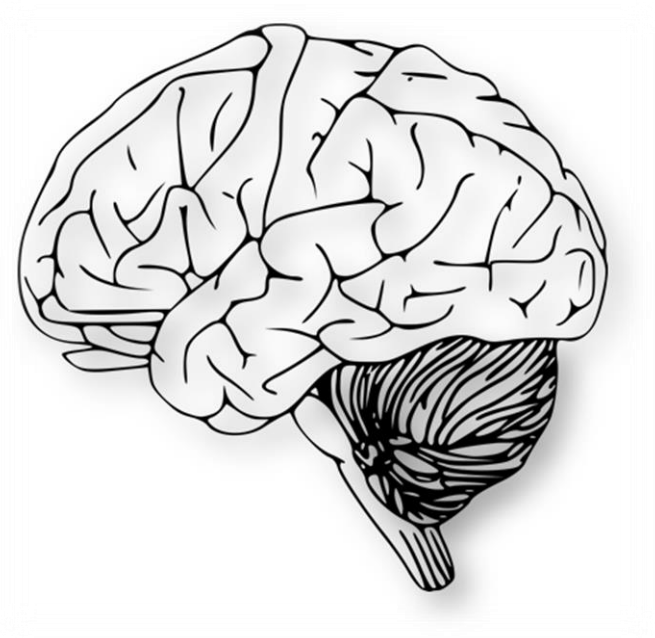
ALZHEIMER'S DISEASE: FROM THE PAST INTO THE FUTURE



A hundred and ten years ago, in 1906, Alöis Alzheimer, a histologist and physician, presented to the "Society of German Alienists" the clinical case of a 51-year-old woman (August D.) who had died in a mental asylum in Frankfurt, Germany. He described her clinical evolution as a "peculiar disease of the cerebral cortex". The first symptoms were observed five years before her admission into hospital. She had progressively ceased to take care of herself, rejecting any external aid. After her hospitalization the symptomatology worsened, and included disorientation, loss of memory and an impaired capacity for reading and writing. The age of the patient caused this deterioration to be classified as "pre-senile dementia". At that time dementia was regarded as a normal consequence of the aging process.

Another famous clinical case was that of a 56-year-old woodcutter, Johann F., who was admitted to Munich's psychiatric clinic on 12 September 1907, and died in 1910. Post-mortem histological studies revealed alterations in his brain tissue similar to those observed in the Frankfurt case.

Histological studies by Alöis Alzheimer also revealed a degeneration of small cerebral arterioles; a process later known as "Alzheimer's sclerosis".

Alöis Alzheimer was born in Markbreit, Bavaria, on July 14, 1864, and died 51 years later, on 19 December 1915, in Breslau, Prussia (modern day Wroclaw, Poland), during The Great War. He studied at several universities; Aschaffenburg, Tübingen, Berlin and Würzburg. His doctoral thesis focused on the wax-secreting glands of the ear. His doctoral work was supervised by Albert von Kölliker (1817-1905), Swiss histologist and physiologist.

From 1888, having been a disciple of his friend Franz Nissl (remember the "Nissl corpuscles"), Alzheimer become interested in psychiatry. Both Alzheimer and Nissl made histological comparisons of normal and pathological cerebral cortex. Alzheimer's studies were compiled in his six-volume "Histology and Histopathology of the Cerebral Cortex", published between 1906 and 1918; the last few volumes published posthumously.

Franz Nissl focussed his studies on the evolution of the neuron after its separation from its axon, while Alzheimer tried to relate his histological findings to a clinical neuro-degenerative process.

In 1895 Nissl was the leading figure in psychiatry in Germany. Emil Kraepeling later took over the position, and would become known as the "Linnaeum of Psychiatry." Kraepiling's text served as a model for the famous DSM (Diagnostic and Statistical Manual of Mental Disorders) - published five times and reprinted on numerous occasions. When Kraepeling stopped running the Irrenanstalt (mental asylum) in Munich, Alöis Alzheimer took over the job. So, from 1903, Alzheimer began his studies on the differential diagnosis of "progressive paralysis". Irrenanstalt became a meeting place for the most important psychiatrists of the day: Ugo Cerletti (1877-1963), Hans

Gerhardt Creutzfeldt (1885-1964), Alfons Maria Jakob (1889-1931), Fritz H. Lewy (1885- 1950), and Gaetano Perusini (1879-1915), among others.

At this clinic in Munich, Alzheimer described the signs and symptoms of the patronymic disease. He also carried out microscopic research into other diseases. For example, he described various histological issues concerning athero-sclerotic disease, neuronal loss in "agitating paralysis" - later known as Parkinson's disease - Huntington's chorea, epilepsy, and advanced stages of syphilis. Let us not forget that most of the beds at psychiatric hospitals at that time were occupied by syphilis patients at advanced stages of the illness, along with patients suffering severe forms of epilepsy.

In 1910, four years after Alzheimer's first report on August D., Gaetano Perusini published reports on four other clinical cases, emphasizing the difference between "pre-senile dementia" and other types of senility regarded as "physiological" at that time. After some discussion, "pre-senile dementia" was considered a new nosological entity. Emil Kraepeling proposed that it be called "Alzheimer's disease", while Italian psychiatrists claimed that it should be called "Alzheimer and Perusini disease", although the eponymous "Alzheimer's disease" eventually won out.

On July 16, 1912, Kaiser Wilhelm II of Prussia appointed Alzheimer as Professor of Psychiatry at the University of Breslau (now Wroclaw, Poland), but he would never take possession of the post. On the way to Breslau, he contracted a serious illness leading to an endocarditis, of which he died on December 19, 1915, while Europe was tearing itself apart.

Alzheimer's disease accounts for 60% to 80% of all dementias. Loss of memory, especially the short-term memory is the first and most notable symptom of the disease, but there are more subtle symptoms, such as anosmia.

Other causes of dementia, in addition to Alzheimer's disease, are the after effects of a stroke, Parkinson's disease, Huntington's disease, and several encephalopathies (the most common of which is known as "Creutzfeldt-Jakob disease").

One of the problems Alzheimer patients have to face is a loss of orientation, even in familiar environments. Experiments on rodents have revealed how our spatial orientation system works. It consists of two types of neurons, known as "positioning cells" and "network cells", located in a region close to the hippocampus, an essential cerebral structure in the shape of a sea horse. The discovery of these cell lines was acknowledged with the Nobel Prize for Physiology and Medicine in 2014 awarded to John O'Keefe, an Anglo-American, for the discovery of the "positioning cells" *ex aequo* with the Norwegian married couple May-Britt and Edvard Moser in recognition of their work on "network cells", located in the entorhinal region, which is a kind of halt in the transit of information between the hippocampus and the cerebral cortex. These cells register what is seen, and what is unseen, helping us to develop a kind of three-dimensional construction of the world around us. All patients with Alzheimer's have damaged enthorhinal cortex; the reason for the patients' striking loss of special-temporal orientation.

Alzheimer's dementia is not only a very serious medical problem - governments should tackle the consequences of an incurable disease that affects without distinction of sex, education, income and other parameters. It is a disease that inexorably saps memory, judgment, dignity and identity. Those affected ultimately depend on family and caregivers for all tasks, including the most intimate. Families suffer an emotional and financial burden that few can be fully assumed by socio-sanitary structures.

The likelihood of Alzheimer's disease doubles annually after the age of 65. Beyond 80 years, half of the population suffer some degree of cognitive deterioration, estimating

the dementia of Alzheimer's in a percentage of 25 to 50%. The worldwide prevalence of Alzheimer's disease is 0.5%, that is, more than 47 million people; about 12 million in the European Union. In Spain there are about million and a half Alzheimer's patients. One current goal is to control Alzheimer's dementia by the year 2020. This is important not only from a medical point of view, but also an economic one. We must develop strategies to safeguard our collective future.

In the current situation, for each monetary unit invested in research into Alzheimer's disease, society spends 3.5 monetary units in the care of this sick. Thus, investing in research is a bet for the future. The economic cost of not doing so is very high. A study in the United States concludes that the cost of caring for people with Alzheimer's dementia is currently $ 172 trillion. Without substantial advances in treatment, the cost in 2020 will be $ 2 trillion, and 20 trillion in the year 2050.

The preventive treatment of the disease is logical. If the onset of dementia could be postponed five years, countless beds in assisted centres would be free.

Experience has shown that there are no objective strategies to prevent the onset of the disease. We all know close cases, and we know that there are no criteria to predict the risk of suffering, beyond the genetic tendency for early onset forms. Intellectual activity, regular physical exercise, and a projective social life do not protect against the risk of suffering this pathology. Cases are numerous among people of any social, economic or educational status.

Medications marketed a few decades ago seemed to slow down the progression of the disease when at its early stages. Their results have been very poor, medium and long term - no higher than those observed in the placebo groups. These lines of research have been almost completely abandoned. However, there are exceptions: a recent drug, LMTX, developed by the Canadian company TauRX Therapeutics has shown very poor

results in a clinical trial. The mechanism of action of LMTX raised unexpected expectations. It seemed to undo the protein aggregates τ. An attempt to amortize the investment made has wanted to see some degree of improvement in a subgroup of patients. Based on these results the laboratory intends to carry out a larger clinical study that allows request the authorization to the US Food and Drug Administration.

The mechanism of action of LMTX is seen as promising by other laboratories. Eli Lilly, Biogen, Roche Ltd., maintains several lines of research. LMTX is a derivative of the methylene blue dye. This dye has been studied in a neuro-degenerative pathology known as "frontal-temporal dementia". As can be inferred from its denomination, a degeneration of the frontal and temporal lobes, affecting the behaviour (associated to the frontal lobe) and of speaking (temporal lobe) occurs. The diagnosis of "frontal-temporal dementia" is very uncertain, often confused with serious psychiatric illnesses and even Alzheimer's dementia.

Until now Alzheimer’s disease is a dumping ground for experimental drugs, with very poor clinical results.

During the last decade, drugs authorized for the treatment of Alzheimer’s disease should demonstrate that they improve the memory and other "functional assessment scales". The US Food and Drug Administration decided to lower the requirements for the approval of new drugs against this disease. In this way The Food and Drug Administration hopes to encourage research. Taking into account the limited success of treatments when the neuro-degenerative process has already been established, the current trend is aimed at preventing its occurrence. However, how can avouch that a drug is really effective when it is given to people whose "only symptom" is a statistical risk of developing the disease?

There are two types of protein aggregates associated with Alzheimer's disease: β-amyloid protein (with the barnacles' hard appearance), and neuronal-fibrillar protein τ plates. These protein aggregates end up destroying neurons. According to some experts, Alzheimer's disease could spread between adjacent neurons as if it were an infectious disease - the "germ" being the protein τ. This leads to an intriguing question: do some neuro-degenerative diseases progress through the transmission of proteins between neurons?

When in the mid-1980s society came up with the urgency to seek strategies against AIDS, it took more than ten years of continuous research, with an investment of about ten trillion dollars, to develop drugs that would turn a fatal disease into a chronic pathology. It was necessary to raise the budget up to 1.4 trillion in order to achieve this. Let us not forget that the disease continues to be incurable. The US National Institutes of Health spend $ 3 trillion a year on research into new anti-retroviral drugs, while investment in the research into Alzheimer's, with a number of patients five times greater than AIDS, has a budget of $ 469 million.

There are doubts as to whether deepening the understanding of the biochemical mechanisms that underlie the disease will help to develop new drugs. Perhaps success will have to come from a mixture of basic research and empirical experimentation. This has happened on numerous occasions during the development of pharmacology. There is a certain disappointment among the experts when we observe that this approach is directed more towards the prevention of the emergence of the disease, or to slow down its progression, than towards clinical cure. This is logical, since, so far, no neuro-degenerative disease has been cured by pharmacological treatment alone. On the other hand, the cerebral blood cell barrier, which so effectively isolates our nerve tissue from the rest of the body, also blocks access to potential effective medications.

While some ambitious projects with a fixed deadline have been able to rise to the occasion (landing on the moon by 1969 as set by President J.F. Kennedy), others, mainly related to health, have failed. Such was the case of the project "War on Cancer", during the presidency of Richard Nixon. It remains to be seen what will be the outcome of the strategic plan against Alzheimer's disease by 2020. The US Congress has allocated an annual budget of $ 2 trillion for this purpose. It is very likely that Alzheimer's disease cannot be managed in such a short time, but substantial progress may be achieved.

Pharmaceutical science must be relied upon to relegate dementia to the list of other once intractable diseases, such as typhoid fever, polio, and many childhood cancers, to mention well-known examples. It is a priority task, before the "baby-boom" society reach the age of risk for suffering Alzheimer's disease. The aging of the population in developed countries translates into triumph or tragedy. This will depend on our ability to curb this disease before it causes a social bankruptcy.

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