the color of the cerumen seems to indicate another origin." (13) Some 20 years later, Guichard Joseph Duverney (1648-1730) mentioned these tiny, yellowish structures, buried in the skin of the

EAC, with the following words: "This skin [...] is strewn with an infinite number of small yellowish glands, tending towards an oval shape, which lie under this skin, and are somewhat depressed into its thickness. Each gland has a small duct, which opens into the cavity of the canal [i.e. EAC] among the little hairs with which it is lined: these are the small ducts which emit that thick, glutinous, yellow humor [matter], which is commonly found in the canal of the ear [i.e. EAC]." (14) These glands were responsible for the secretion of cerumen. Antonio Maria Valsalva (1665-1723) completed this description in 1704, in explaining that these glands found in a kind of reticular fibrous tissue "may possess particular excretory canals correspon-

ding to the skin foramina”⁽¹⁵⁾. About twenty years later, Jean Palfyn (1650-1730) wrote that the glands in the skin of the EAC, named “small glands”, differed structurally from the other skin glands, being yellowish and oval with a small excretory vessel⁽¹⁶⁾. It took many years to demonstrate that, in fact two types of glands were found in the external ear, CG and sebaceous glands. John Cunningham Saunders (1773-1810) wrote in 1806: “The skin of the auricle, and that of the meatus externus [i.e. EAC], are both perforated with numerous small holes, the orifices of sebaceous follicles in the former, in the latter of the ceruminous ducts. The ceruminous glands themselves are placed exteriorly to the cutis of the meatus externus, in the interstices of a reticular membrane. They are about the size of millet seed, approach to a spherical or elliptical form, and are tinged of a slight yellow by the cerumen which they contain. Each little gland sends a small duct, that opens in the meatus externus, and discharges the cerumen, which is there found.”⁽¹⁷⁾ Progressively, it was clearly established that in the EAC, ceruminous and sebaceous glands were found but their relations were discussed. In short, for Emil Huschke (1787-1858) and other colleagues, the ceruminous glands were the result of a transformation of the sebaceous glands in the EAC⁽¹⁸⁾. For Kölliker⁽¹⁹⁾ and later Heinrich Auspritz (1835-1886)⁽²⁰⁾, they were two different types of glands, and the ceruminous glands, because of their spiral shape form, had a relation with the sweat glands in the EAC. Cerumen was, in fact more a secretion from the sebaceous glands than from the ceruminous ones. Joseph Toynebee (1815-1866) shared the same opinion⁽²¹⁾ as Salomon Stricker (1834-1898) who wrote: “The ceruminous glands resemble the sweat glands, not only in the time and manner of their development, but also in their external form and their minute histology; this is also true of the contents of the ceruminous glands, so far as the microscope allows us to judge, the only difference being that in cerumen masses often very fine corpuscles of coloring matter are found.”⁽²²⁾

Other anatomists began to describe in detail the fine histological structures of these various glands and the surrounding hair follicles, notably where the excretory canal of the glands exactly emerge in the EAC. It enlarged the problematic discussions

and opened new ones between the anatomists of the second part of the 19th century. It certainly conducted to Alzheimer’s dissertation. In his mentor’s histological textbook, published in 1887, the “coil-glands [Knäueldrüsen]”, i.e. the ceruminous glands, were described as follows: “In some respects, these glands correspond with the ordinary larger coil-glands (sweat glands) of the skin; like these, they possess an excretory duct, lined by several layers of epithelial cells; the tubules of the coil contain a simple layer of cubical glandular cells, resting on smooth muscular fibers and a conspicuous membrana propria externally; they differ from the sweat glands by the very wide lumen of the coiled tubule, that especially in adults [...] The excretory ducts are narrow, and open in the hair follicles.”⁽²³⁾ Stöhr accompanied his text with a drawing of the gland, drawing which remained the same, at least, until the first English edition in 1896 (Figure 3)⁽²⁴⁾.

Alzheimer’s real task was to answer the question, not conclusively clarified by his predecessors and colleagues, where the excretory canal of the CG ended, whether in the hair follicles, or in the free skin of the EAC. According to his histological investigations of six adults and three small children, Alzheimer came to the following conclusions:

1. *The ceruminous glands are produced by the growth of the outer root sheath of the hair follicle.*
2. *They open in the hair follicles in the newborn. However, the opening slowly and*

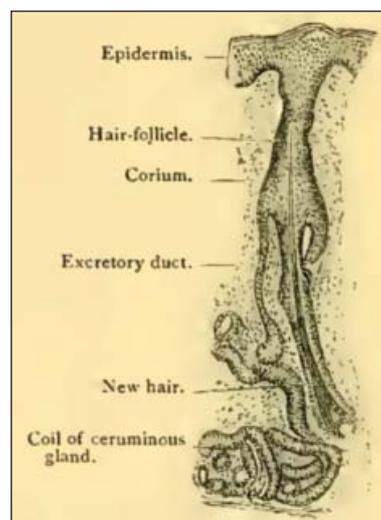


Fig. 3 Stöhr’s drawing of the ceruminous gland

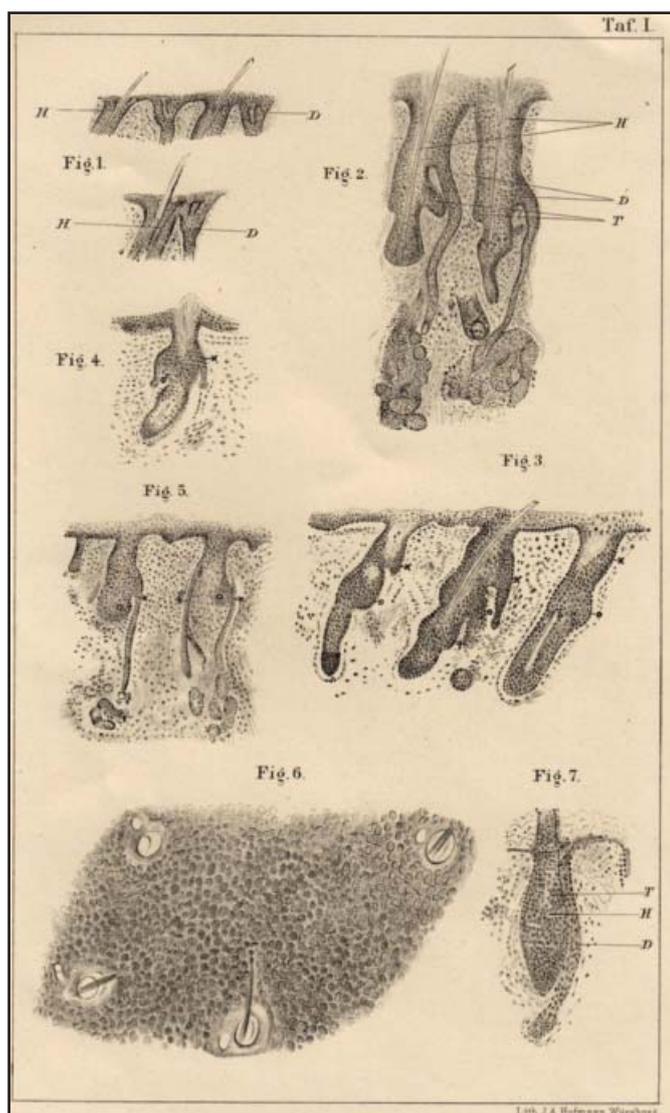


Fig. 4 Plate I of Alzheimer's dissertation

gradually become higher in the hair follicle, in order to usually end up in the adult skin on the free skin surface. Some will remain to the old relationship."

Alzheimer confirmed that the "ceruminous glands" are effectively glandular glands, and they consist of a more or less deeply subcutaneous gland, an excretory duct and a funnel-shaped opening, the "Alzheimer's terminal funnel [sic] (Alzheimer's Terminaltrichter)" ⁽²⁵⁾. He is also extensively devoted to the epithelial lining, muscular and nervous supply. Even more, he performed numerous other histological studies and researches on various mammals (cattle, sheep, pig, goat, roe deer, dog, cat, bats, mole, rabbit,

hazel, house mouse and guinea pig). He notably compared the inflorescences of minor and morbid glands of the eyelids and the axillary sweat glands. He pointed out the functional and histological similarity of sweat and scent glands.

Oskar Wagener (1878-1942) later repeated these investigations again and unequivocally stated that "the ceruminous glands, named coil-glands do not produce the ceruminous fat, but the sebaceous glands of the EAC." ⁽²⁵⁾

Alzheimer added some comments about the old idea that cerumen was a waste product of brain activity and confronted his own investigations on the composition of the cerumen. It "*consists essentially of numerous fat granules and yellowish-brownish irregular crumbs, as well as fat cells filled with potassium salt, undoubtedly derived from sebaceous glands, and by accidental constriction of epidermis and hair.*" To support his research and demonstrate the exact place of the opening of the excretory duct of the cerumi-

nous glands, Alzheimer completed his text by two hand-drawn plates of histological preparations.

The first plate presents seven drawings of histological cuts of the skin of the cartilaginous part of the EAC with the nearly whole glands (*Figure 4*).

The second plate added seven other drawings detailing the fine cellular structures of the different parts of the glands (*Figure 5, p.168*).

Very quickly, these new observations were integrated in the classical histological and otological textbooks, such as the one pu-

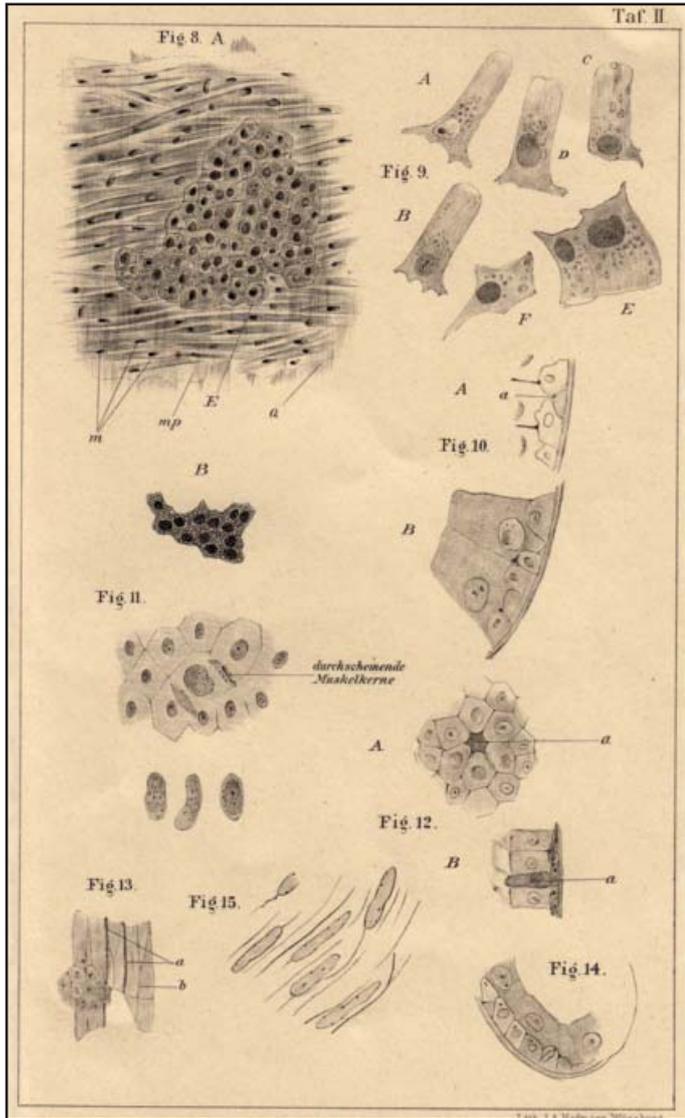


Fig. 5 Plate II of Alzheimer's dissertation

blished by Adam Politzer (1835-1920) one year later. Interestingly, he does not refer to Alzheimer, but to his mentor Stöhr: "The sebaceous glands discharge for the most part laterally into the hair follicles, less frequently on the surface of the cutis. Below the layer of the hair follicles there lie, in the subcutaneous connective tissue, rolled up like a ball, the ceruminous glands, resembling the sweat glands [...]. Their excretory ducts are narrow, and open, according to Stöhr, in children laterally into the hair follicles, in adults on the surface of the meatus, close to the hair follicles." (26) It is still common and typical today that mentors publish the results of the work of their doctorates under their own name. Nevertheless, Politzer mentioned Alzheimer's thesis in his history of otology (27). Louis

Blau (1848-1921) gave a 4-page comment on Alzheimer's work in 1890 (28), and Hermann Schwartz (1837-1910) added a drawing referring to it in 1892 (Figure 6) (29). Very quickly, the name of Alzheimer disappeared from the usual histological and otological textbooks, but his description remained.

Shortly after his state exams Alzheimer worked a short time at the Histological Institute of the University of Würzburg. Afterwards, he went on a journey with a "mentally ill lady" for a few months as personal physician. He then took a position as assistant physician in Frankfurt am Main at the "Municipal Asylum for the insane and epileptic [Städtische Anstalt für Irre und Epileptische]". This clinic was founded by the psychiatrist Heinrich Hoffmann (1809-1894), author of the famous book for children *Shockheaded Peter* (*Der Struwwelpeter*). Emil Sioli (1852-1922) succeeded him and from his arrival headed the institution. Alzheimer quickly became friend with his senior physician and later best man Franz Nissl (1860-1919), who was also very interested in histological research (Nissl-staining method with aniline based cresyl violet to enlighten nervous structures). They published many histological texts together. With Sioli and

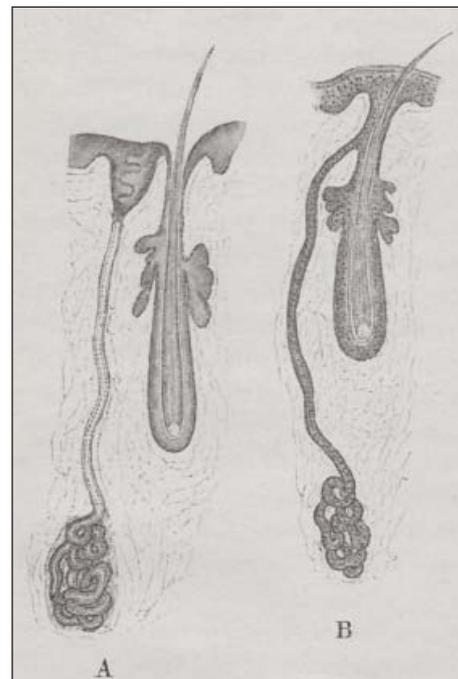


Fig. 6 Schwartz's drawing of the ceruminous gland, A adult, B child

Nissl, Alzheimer transformed the Frankfurt Asylum into a state of the art mental health care facility. He was very versatile in his research and interested himself in various topics and general paralysis was one of his main research domains. During this time, Alzheimer also studied in great detail a demented patient admitted to the Asylum in 1901 and named Auguste D. She had a striking cluster of symptoms that included reduced comprehension and memory, as well as aphasia, disorientation, unpredictable behavior, paranoia, auditory hallucinations, and pronounced psychosocial impairment⁽³⁰⁾. In 1903, he left Frankfurt to become a scientific assistant of Kraepelin in Heidelberg, whom he then followed without any payment to the Royal Psychiatric Clinic at Munich⁽⁷⁾. There he also directed the Neuroanatomical Laboratory, which soon became an important international center for brain research. In 1904 he received his title 'Privatdozent' in Munich from the Ludwig Maximilian University on the basis of his habilitation thesis *Histological studies on the differential diagnosis of progressive paralysis (Histologische Studien zur Differentialdiagnose der progressiven Paralyse)*⁽³¹⁾. Based on research initiated in Frankfurt, the work meticulously detailed the microscopic pathology of the cerebral cortex in general paresis. It was considered as an extraordinary achievement in neuropathological knowledge⁽³²⁾. In 1906 his highly demented patient Auguste D. died in Frankfurt. In the brain section, which Alzheimer personally performed in Munich, he discovered the plaque-like brain changes, which today are regarded as characteristic of the disease named after him. He quickly presented his histological discoveries related to the symptomatology of Auguste D. at a congress in Tübingen (November 3, 1906). His lecture was entitled *On a peculiar disease process of the cerebral cortex (Über eine eigenartige Erkrankung der Hirnrinde)*⁽³³⁾. Alzheimer was very disappointed that there was no response or discussion after his lecture at this congress. Disturbing the psychiatric world, it took one year for the publication of the full report⁽³²⁾. In 1906, Alzheimer also became Head of the Royal Psychiatric Clinic at Munich. Six years later he moved to Breslau University as Ordinarius for neurology and psychiatry. Alzheimer died December 15, 1915, at the age of 51 from renal and respiratory failure.

Until the second part of the 20th century, Alzheimer's disease was regarded as rare, confined to young patients and considered to play only a minor role in neurology and psychiatry. At the same time, senile dementia was variously considered as an exaggerated aging due to atherosclerotic changes in the brain. Since clinicopathological studies have clarified that Alzheimer's disease and senile dementia are part of the same spectrum of disease, Alzheimer was then linked to the most common cause of dementia.

Today, Alzheimer is a worldwide known eponymous name, but his inaugural otological dissertation disappeared into the darkness of medicine. CG were never a fascinating subject of research. In a PubMed search (June 26, 2017), ceruminous glands gave 10 items and ceruminous glands, 110 items. On the contrary, Alzheimer was associated with 92114 items! Alzheimer and ceruminous glands together gave no item.

Even short in its number of pages, Alzheimer's dissertation is a very good example of a good conducted acribic research. After a historical introduction, allowing an overview of the subject and the preceding research, Alzheimer raised a clear histological question concerning the position of the opening of the secretory canal of the CG. It conducted him to prepare, study and evaluate hundreds of histological sections in children and adults to be finally able to give a clear answer. The abilities acquired during this research certainly played a major role in his further aptitude to study neuropathological histological sections of the brain and finally describe his eponymous disease. In 1924, Kraepelin said of him: "Alzheimer wanted to help psychiatry with the microscope"⁽⁷⁾. At the same time other colleagues spoke of the "physician of insane with the microscope"⁽⁷⁾.

Even if it concerns only a peculiar but important anatomical detail of the EAC, Alzheimer's inaugural dissertation can be considered as a key work in his career, which was the first milestone on the way to become one of the fathers of neuropathology, and the founder of the German school of neuropathology⁽³⁴⁾.

References

1. Hippus H, Müller N. The work of Emil Kraepelin and his research group in München. *Eur Arch Psychiatry Clin Neuosci* 2008; 258(Suppl 2):3-11.
2. Toodayan N. Professor Alois Alzheimer (1864-1915): Lest we forget. *J Clin Neurosci* 2016;31:47-55.
3. Kaau-Boerhaave A. *Perspiratio dicta Hippocrati*. Lugduni Batavorum: Luchtmans, 1738, p.110-111.
4. Ballachanda BB. The human ear canal. San Diego: *Singular*, 1995, p.187.
5. Lucente FE, Lawson W, Novick NL. *The external ear*. Philadelphia: Saunders, 1995, p.10.
6. Waldeyer HWG. Ueber den lymphatischen Apparat des Pharynx. *Dtsch Med Wochenschr* 1884;10:313.
7. Maurer K, Maurer U. *Alzheimer: Das Leben eines Arztes und die Karriere einer Krankheit*. München: Piper, 1998.
8. Alzheimer A. *Über die Ohrschmalzdrüsen*. Würzburg: Stahel, 1888.
9. Alzheimer A. *Über die Ohrschmalzdrüsen*. *Verhandl Phys Med Ges Würzburg* 1888;22:1-20 (221-240).
10. Itard JMG. *Traité des maladies de l'oreille et de l'audition*. Vol. I. Paris: Méquignon-Marvis, 1821, p.134.
11. Casserio G. *Pentaestheseion, hoc est, de quinque sensibus liber*. Francofurti: Bassaei, 1610, p.234.
12. Mudry A. *History of otology*. Piribebuy: Wayenborgh, 2015, p.19.
13. Steno N. *Observationes anatomicae*. Lugduni Batavorum: Chouët, 1662, p.87.
14. Duverney GJ. *Traité de l'organe de l'ouïe*. Paris: Michallet, 1683, p.7.
15. Valsalva AM. *De aure humana tractatus*. Bononiae: Pisarius, 1704, p.12.
16. Palfijn J. *Anatomie du corps humain*. Paris: Cavelier, 1726, p.100.
17. Saunders JC. *The anatomy of the human ear*. London: Phillips, 1806, p.4.
18. Huschke E, Soemmerring ST. *Vom Baue des menschlichen Körpers*. Leipzig: Voss, 1844, p.819.
19. Kolliker A. *Mikroskopische Anatomie*. Vol. II. Leipzig: Engelmann, 1850, p.174-179.
20. Auspitz H. Das Eczem des äusseren Ohres. *Arch Ohrenheil* 1864;1:124-135.
21. Toynbee J. External meatus – ceruminous glands – accumulation of cerumen. *Med Times Gaz* 1856;34(New series 13):185-187.
22. Stricker S. *A manual of histology*. Transl. by Buck AH. New York: Wood, 1872, p.951.
23. Stöhr P. *Lehrbuch der Histologie*. Jena: Fischer, 1887, p.232-233.
24. Stöhr P. *Text-book of histology*. 6th ed. Transl. by Schaper A. Philadelphia: Blakiston, 1896, p.268.
25. Denker A, Kahler O. *Handbuch der Hals- Nasen- Ohrenheilkunde*. Vol. VI. Berlin: Springer & München: Bergmann, 1926, p.261.
26. Politzer A. *Die anatomische und histologische Zergliederung des menschlichen Gehörorgans*. Stuttgart: Enke, 1889, p.199-200.
27. Politzer A. *Geschichte der Ohrenheilkunde*. Vol. II. Stuttgart: Enke, 1913, p.7.
28. Blau L. *Bericht über die Leistungen in der Ohrenheilkunde während der Jahre 1888 and 1889*. Leipzig: Wigand, 1890, p.1-4.
29. Schwartze H. *Handbuch der Ohrenheilkunde*. Vol. I. Leipzig: Vogel, 1892, p.52.
30. Maurer K, Volk S, Gerbaldo H, Auguste D and Alzheimer's disease. *Lancet* 1997;349 (May 24):1546-1549.
31. Alzheimer A. *Histologische Studien zur Differentialdiagnose der progressiven Paralyse*. Jena: Ludwig-Maximilians-Universität Muenchen, 1904.
32. Cipriani G, Dolcietti C, Picchi L, Bonuccelli U. Alzheimer and his disease: a brief history. *Neurol Sci* 2011;32:275-279.
33. Alzheimer A. *Über eine eigenartige Erkrankung der Hirnrinde*. *All Z Psychiat* 1907;64:146-148.
34. McHenry LC. *Garrison's history of neurology*. Rev. and enlarged ed. Springfield: Thomas, 1969, p.262.