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Memory and Alzheimer's Disease

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ABSTRACT

Memory and Alzheimer's Disease

Memory (including its disorders) has always been an extensively discussed topic in psychiatry. Although the association between memory and Alzheimer's disease (AD) is now taken for granted, it has been less explicitly noted in the history of this disease. Alois Alzheimer's first observations of symptoms in a 51-year-old patient mentioned memory disorders, but without explaining their role, and the same can be said of many studies on the subject since then. Only since the 1990s have studies on the pathologies of memory and its functioning been analyzed and taken into greater depth in a vast array of fields ranging from psychiatry to psychology, and from neurology to neuroscience. Memory has thus become one of the correlatives of AD, the particular form of dementia which is among the most common pathologies related to brain aging today. This paper shows how different research fields have integrated their knowledge to define the role of memory in detecting AD as well as to understand the function of memory in brains affected by dementia. The author's historiographical approach inserts the micro-history of Alzheimer's research into the macro-history of psychiatric classification as proposed by Emil Kraepelin, following the relationship between dementia and memory up to the current scenario as it has evolved in the various editions of the *Diagnostic and Statistical Manual of Mental Disorders - DSM*.

Keywords: Alzheimer's disease - History of memory - History of science and medicine - Emil Kraepelin - *DSM*

Contrary to current widely accepted notions on the relationship between Alzheimer's disease and memory, this link has not always been so immediate. In fact, when Alzheimer observed the first clinical case in 1906, he did not pay particular attention to memory loss or specific memory disorders. Nevertheless, in his description of the case of Auguste D., in the subsequent one by Emil Kraepelin (1856-1926), and in further studies by the Italian collaborators who worked with Alzheimer's disease in the Munich clinic, memory was one of the terms that accompanied - but that did not determine - Alzheimer's disease. Writing a history about how memory figures in Alzheimer's disease may therefore seem premature today since only the most recent studies in a specialized scientific field accurately deal with this topic. However, the current history of research on Alzheimer's disease makes it possible to begin to "read" the role that memory has played (and increasingly seems to play) in this pathology, thus revealing traces that allow us to decide which path to take as we venture into the field of research on the relationship between memory and Alzheimer's disease.

The history of AD began in 1901 with a meeting between Mrs. Auguste D. and Alois Alzheimer[1]. The attending physician who in that same year had suggested that she be admitted to the clinic presented her as a woman suffering from memory weakness, persecution delusions, insomnia, and agitation. Incapable of doing any physical or mental work, she needed treatment in the psychiatric clinic in Frankfurt headed by Emil Sioli, who entrusted the patient to Alzheimer's care. Through careful observation of the patient and repeated interviews with her, Alzheimer began to get a clearer idea of her clinical picture. He noted serious language disorders, in particular, aphasic-like symptoms which were strangely present at an early age (the patient was fifty-one years old), and their severity intrigued Alzheimer. He followed Auguste closely, even when he went to work in Munich a few years later in the clinic headed by Emil Kraepelin, the father of modern psychiatry, already considered the scientific reference point in Europe at the end of the nineteenth century. When the woman died in 1906, Alzheimer arranged for her brain to be sent to his laboratory, where he performed a detailed autopsy. Working with Auguste Deter while she was still alive, Alzheimer had already noticed a form of mental decay that immediately struck him as being so peculiar as to warrant a thorough study of the case. In carrying out the autopsy, what he observed in the histological preparations under the microscope convinced him that he had to share Auguste's case with the scientific community during the 37th meeting of South-West German Psychiatrists, held in Tübingen in November 1906. With the autopsy of this singular patient, Alzheimer had found something unusual that would soon open a new path of study.

The symptoms encountered by Alzheimer during Auguste's hospitalization indicated several pathological conditions: personality problems (jealousy), impaired memory, faulty perception, and language disorders (aphasia). Alzheimer considered it essential to note and describe the linguistic disorders of his patient, whose symptoms he could

not find within the great classification system introduced at the end of the nineteenth century by Emil Kraepelin. When he examined the histological data of Auguste D.'s brain, he considered the possibility that he was dealing with a hitherto undescribed anatomopathological picture. As the first to observe a specific form of metabolic production, Alzheimer identified a process in which the neuron was switched by neurofibrillary tangles which, in replacing its nucleus and the cytoplasm, determined the death of the neuron itself. The text of the clinical case he described explains this aspect:

> *Bielschowsky's silver stain preparation showed very characteristic changes in the neurofibrils. [...] At a more advanced stage, some fibrils arranged parallel showed the same changes. They then accumulated in dense knots that gradually advanced towards the surface of the cell. Over time the nucleus and cytoplasm disappeared, and only a superimposed web of fibrils remained to indicate the place where the neuron had once been. [...] It seems that the transformation of the fibrils goes hand in hand with the accumulation of a pathological product of metabolism in neurons that has not yet been thoroughly examined. About a quarter to a third of all neurons in the cerebral cortex exhibited these changes. Many neurons, especially in the upper levels of the cells, were completely gone. [...] The glia had abundant fibers already formed; in addition, some glia cells showed noticeable deposits. There was no infiltration between the vessels. Conversely, focal lesions could be observed in the endothelium, and in some places, the formation of new vessels could also be seen. With these premises, it is evident that we are facing a very little-known disease process*[2].

Alzheimer's observations could not be associated with anything known up to that point. The possibility of identifying specific neuronal structures primarily depended on the methods used in the preparation of the material to be analyzed, but an important aspect was also determined by the theoretical choice that conditioned the reading of the data. In scientific research between the nineteenth and twentieth centuries, "theoretical elaborations" were linked to "technical skills". Therefore, it was through these two aspects - in the variety of histological research methodologies - that advancements in neurological and psychiatric knowledge could be expressed. Histology was the borderland where the fundamental epistemological question of psychiatric knowledge resided: how to acquire true, reliable knowledge?

One of the most prolific fields of research which experienced an intense period of construction of knowledge until the first decade of the twentieth century concerned observations of the cytoplasm in neurons. The analysis of the cytoplasmic content of nerve cells was not feasible with basic histological skills alone. The required staining methodology (generally included in the special techniques section of microscopy manuals) used silver-based preparations. There were two methods for carrying out silver-based coloring, by precipitation and by reduction. The precipitation process was invented by Camillo Golgi in 1873. This methodology used chromate solutions to transform soluble silver salts into insoluble silver deposits. Instead, the reduction process was based on the process by which the silver salts became metallic silver[3]. The main promoters of this second method were Santiago Ramón y Cajal and Max

Bielschowsky. In particular, Bielschowsky had developed methods for observing the lining of nerve fibers and their branches, synapses deprived of myelin, white matter (the presence of which determines the speed of impulse conduction), and neurofibrillary intertwining. Bielschowsky's method played a central role in Auguste's case. Alzheimer chose to use it to demonstrate that what he hypothesized and observed did not depend on changes caused by syphilis or arteriosclerosis.
The coloring process devised by Bielschowsky required considerable experience and advanced technical skill. Among the problems associated with the use of silver solutions was the toxicity of ammonia vapors. Furthermore, the risk of losing the collected data was very high as silver sulphates can explode. Alzheimer was well aware of the problems associated with coloring processes using silver-based solutions, but through his expertise, he was able to overcome these problems:

> *As the fibrils can be stained with different dyes than those used to stain normal neurofibrils, a chemical transformation must have occurred in the substance of the fibrils. This could be the reason why the fibrils survived the destruction of the cell*[4].

The explicit choice to use Bielschowsky's stain combined with the implicit choice to follow Franz Nissl's theory of the neuron[5] (according to which the functions of neurons were determined by the structure of the cytoplasm) allowed Alzheimer to observe by contrast the materials present in the cytoplasm and to find some types of neurofibrils there.
The question of the right staining technique was one of the critical points in the studies that later tried to repeat Alzheimer's observation. The epistemological doubts he expressed during *in vivo* observations correlated the clinical data of Auguste D. with the decision to use Bielschowsky's stain to search for possible modifications in the cytoplasm of nerve cells. The theory supported by Nissl and widely accepted in his time stated that the functional difference of the neuron was not given by its shape but was determined by the composition of its cytoplasm. The liquid nature of the cytoplasm was interpreted as the neuron's *vis active* that determined its intrinsic and specific characteristics. All this is related to the inspection of the histological observations.
If the diagnosis of dementia already supported further autopsy research, the presence of aphasic symptoms also pointed in the same direction. A symptom involving language disorders that occurs during the life of a patient - and that referred with certainty to correlated anatomical damage - thus assumed an absolute value since it corresponded to the epistemological framework of psychiatry based on the anatomo-clinical perspective. Alzheimer's interest in the characteristics of Auguste D.'s psychic decay stemmed not only from disorders such as aphasia, but above all from the severity of these symptoms in a non-elderly patient. This interest prompted Alzheimer to seek an answer, which he found thanks to the autopsy. He thus described a fact that had not yet been associated with anything known thus far. The fact that Alzheimer

could observe phenomena at the neuronal level as he did depended on two factors: the types of histological staining and the theoretical choice that guided the eye using the microscope and linking the researcher's expectations to a specific theory.

However, Alzheimer expressed doubts that he had truly discovered a new pathology. He did not continue his research on similar cases in the following years but, on the contrary, he left similar cases to two of his Italian collaborators, Gaetano Perusini and Francesco Bonfiglio, to work on. Eventually, however, Alzheimer's disease found its place in the eighth edition of Emil Kraepelin's famous manual, published in 1910. It was in this text that the term *Alzheimerische Krankheit* first appeared. From that moment on, the entire scientific community was informed of the existence of this particular disease, and the search for other clinical cases that might be associated with it began. Here this story becomes more complicated: Alzheimer's observations were possible only because of his specific staining method and microscope. In other parts of Europe, the same color was not available, and although similar microscopes existed, none were identical to his. No one was able to confirm what Alzheimer had described in Auguste's *postmortem* brain analysis except for a very few (and not very widely circulated) Italian studies reporting similar cases. Some of the data on which Alzheimer's research hinged could be considered widespread knowledge. The finding of senile plaques had long accompanied the diagnosis of dementia. The new "neurofibrillary degeneration" described by Alzheimer could be determined by a set of causes, and not necessarily a datum that led to a new type of diagnosis (i.e., it could simply constitute an additional datum). However, Alzheimer did grasp a specific meaning in the new neuropathological data, which makes it a real discovery.

The clinical case of Auguste D. was discussed in the Munich laboratory, and some specific aspects were investigated, from issues related to histological techniques for the observation of brain tissue to theories on the causes and nature of the pathological phenomena involved in that particular diagnosis of dementia. The first series of studies had the precise task of validating the case of Auguste, which fell to Gaetano Perusini. The second group of works concerned the contribution of specialized literature, namely the cases identified by the authors who dealt with dementia. In this research group we find the works of Francesco Bonfiglio, Ugo Cerletti, and Umberto Sarteschi. Sarteschi's contribution, published in 1909, assumes particular importance for the breadth of the data it reports and for its comparison with the research and cases analyzed by Alzheimer himself. As already mentioned, the symptoms encountered by Alzheimer during Auguste's hospitalization indicated problems with personality (jealousy), perception and language disorders (aphasia), and - last but not least - memory decay. Observing a symptom identifiable as a language disorder in a patient and having the possibility of researching its correlated anatomical damage *postmortem* conformed to the paradigm of Kraepelin psychiatry based on anatomo-clinical research.

Emil Kraepelin's method of classification started with the observation of the patient - daily observation that followed each case/pathology independently, taking note of each one's evolving behaviors, and recording them in real "diaries". The *intra vitam* pathological course of the single subject was summarized in specially created clinical records. After death, annotations on the patient's "deviant" behavior generally increased the number of cases relating to a specific nosographic category. This practice allowed Kraepelin to justify the phases of observation of the forms of dementia with a scientific criterion, and thus to standardize a new psychiatric method.

It should be noted here that at the end of the nineteenth century, the term dementia meant both senile dementia and progressive paralysis. As for the latter, the semantic field was related to neurology, but this term encompassed a multiplicity of possible pathologies (both disabling movement and related to cognitive impairment) which were attributable to various types of disease ranging from neurosyphilis to tabes dorsalis and from Lewy Body Dementia to severe forms of dementia including Alzheimer's disease. Psychiatric nosography is a story that certainly deserves to be explored, but this is not the place to tackle such a research project. If a patient was elderly, then the category "senile dementia" was used; if he or she was middle-aged, the disease was then generally referred to as progressive paralysis. In a nutshell, this was the first distinction made by Kraepelin.

This powerful tool used to validate diagnosis - the actual term is "follow-up study" - was popularized by Kraepelin. In particular, his recognition of the importance of the longitudinal course introduced the idea that dementia was characterized by deterioration from a previous level of functioning. Kraepelin considered both evolution and outcome as the two crucial criteria in trying to diagnose a form of dementia. He established the major subdivision in psychiatry, distinguishing between curable diseases (melancholy, mania, delirium, states of acute exhaustion) and incurable diseases (periodic or circular madness, dementia). As with the French physician Philippe Pinel (1745-1826), who was among the first to shape the field of knowledge of psychiatry, German research followed a long tradition. Kraepelin's main question was how to make a real prognosis. Since the natural history of the disease made it possible to reconstruct each peculiar pathology, Kraepelin's purpose was to observe how mental disorders develop through time, through longitudinal observation. Thus, he used this method and the cited techniques above to measure symptoms like fatigue and memory impairment. Kraepelin conceptualized thought disorder in terms of association psychology. For him, many of the "psychic symptoms" of *dementia praecox* were manifestations of thought disorder, and they included injury of judgment, stereotypes, inconsistency in the sequence of reasoning, derailments in linguistic expression, paraphasias, neologisms, impairment in the construction of sentences, as well as akataphasia (the inability to find the appropriate expression for a thought). The eighth edition of Kraepelin's manual, dated 1910, played a fundamental role in

this particular story. Here, for the first time, the term *Alzheimerische Krankheit*, or Alzheimer's disease, was used.

While the eighteenth century's interpretation of forms of insanity was cross-sectional and related to specific life events, the nineteenth century's view was longitudinal and better defined, particularly in the work of Kraepelin. In his categorization, the number of forms of insanity decreased drastically. The two macro-categories of psychoses were characterized by stable and overlapping symptom clusters. Organic etiology and recognizable natural history and prognosis became the final diagnostic criteria. At the end of the century, Kraepelin's influential dichotomy divided pathologies into two groups. On the one hand, there were nondeteriorating conditions (affective disorders) grouped as manic-depressive disease, and on the other, deteriorating conditions (thought disorders) grouped as *dementia praecox* (and later schizophrenia). Kraepelinian psychiatry also dealt with qualities rather than quantities, as it was devoted more to accurately describing patients to determine which diagnostic category to put them in. A correct diagnosis was important to Kraepelin because he believed that the various syndromes had distinct prognoses - some hopeless, others optimistic. His main idea was that the most important changes concern the subdivisions of endogenous psychoses. Kraepelin believed that since senile dementia occurred due to aging, there was no clear line between dementia and the normal aging of the brain.

Alzheimer, who was well-versed in both progressive paralysis research and mental illness in general, looked at his patient's symptoms, including impaired memory, speech, and a variety of others. In studying Auguste D.'s brain after her death, he detected cerebral atrophy, senile plaques, and neurofibrillary alterations, and concluded that Auguste D.'s disease was different from any known up to that moment. Alzheimer was always skeptical of Kraepelin's approach. Not entirely convinced that he had discovered a new pathology, he criticized the near-sightedness of the master's nosographic apparatus, which he considered too general and not attentive enough to the individual variable of each patient. From the histological observations Alzheimer conducted on the brain tissue of patients, sufficient material emerged to support that each subject could - or indeed should - correspond to a specific pathological profile. Nonetheless, Emil Kraepelin called this pathology "Alzheimer's disease" and described it as presenile dementia, arguing in favor of the hypothesis that the pathological findings of the brain suggested it was a severe type of senile dementia.

Today we know that the various bodies observed in the cytoplasmic fluid are proteins that neurofibrils are also part of, but this notion was not yet available at the time Alzheimer observed Auguste D. The history of the relationship between memory and Alzheimer's disease goes hand in hand with the success of Kraepelin's manual - published in 1910 - which acknowledged the existence of *Alzheimerische Krankheit*. The life situation in which dementia was identified as a probable prognostic outcome was identified by Kraepelin in a specific condition: old age. The development of the invo-

lutional characteristics of senile thought was not only a generically "natural" datum but also a situation that was not considered to be pathological to a large extent. The pathology emerged clearly when, prospectively, the elderly subject moved towards that *terminus ad quem* which, according to the Kraepelinian nosographic conceptualization, indicated the presence of a *Geistesstörung*, or mental disorder. For this research, Kraepelin maintained the structure of the previous editions of the manual: the seventh chapter was entitled *Senile und präsenile Irresein* (senile and presenile mental alienation), and developed according to a previously tested classification: a) presenile mental alienation; b) mental alienation from arteriosclerosis; c) senile dementia. In the group dedicated to senile dementia, the denomination of disease as applied to Alzheimer's research appeared for the first time. Kraepelin's text was very complex, and the author considered it essential to label the images accompanying this presentation in the table of figures with the caption "Images of fibrils in Alzheimer's disease, Bielschowsky's silver coloring method". Thus, Kraepelin was sure of his proposal of a nosographic novelty that could be supported by histopathological evidence. In the introduction to the manual, he acknowledged the fundamental contribution of Alzheimer's anatomopathological research:

> *With particular satisfaction, I must note the ever-present support of my long-time faithful collaborator, Professor Alzheimer, who has enabled me to insert reliable results of pathological anatomy useful for the clinic in the text and images of my exhibition. (Munich, July 15, 1910)*[6].

Today, Alzheimer's disease is universally considered the most widespread neurodegenerative disease in the world. It is characterized by progressive cognitive impairment and behavioral disturbances that lead to functional impairment (Cummings and Cole 2002). The neuropathological characteristics of the disease affect the cortical and subcortical neuronal sites and concern synaptic loss. These signs are associated with the appearance of senile plaques and neurofibrillary tangles, the latter formed mainly by deposits of beta-amyloid and phospho-tau proteins. The history that led to this shared knowledge is the result of long traditions of research which, proceeding hand in hand with the great advances in pharmacological research, have paid particular attention to Alzheimer's disease, especially since the 1950s. As for this particular form of dementia, that history is still in progress in our own day.

At present, we can easily identify the fields of investigation that are playing a primary role in the advancement of knowledge on this form of dementia. However, going back through the recent history of the subject, we can see how areas of knowledge have become intertwined, thus determining what is currently known about Alzheimer's disease. While a full historical reconstruction goes beyond the scope of this paper, it is possible to propose a key to interpretation that would go back through the labyrinth of research within various medical and scientific disciplines and find the beginning of the

thread that connects various aspects of this research - psychiatric, psychological, and pharmaceutical, to name a few. Everything is linked to the fortune of Emil Kraepelin and his aforementioned manual, the reference point for psychiatry in the early twentieth century. The next junction concerns another manual which enjoyed - and still enjoys - fame comparable to Kraepelin's: *The Diagnostic and Statistical Manual of Mental Disorders – DSM*, the structure of which pays homage to its predecessor's immense work of synthesis and categorization. In the first edition of 1952, Alzheimer's disease, still linked to the nosographic subdivision proposed by Kraepelin, falls under the category of Presenile Sclerosis.

Kraepelin's influence in the field of psychiatry can be detected not only in the narrative structure of the *DSM*, but also in its specific categories. In any event, his main contribution to psychiatric nosography was to direct attention to the course of *visible* mental disorders, given the resources available at the time. Through thousands of detailed clinical cases recorded in "diaries" - (the "natural history" of a disorder), Kraepelin made prognosis the central organizing principle of his diagnostic system. Thanks to this method, he was able to identify precocious dementia (what is now commonly referred to as schizophrenia) as a severe form of psychosis that appeared in young adults and caused progressive deterioration, as well as its three subtypes: paranoid, catatonic, and hebephrenic, the latter characterized by confusional and incoherent behaviors. As acknowledged by Allan Horwitz:

> *In general, early twentieth-century American psychiatrists displayed less interest in classification than did their European counterparts. The Kraepelinian emphasis on specific diseases was not immediately accepted in the United States, where diagnostic uncertainty persisted. The only widely accepted distinction was between the two very general categories of psychosis and neurosis*[7].

The first edition of the *DSM* contained twenty-one major groups of mental disorders. Twenty of these were considered psychoses while the other category, psychoneuroses, was not characterized as psychotic. The "basic division" of the *DSM-I* distinguished between mental disorders resulting from impaired brain function and those resulting from difficulties in adapting to the environment. The purpose of the *DSM-I* was to focus on organic psychoses and conditions due to stress, neurotic situations, or personality disorders. The first group of DSM-I disorders consisted of cases in which some damage to brain tissue produced or precipitated mental function. All twenty-six syndromes in the list resulted in impairments in orientation, intellectual functions, and judgment, as well as unstable moods and memory disturbances. The structure of the various editions of the *DSM* has maintained the division into categories almost unchanged, whereas other aspects have changed a great deal, as for example, in the third revised edition, with diagnostic criteria.

Alzheimer's disease already appeared in the very first edition, where it was classified as "Chronic Brain Syndrome with other disturbance of metabolism." In *DSM-II* it

appears under the (Kraepelinian) category "Presenile dementia". Only since *DSM-III* has Alzheimer's disease been included in the vast group of forms of dementia. The rules of engagement are clear:

> *As with all Organic Brain Syndromes, an underlying causative organic factor is always assumed. In certain clinical states, e.g., Primary Degenerative Dementia, however, it may be impossible to show a specific organic factor as the definitive cause of the disturbance. These conditions may nevertheless be diagnosed as Dementia if (a) the impairment is a multifaceted loss of intellectual ability, (b) there is no evidence for a diagnosis other than an Organic Mental Disorder, and (c) a diligent search has failed to reveal a specific organic etiologic factor. In the past, the term Dementia often implied a progressive or irreversible course. The definition of Dementia in this manual, however, is based on clinical symptoms alone, and carries no connotation as to prognosis. Dementia may be progressive, static, or remitting. The reversibility of a Dementia is a function of the underlying pathology and of the availability and timely application of effective treatment. Memory impairment is usually the most prominent symptom*[8].

Given these premises, the association with Alzheimer's disease, cited below, is linear, and undoubtedly linked to issues of memory: "Etiological factors. Primary Degenerative Dementia of the Alzheimer type is the most common Dementia"[9]. And yet difficulty in defining Alzheimer's Disease remains in all its uncertainty:

> *The Dementias associated with Alzheimer's and Pick's diseases have been referred to as Senile and Presenile Dementias, the former arbitrarily signifying an age at onset over 65. Since nearly all cases of these Dementias are associated with Alzheimer's disease and the identification of Alzheimer's and Pick's diseases is largely or entirely dependent on histopathological data, it seems more useful to have in a clinical classification of mental disorders a single category that encompasses the syndrome of Primary Degenerative Dementia. This category is subtyped according to the age at onset, for the purpose of historical continuity and to maintain comparability with ICD-9-CM. The clinician will rarely be in a position to identify the specific associated neurological disorder*[10].

This association is articulated even more in the fourth edition of the *DSM*, where we read:

> *A dementia is characterized by multiple cognitive deficits that include impairment in memory. The dementias are also listed according to presumed etiology: Dementia of the Alzheimer's Type, Vascular Dementia, Dementia Due to Other General Medical Conditions (e.g., human immunodeficiency virus [HIV] disease, head trauma, Parkinson's disease, Huntington's disease), Substance-Induced Persisting Dementia (i.e., due to a drug of abuse, a medication, or toxin exposure), Dementia Due to Multiple Etiologies, or Dementia Not Otherwise Specified (if the etiology is indeterminate)*[11].

Memory increasingly defines cognitive impairment, and Alzheimer's disease is one form of dementia, arguably the most prevalent. After a period in which excluding the term Alzheimer's disease in future editions of the *DSM* was hypothesized, the *DSM-5* includes Alzheimer's disease among the "causes" of severe and mild Neurocognitive Disorders. As stated by Horwitz:

> *A variety of other forces also influences the DSM. One is the National Institute of Mental Health, which partnered with the APA in shaping every DSM before a sharp break between the organizations arose during the development of the DSM-5. Since the 1960s, private and public insurance programs have also had major impacts on the DSM. These third parties set the parameters for which diagnoses are acceptable for reimbursement for treatment. In addition, patients require DSM diagnoses to obtain insurance coverage for drugs, psychotherapies, and other benefits. Furthermore, a variety of advocacy groups have formed to oppose the narrowing, promote the broadening, or, more rarely, abolish diagnostic criteria for particular DSM conditions. Finally, pharmaceutical companies have been intimately connected to diagnostic classification systems. Since the early 1970s, the Food and Drug Administration's (FDA) regulations have required the drug industry to market its products as treatments for particular DSM diagnoses. Drug companies are also a major source of income for departments of psychiatry in medical schools, psychiatric researchers, and the APA. The web of affiliations between the industry and the psychiatric profession is tight enough that nearly three-quarters of the members of the latest DSM task force had ties to drug companies. Moreover, pervasive drug advertisements are probably the most significant conduit of information to the general public about DSM diagnoses*[12].

In the *DSM*, we find the synthesis of research associated with premature subcortical degeneration, which occurs when the levels and function of different neurotransmitters are interrupted. Relationships and attention to biochemical interactions, therefore, are one of the recurrent themes in psychiatric treatises that follow the classification of the *DSM*. Among these, acetylcholine was the first biochemical dysfunction to be associated with Alzheimer's disease. Dysfunctions related to glutamate, norepinephrine, serotonin, histamine, and dopamine were subsequently observed. Over the past decade, studies relating to the hippocampus, the cerebral cortex, and their functions in Alzheimer's disease have steadily increased[13]. Taking into account the pathophysiology of Alzheimer's, one of the main lines of treatment research in the pharmacological field concerns ways to inhibit the protein aggregation that Alzheimer had previously described. Another later line of research focused on the hyperphosphorylation of the Tau protein, which is believed to play a fundamental role in the (still unknown) etiology of Alzheimer's disease. This field of research has launched the hypothesis that specific drugs could stop or even reverse the decay process caused by the disease, although none of those examined thus far have shown significant clinical benefits. This is one of the reasons why only symptomatic drugs that seek to restore neurotransmission are available today. This category concerns acetylcholinesterase inhibitors, which normalize acetylcholine levels, and NMDA[14] receptor antagonists, which modify the effects of pathologically elevated glutamate. These drug groups include rivastigmine, donepezil, and galantamine, which are approved and used for mild to moderate Alzheimer's dementia. Memantine, on the other hand, is the only authorized treatment for moderate to severe Alzheimer's disease. In the final analysis, AD is not only a medical issue. Today, Alzheimer's disease is a major concern both in terms of the social perception of dementia and in the world of research. In many studies, it even appears among the top five causes of death in in-

dustrialized countries because the average age of the population and the pathologies related to cognitive impairment are constantly increasing. If we consider the past thirty years' publications with the term Alzheimer in the title, the total number of medical treatises and articles exceeds 120,000 units, while there are 29,000 articles in pharmacology studies on Alzheimer's, and 23,000 works dealing with the relationship between Alzheimer's disease and memory. The present paper has shown that the initial framework of anatomo-clinical and histopathological knowledge has changed, especially from the second half of the twentieth century onwards. In fact, new paths of investigation have been made possible by new studies at the molecular, neurochemical, and genetic level, as well as by the possibility of carrying out in vivo investigations of brain functioning (neuroimaging) and pharmacological studies. These lines of research on Alzheimer's disease are still in progress, and will constitute a field of investigation for medical historians to define more clearly in the future.

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13. Cfr for example the works of Simic and Trillo.
14. The N-methyl-D-aspartate receptor is both a glutamic acid receptor and a receptor present on the membrane of nerve cells. It plays an essential role in both synaptic plasticity and memory consolidation.

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