

## Nicolás Achúcarro (1880-1918): First Histopathologist of the Government Hospital for the Insane in Washington, D.C.

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### INFORMACIÓN ART.

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### ABSTRACT

On one of his visits to the Munich Psychiatric Clinic in 1908, Smith Elly Jelliffe asked Alois Alzheimer who the best person would be to set up a histopathology laboratory at the Government Hospital for the Insane in Washington, D.C. Alzheimer replied that Achúcarro was the man for the job.

Nicolás Achúcarro was a Basque neuropsychiatrist born in the industrial city of Bilbao. He had been trained in some of the best clinics in Europe before travelling to Munich, where he studied brain injuries in rabbits infected with rabies. In September 1908, he moved to Washington, D.C., launched the histopathological laboratory and published several important articles before returning to Spain in May 1910 to work with Santiago Ramón y Cajal in the biological research laboratory at the University of Madrid. Later, in September 1912, he was invited by the Fordham University of New York to teach in the International Extension Course in Medical and Nervous Diseases, together with the English neurologist Sir Henry Head and the Swiss psychoanalyst Carl G. Jung, among other prominent figures.

Drawing on the writings of Achúcarro, letters to his family, and the press of the time, this paper analyzes his work in the United States as well as his contributions to neuroscience before his untimely death in 1918 at the young age of 37.

### Nicolás Achúcarro (1880-1918): Primer Histopatólogo del Hospital Psiquiátrico Gubernamental de Washington, D.C.

### RESUMEN

En una de sus visitas a la Clínica Psiquiátrica de Munich en 1908, Smith Elly Jelliffe le preguntó a Alois Alzheimer quien era la persona más adecuada para dirigir el nuevo laboratorio de histopatología en el Hospital psiquiátrico gubernamental de Washington, D.C. Alzheimer le respondió que Achúcarro era la persona mejor preparada para esa tarea.

Nicolás Achúcarro era un neuropsiquiatra vasco, nacido en la ciudad industrial de Bilbao, que se había formado en las mejores clínicas psiquiátricas europeas antes de llegar a Munich, donde estaba investigando las lesiones cerebrales causadas por la rabia en los conejos. Al llegar a Washington en septiembre de 1908, lanzó el laboratorio histopatológico y publicó importantes artículos hasta el mes de mayo de 1910 en que regresó a España para trabajar con Santiago Ramón y Cajal en el Laboratorio de Investigaciones Biológicas de la Universidad de Madrid. Dos años después, en septiembre de 1912, la Universidad Fordham de Nueva York le invitó a colaborar en el Curso Internacional de Enfermedades Médicas y Nerviosas, junto con el neurólogo inglés Sir Henry Head y el psicoanalista suizo Carl G. Jung, entre otras figuras estacadas.

Tomando como base los escritos de Achúcarro, cartas a la familia y prensa de la época, este artículo analiza su trabajo en los Estados Unidos, junto con sus contribuciones a la neurociencia hasta su muerte prematura en 1918 a los 37 años.

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Nicolás Achúcarro Lund (1880-1918) was deemed the most brilliant, independent and creative among the disciples and collaborators of Nobel laureate Santiago Ramón y Cajal (1852-1934), head of the so-called Spanish School of Neurology. With his background, international contacts, intelligence and human qualities, he would have been Cajal's successor in the Spanish neurology had he not died prematurely at age 37.

Studies on his life and work refer to his time in Washington, D.C., as the first director of the histopathology laboratory at the Government Hospital for the Insane from 1908-1910 (Moya, 1968; Rodríguez Lafora, 1918, 1968; Vitoria Ortiz, 1977), and the honorary doctorate awarded to him in 1912 by Fordham University, New York. It has also been pointed out that Achúcarro published the first American case of Alzheimer disease (García-Albea & Pérez-Trullén, 2003). But his histopathological work in one of the most advanced psychiatric hospitals in the United States has not received the attention it deserves, probably because his histopathological papers were not as numerous as his contributions to the study of the nervous system. Therefore, this article is mainly focused on his contributions to histopathology during this stage of his career.

### A Cosmopolitan Basque

The son of a well-to-do ophthalmologist and a cultured housewife of Norwegian descent, Nicolás Achúcarro was born in the industrial city of Bilbao, Biscay, on June 14, 1880.

His father, Aniceto Achúcarro, was a noted ophthalmologist who persuaded local authorities to open a free clinic to prevent the spread of eye diseases among children. His mother, Juana Lund, was the daughter of a Norwegian merchant who married a Basque woman and established a codfish distribution business in Bilbao. Both she and her husband shared a common interest in culture, art, music and foreign languages, and tried to give their children a liberal education open to European culture.

After completing his secondary education at "El Instituto," the public high school in Bilbao, the young Nicolás spent a year in Wiesbaden, Germany, where, in addition to learning German in the local Gymnasium, he became fond of classical music.

In October 1897, he enrolled in the medical school of Madrid's Universidad Central, where he studied histology under Santiago Ramón y Cajal. The Spanish university, however, was not the center for scientific progress that Achúcarro had imagined; to the contrary, it was convulsed by the moral, political, and social crisis following the loss of the colonies of Cuba, Puerto Rico and the Philippines after Spain's defeat in the Spanish-American War of 1898.

Disappointed, Achúcarro moved to Germany at the end of summer 1899 to continue his studies in pathology and further his training in physiology and chemistry at the University of Marburg. There he became acquainted with new developments in experimental physiology. However, his time in Germany was cut short when his younger brother, who was staying with him in Marburg to learn German, contracted a serious illness and the two returned to Spain in March 1900.

In the following years Achúcarro combined study at the university with laboratory research and extensive reading of scientific literature.

He established a good relationship with Luis Simarro (1851-1921), a prestigious neuropsychiatrist who founded the first Spanish laboratory of experimental psychology at the University of Madrid (Carpintero, 2014; Carpintero, Campos, & Bandrés, 2002). After obtaining his degree in medicine in June 1904, Achúcarro moved to Paris on the advice of Simarro to study neurology under Pierre Marie (1853-1940) at the Hospital of Bicêtre and attended lectures by Joseph Babinski (1897-1932) at the Hospital of La Pitié. Finally, after a few months' stay in Florence, Italy, improving his clinical training at the Psychiatric Clinic of San Salvi, Achúcarro moved to Munich to study under Emil Kraepelin, the eminent German psychiatrist.

Emil Kraepelin (1856-1926) was at the height of his career trying to improve his anatomo-clinical method in collaboration with Alois Alzheimer (1864-1915), his research assistant and director of the anatomical laboratory. Friend of hierarchy and opposed to any kind of flattery or adulation, Kraepelin was the typical German professor whose guiding principles of nosography and histopathological specificity of the various psychoses were influential in the European psychiatry of the time. Achúcarro accepted his scientific approach to psychiatry but did not like the narrow view of some Kraepelin school members. Opposed to dogmatism, he was more open to the dynamic factors operating in symptom formation.

What Achúcarro most liked at the Munich clinic was the histopathological work of Alzheimer, who in November 1906 gave his famous lecture on the nervous disease named after him (Alzheimer, 1907). A mutual friendship soon flourished between them. Achúcarro admired Alzheimer's remarkable methods of brain research, while Alzheimer appreciated Achúcarro's creativity and attention to detail in histological research in the laboratory.

On December 10, 1906, Achúcarro submitted to Madrid University his doctoral dissertation on brain injuries caused by experimental rabies in rabbits (Achúcarro, 1906). Back in Munich, he continued his research on the neuroglia and flat-granular cells in the Ammon's horn of the rabbit (Achúcarro, 1909a), and contributed to Franz Nissl's third volume of *Histological and Histopathological Studies on the Cerebral Cortex* with an extensive chapter on the histopathology of the central nervous system in rabies (Achúcarro, 1910e).

Two years later, in one of his visits to the Psychiatric Clinic in Munich, the American psychiatrist Smith Ely Jelliffe (1866-1945) asked Alois Alzheimer who he thought was the best person to organize and lead the histopathology laboratory at the Government Hospital for the Insane in Washington, D.C., run by his friend William Alanson White (1870-1937). Without the slightest hesitation, Alzheimer replied that Achúcarro was the man for the job.

The task of establishing a new laboratory in a major American hospital was a challenge for the young Achúcarro, who had no experience in that position and knew very little spoken English. However, it offered him the opportunity to complete his professional training in one of the best hospitals in the United States, so he accepted the job hoping it would later help him secure a place at the University of Madrid.

After a short summer break in Spain, Achúcarro embarked at Le Havre in September 1908 bound for New York. Upon arrival in the United States, he moved immediately to Washington, where he was cordially received by his American colleagues. With an

abundance of resources and full freedom to work, he launched the histopathological laboratory and taught the personnel in the practice of modern histochemical methods. In addition, he contributed a series of articles to the hospital *Bulletin*, which earned him a solid scientific reputation.

### Saint Elizabeths Hospital

The Government Hospital for the Insane in Washington, popularly known as *St. Elizabeths* after the name of the place where the center building was built, was created in 1885 through the efforts of Dorothea Lynde Dix (1802-1887), whose pioneering work led to the reform of psychiatric hospitals in the United States. It was she who convinced U.S. lawmakers of the urgent need to provide the country with mental hospitals where patients could be treated humanely in accordance with the concept of moral treatment advocated by Dr. Philippe Pinel (1745-1826), the renovator of French psychiatry.

The hospital's central building was built on a broad plateau of about 185 acres on the east bank of the Anacostia River surrounded by gardens with views of the city of Washington. Over time, and after the reforms of 1902, the hospital became a campus of more than thirty buildings that served a population of about 3,000 patients of both sexes (Otto, 2013).

Superintendent of St. Elizabeths from 1903, William Alanson White (1870-1937) was a young psychiatrist and early proponent of psychoanalysis, committed to renovating and updating the hospital. He placed great importance on research and university teaching, given his status as a professor at George Washington University, and was very interested in having a histopathology laboratory, which explains the warm welcome he gave to Achúcarro.

According to Gonzalo Rodríguez Lafora, who succeeded Achúcarro as head of the laboratory, the hospital had a staff of 34 clinical psychiatrists of both sexes and a scientific department headed by the psychologist Shepherd I. Franz. The department included a veteran autopsy specialist, Dr. Isaac W. Blackburn (1851-1911), who had just published an important book on the morbid brain anatomy in the insane (Blackburn, 1908), and a clinical analyst-serologist (Rodríguez Lafora, 1968).

Shepherd I. Franz (1874-1933) was a psychologist of the first generation of Americans who travelled to Germany to study at the Leipzig Institute under Wilhelm Wundt (1832-1920), the founder of experimental psychology. He became Achúcarro's closest friend since he spoke German, which allowed the two to communicate in the early days before Achúcarro was fluent in English. Professor of Physiology at the George Washington University School of Medicine, Franz was an authority on psychopathology based on his clinical and experimental research on the pathology of the nervous system. His experiments on the effects of brain injuries, together with his work on the rehabilitation of neurological patients (Franz, 1912), made him one of the pioneers of modern neuroscience (Colotla & Bach-Y-Rita, 2002).

In his article on American psychiatry, Achúcarro presented Franz as "almost certainly the most important American psychologist dedicated to the study of the mentally ill and known for his new

training method... in the experimental study of brain physiology" (Achúcarro, 1909b, p. 9).

Franz, on his part, recalled the encouragement he received from Achúcarro to continue his research in clinical and experimental neurology. In addition, he wrote in his autobiography, "At about 1908, Achucarro (*sic*) and I conducted a series of general neurological examinations of a large group of patients who were without obvious organic neurological disturbances. Some of them had shown evidences of what may be called proprioceptive hallucinations and delusions" (Franz, 1932, p. 111).

Impressed by the welcome they had given him, Achúcarro praised the hospital staff in his letters for their willingness to help him at any time and he was amazed at his modern facilities. For example, in a letter to his mother shortly after arriving to Washington, he wrote:

I'll be fine here as soon as I can speak English a little bit well. The people, very kind. Approximately as in Florence, but with a cleanliness compared to that, which already enters aseptic practices. It is what has most struck me, how clean everything is. In addition, there is nothing of all those greetings and that Germanic rigidity. We have two doctors and there is a hive of nurses who decorate all this pretty. All dressed in white. Excellent food and lots of vegetables (...). As I told you, it takes three quarters of an hour to go to Washington, but you really do not need to go there except in exceptional circumstances. There is everything inside the house, including mail and telegraph (Achúcarro, 1908-1968a, p. 130).

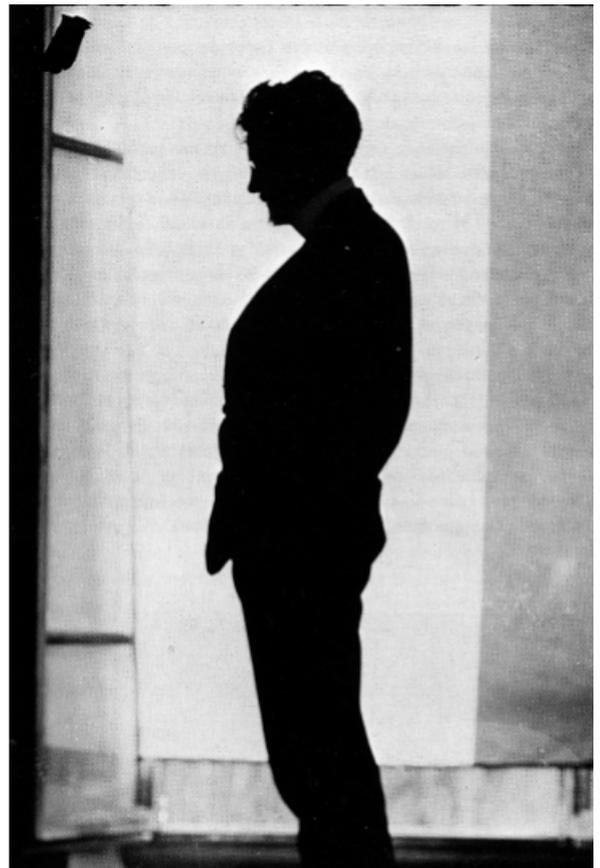


Fig. 1: Achúcarro's self-portrait

Achúcarro had the time and freedom to visit the Library of Congress, attend concerts by major symphony orchestras and visit other cities like Trenton, New York, Boston and Philadelphia. As he wrote in another letter dated November 18: "I have come absolutely to do what I want. And everything I do seems to them better than it is. Of course, I leave to the town or further away without telling anyone and when I please" (Achúcarro 1908-1968b, p. 137).

By mid-November, the staff now trained in the different skills and procedures, the histological laboratory operated at full capacity. Achúcarro performed a great number of necropsies, examined and classified brains of deceased patients to study the pathology of the central nervous system. He also visited the school of medicine at the George Washington University, praising the teachers' informal style and easy manner, which allowed them to work closer to patients than the German professors. In early December, he moved to a larger apartment with a bedroom, office and bathroom in the same private building where his friend Shepherd I. Franz was staying.

He also had the opportunity to attend a White House reception hosted by the President of the United States, Theodore Roosevelt, on the evening of February 4, 1909, for prominent figures in political and social life. A little later, he turned down an offer to teach histology at the George Washington University as he was determined to return to his country as soon as possible.

In August 1909, he moved to Madrid to prepare for his medical entrance exams for a staff position at the Madrid General Hospital. He responded so wisely to the exam questions on cerebrospinal fluid that he received the most enthusiastic approval by Cajal, member of the examination board. After passing the exam, he returned to Washington on November 6 to complete all work in progress. Upon arrival, he became part of an official Commission to prepare a report on diseases caused by nutritional deficiencies. He also rejected a grant from the University of Liverpool to work with the famous neurophysiologist Charles S. Sherrington (1857-1952).

On May 14, 1910, he resigned from his position and returned to Madrid after paving the way for the appointment of his colleague Gonzalo Rodríguez Lafora (1886-1971) as director of the Washington histology laboratory.

### **Histopathology and Mental Disease**

Achúcarro wrote several papers in the *Bulletin of the Government Hospital of the Insane of Washington* edited by William A. White. The first, entitled "The standpoint of histopathology in the study of mental diseases," was an intelligent defense of the histopathology laboratories in a country where the opposite functional trend was prevalent in medicine. Simply but firmly, he started by pointing out that the main goal of histopathology was not to discover the essence of mental disease, but to gather pathological data on the cerebral cortex and thereby help to solve the problem of clinical diagnosis.

In his opinion, clinicians and histopathologists should exchange their data in order to be more effective, because they were dealing with problems that were not so different. Although the histopathologist worked with corpses and the clinician with living

patients, the difference was not absolute because histopathology also played an important role in the study of blood or skin diseases.

In fact, the brain was almost inaccessible to direct pathological examination during life. The first attempts at morphological examinations were the punctures and exploratory trepanations made by surgeons, which facilitated the diagnosis of cerebral tumors. The cerebrospinal fluid was then subjected to histological, chemical, and serological analysis, and the results, though uncertain, were useful for suspected cases of general paralysis or cerebral syphilis. Histopathology also contributed to the separation of general paralysis from diffuse cerebral syphilis and from senile psychoses, as well as the diagnoses of different forms of mental retardation.

According to Achúcarro, the efficiency of histopathology in these cases had been sufficiently demonstrated and it seemed possible to construct a general cerebral histopathology through the exclusive study of the brain, although he didn't like it because it would leave the new science incomplete. As he wrote, "if cerebral histopathology is to be of some benefit in mental diagnosis (...), it is necessary that the connections between the clinic and the anatomical laboratory be most close" (Achúcarro, 1909c, pp.45-46). Since clear signs of disease were extremely rare, a diagnosis had to be made covering all the pathological elements from different fields; it was the complete picture that really mattered.

Achúcarro was aware of the difficulty of establishing a clear link between morphological facts and mental processes but felt that this should not be used as an argument against histopathology, especially considering the lack of knowledge about the cerebral structure and its higher functions. However, he was convinced that research on abnormal histological changes in the diseased brain would lead to isolating the histological complexes corresponding to clinical complexes, as recent studies on general paralysis had shown.

In Achúcarro's opinion, the new lines of research with modern methods of staining opened the door to new insights especially where no structural flaws were found in the brain. As Cajal had demonstrated in animals inoculated with hydrophobia, the histological picture of the neurofibrillary apparatus underwent a marked enlargement of only single neurofibrils (Ramón y Cajal & García, 1904). Alzheimer found that in the senile brain the neurofibrillary apparatus was reduced to a single bundle of fibrils wound in several spiral curves in the cell body; the remaining cellular structures disappeared, and the general shape of the whole kept the form of the destroyed elements. Not only the morphological, but also the chemical behavior of the neurofibrils was modified. Scattered in the cortex were small plaques of different sizes, circular in most cases, consisting of groups of axiscylinders having undergone considerable changes by formation of enlargements and club-like prolongations which sometimes appear in radial disposition in relation to the center of the plaque. According to Achúcarro, the proliferation of glia accompanying destruction of ganglion cells and nervous fibers:

expressed a principle of fundamental importance, namely, the close connection shown between the nervous structures and the neuroglial elements in pathological conditions (...). The interstitial tissues in general are no longer considered only as the mechanical support of the organs they contribute to build.

Their functions extend far beyond these limits into the realms of the metabolism of the whole organ. Also, the neuroglia in the nervous tissue is no longer barely considered as a support tissue, but as a constituent playing a large part in the nutritive and the metabolic functions of the organ in both normal and pathological conditions (Achúcarro, 1909c, p. 52).

The satellite glial cells exerted phagocytic functions when proliferating in great numbers around ganglion cells, and neuroglia could accomplish other functions than reducing the defects produced by the destruction of the structural elements. A good example of the plasticity of the interstitial elements was the relationship of the satellite neuroglia to the ganglion cells, shown experimentally by Achúcarro in connection with the rod-shaped cells (Achúcarro, 1908).

Achúcarro also mentioned the recent studies on the lamination of the cell layers in the cortex, which had given a more accurate standard for the appreciation of developmental abnormalities. Thus, the presence of an infantile type of cytoarchitecture in Huntington's chorea and in microcephalic individuals opened a wide field of research for the study of the abnormal cortex. And the similarities found between the histological pictures of general paralysis and nervous affections caused by trypanosomiasis contributed to a better understanding of the syphilitic processes in the cerebral cortex.

All these findings would be enough to demonstrate the usefulness of histopathology laboratories to those who opposed their use for clinical diagnosis, especially the functional neuropsychiatrists, to whom the last few sentences of the article were addressed:

We do not think to overestimate the importance of morphological studies of diseased organs by saying that even if the ascertaining and the recovery of functions are the only problems concerning practical medicine, the evidence of formal modifications must be in many cases at least the most natural and most instructive expression of the impaired function. This statement would seem a superfluous one if the representatives of the functional side of the question should not seem sometimes to consider morphological examinations lacking in any practical efficiency and almost barely ritual vestiges overloading practical medicine (Achúcarro, 1909c, p. 54)

Despite criticism from opponents, histopathology laboratories were essential for the diagnosis and effective treatment of a great variety of mental illnesses.

### First American Case of Alzheimer Disease

The next article published in the second issue of the *Bulletin* under the title "Some pathological findings in the neuroglia and in the ganglion cells of the cortex in senile conditions" (Achúcarro, 1910d) presented the first American case of Alzheimer's disease. The article described that Achúcarro also found a number of fibrillar neuroglia baskets similar to the ganglion-cell lesions pointed out by Alzheimer.

By applying slightly modified silver methods, Achúcarro observed

many pathological alterations in the glial cells which, in his opinion: have some interest because they are, so far as I can see, a part of a not well-known and complicated process of incrustation of the nervous tissue structures. This process will also include the modifications of the ganglion cells described by Alzheimer (1907) and his pupils in certain senile and presenile conditions" (Achúcarro, 1910d, pp. 81-82).

As indicated above, Alzheimer discovered that bundles of fibrils wound into a ball took the place of the ganglion cells nuclei and that they were quite different from the normal neurofibrils so far as their colorability was concerned. Therefore, he assumed that they were formed by a special chemical change in the neurofibrillary apparatus.

Achúcarro did not quite agree with some members of Alzheimer school, such as Donaggio (1906) or Bonfiglio (1908), who considered these ganglion cell changes practically identical to those found in the hydrophobia hypertrophy. In his opinion, these variations of the neuro-fibrils had their own characteristics, different from any other pathological changes found in the ganglion cells.

In the cases studied by Alzheimer the lesion was spread over a great extent of the cortex, so that one-sixth of all impregnated cells could be affected (Perusini, 1910). Achúcarro also found these ganglion cell lesions, although in five of his cases they were fewer in number. Miliary plaques like those described by Redlich (1898) and Fischer

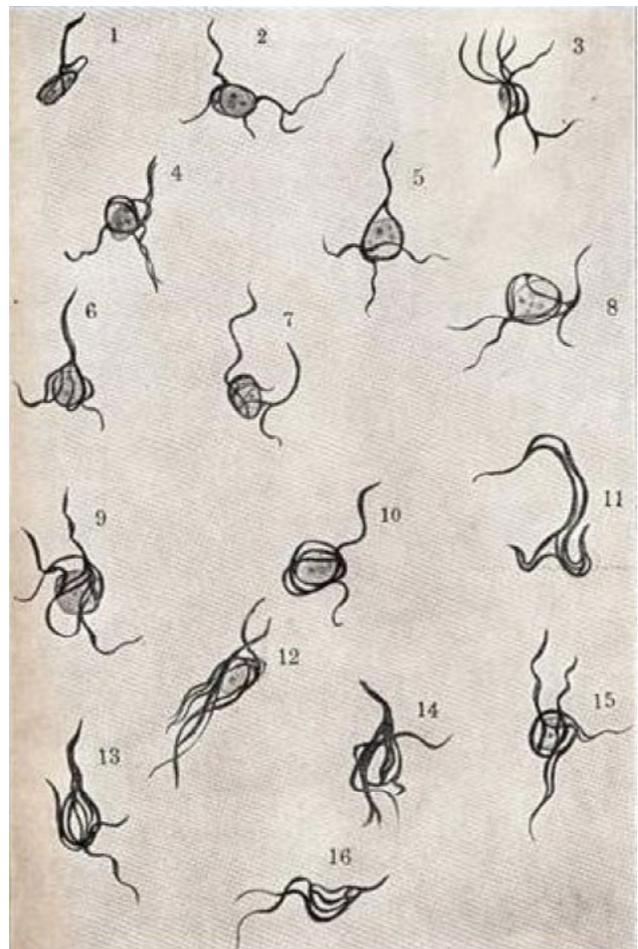


Fig. 2: Neuroglia baskets and ring formations (Achúcarro, 1910b, Plate I)

(1907) were also found in the Alzheimer laboratory, but Achúcarro only found slight indications of these plaques in the American patient with Alzheimer disease.

This patient was a man who died at age of 77 after nineteen years in the hospital in Washington. At autopsy his brain weighed 1,190 grams, and showed a marked opacity of the pia, slight indurations on both hippocampi, and thickened, calcified aortic valves. He had been diagnosed on admission as a chronic dementia case.

The number of glial cells in the brain of this man showed a marked increase in the marginal zone of the cortex and in the white substance, as indicated by the numerous pictures that Achúcarro included in the article. For example, Figure 2 presents multiple photographs of neuroglia baskets and ring formations stained by the Bielschowsky method (Bielschowsky, 1904). The fibrils appear to form rings or basket-like formations surrounding the nuclei (Pictures 1-12), while in Pictures 13 and 14 nuclei are lacking and the formations show faintly stained granules in their center. The multiplicity and variety of these neuroglia ring formations did not exhaust all the pathological forms, although they did provide a view of the general trend. Moreover, their high colorability made them like the ganglion cell lesions described by Alzheimer which also tended to acquire a very deep staining.

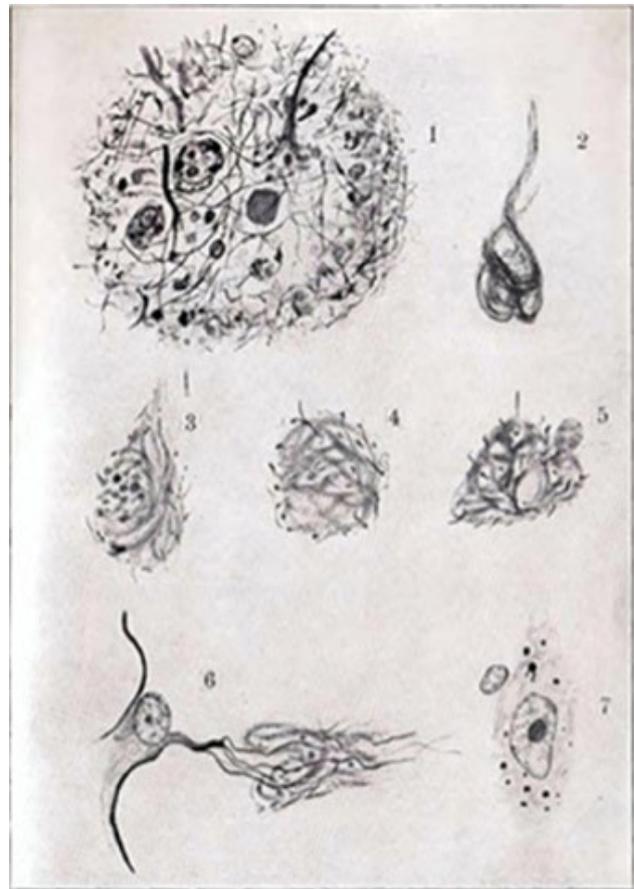


Fig. 4: Different kinds of neuroglia and cell changes (Achúcarro, 1910b, Plate VII)

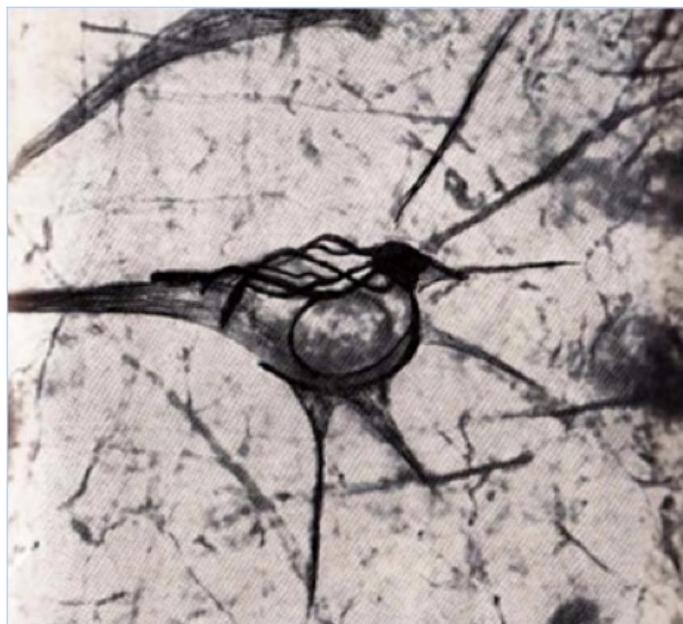


Fig. 3: Basket formation Involving Pyramidal Cell (Achúcarro, 1910b, plate III)

Achúcarro graphically presented the changes observed in the neuroglia satellite cells, where the ring formations surrounding the ganglion cells recalled the shape of the destroyed nuclei. But the most characteristic view of the basket formations involving pyramidal cells was that of Figure 3, where a retouched photomicrograph clearly showed the windings of the neuro-fibrils.

He also found multiple variations of the neuroglial cells located in deep layers of the cortex that might be related to some constituents of the miliary plaques, although he did not intend to deal with them in more detail. He only wanted to point out that they showed the same degeneration products and condensations of neuroglia reticulum reported by Perusini (1910).

In the center of the plaques some “Körnchenzellen” (granule cells) could also be observed, as shown in the first picture of Figure 4, which represents a miliary plaque with complicate structure. These plaques did not appear in the 77-year old American patient, although in the deep layer of his cortex there were changes which related in all probability to the formation of miliary plaques. They seemed to be the result of a process of hypertrophy of the neuroglia fibers and destruction of the nucleus, with bunches of granules remaining at the center of formations.

Since these radiate formations constituting the miliary plaques appeared concomitantly with the neuroglia baskets, Achúcarro thought that they could be explained as modifications of the neuroglia fibers. As he wrote: “The main importance of these formations for our present research lies in their appearance concomitantly with the neuroglia baskets and with the ganglion-cells changes described by Alzheimer. Very probably many of the club-like formations found in the plaques are neuroglial in nature” (Achúcarro 1910d, p. 87).

Alzheimer ganglion cell alterations were present in five Achúcarro American cases with miliary plaques, showing an extraordinary variety of pathological forms in the pyramidal cells. In some pyramidal cells, especially those in the Ammon’s horns, he also found rope-like fibers showing an extraordinary thickness. Other pyramidal cells showed only indications of these colossal fibers in different places. There were also skein-like structures composed of fine fibers which showed a reddish color and sometimes formed loops which recalled

the position of the nuclei, while the whole structure exhibited the general shape and orientation of the pyramidal cells. Other structures, however, were not outlined like the nerve cells, forming simple whirls or fine fibers scattered here and there in the tissue.

This variety of pathological forms was difficult to integrate into a general account. But Achúcarro was convinced that the neuroglia baskets surrounding the ganglion cell bodies were closely related to the alterations described by Alzheimer. As he wrote at the end of the article:

It is however evident that there exists some close connection between the neuroglia changes I have described and the ganglion cell modifications. The latter offer a greater variety than is shown in the drawings of other authors. I am inclined to accept the view that a process of incrustation with a pathological product acting upon different structures, neuroglia, pericellular reticulum, and even the endocellular neuro-fibrils gives rise to the variety of formations that have been shown in this article (Achúcarro, 1910d, pp. 89-90).

The observation of these phenomena influenced Achúcarro's later work, writing several articles on the arrangement of neuroglia in cortical and other brain structures and proposed the term "glioarchitecture" to name the organization of glia tissue, just as "cytoarchitecture" designated the layered arrangement of nerve cells in the cerebral cortex (Achúcarro, 1913a, 1913b; Achúcarro & Gyarre, 1914).

The second issue of the *Bulletin* contained two other articles by Achúcarro entitled "Elongated cells, Stäbchenzellen, neuroglia cells, and fat-granular cells in the Ammon's horn of the rabbit" (Achúcarro, 1910b) and "On certain lesions in form of plaques in the ependyma of the lateral ventricles" (Achúcarro, 1910c), both of which had been published a little earlier in the *Journal of the Biological Research Laboratory of the University of Madrid* (Achúcarro, 1909a, 1909d).

In the same issue of the *Bulletin* Achúcarro included a brief note about the name that should be given to a connective tissue plaque of the dilated fifth ventricle found in mental cases (Achúcarro, 1910a). Finally, he submitted a paper, together with Henry W. Miller, entitled "Report of a case of juvenile paresis," which was read at the sixty-sixth annual meeting of the American Medico-Psychological Association held in Washington on May 3-6, 1910 (Miller & Achúcarro, 1911). His contribution was the histological examination of a twelve-year-old boy and his demented mother, both of whom died in late 1909. The picture of the mother's brain was typical of general paralysis, with diffuse inflammatory processes. There was also a marked destruction of Purkinje cells in her son's cerebellum.

Achúcarro's concern for the treatment of the mentally ill is evidenced in an article he wrote a year earlier on American psychiatry for the *Revista Clínica de Madrid*. The purpose of the article was to draw attention to the poor condition of Spanish mental hospitals, both outdated and lacking in resources (Achúcarro, 1909b)<sup>1</sup>.

## Psychiatry in the United States

Achúcarro began the article by pointing out the rapid development of psychiatry in a country like the United States where psychiatric problems were arousing a great deal of social interest. If New York newspapers published much more information about mental illness than newspapers in Madrid, he wondered if that meant that New York had many more mental patients than Madrid. Or did it mean that New Yorkers paid much more attention to the mentally ill because of greater social interest?

Both alternatives were probably correct, since the complexity of modern life led to an increase in the rate of mental illness and tended to generate a greater awareness of psychiatric problems. However, it seemed difficult to provide an adequate response to this question because there were no reliable statistics in a science as young as psychiatry.

In connection with the increase of mental illness in modern societies, Achúcarro mentioned a recent article by Kraepelin (1908) on the problem of degeneration, in which he listed several factors leading to mental illness in our complex modern societies: defects in the germs of syphilitic and alcoholic parents, separation from natural conditions or "domestication," poor training of mental faculties with negligence of the body and poor development of will, and diminishing of natural impulses. But, as Kraepelin himself recognized, the data on which he relied had no absolute value.

In the United States there was an important increase in psychosis among the African American population, which, according to Achúcarro, could be due to the poverty and neglect they had suffered for centuries and the consequent social negligence regarding mental illness.

Seemingly more significant was the data collected by William A. White on the distribution of mental illness in the different American States (White, 1903). The number of patients admitted to psychiatric hospitals increased significantly from 2,561 in 1840 to 150,151 in the 1903 census, to which should be added the 11,807 patients diagnosed as mentally ill who were in homes for the poor. The growth rate of hospitals was virtually the same, from 31 hospitals in 1840 to 328 in 1903, of which 226 were public hospitals and 102 belonged to private institutions.

This increase in the number of patients and hospitals was due, according to Achúcarro, to the greater attention paid to mental illness. The budgets had grown proportionally from \$10,595,567 in 1890 to \$21,329,228 in 1903 in public hospitals, plus approximately the same amount in private institutions, amounting to a total of \$40,000,000 and 151,000 patients.

The statistical data on the distribution of these patients by race indicated that about one third came from abroad. Moreover, in the state of New York, fifty percent of the 25,000 mental patients were immigrants, and the number of crimes committed by foreigners stood at the same rate, or even higher. This gave rise to anti-immigrant prejudice fueled by the enemies of immigration who claimed that the worst criminals of Europe were coming to the United States. Achúcarro did not criticize these accusations, but simply described the facts without making value judgments. In addition, all mental patients of foreign origin whose disease appeared in the first two years

<sup>1</sup> As the September 1909 issue of *Revista Clínica de Madrid* is not available, we quote from the reprint published by Casa Vidal, Atocha 86 & 98, Madrid.

after arrival could be deported, and the number of people rejected for this reason exceeded 10,000 per year. In 1908, for example, 10,902 immigrants were rejected, representing 1.3 percent of the total.

After these data on immigration, Achúcarro reviewed the positive actions taken to improve the condition and treatment of the mentally ill. The study and scientific investigation on mental disease had begun with some delay compared to the European countries, where scientific medicine had gone beyond the philanthropic patient care and treatment. But it was not until recently that American doctors took up the study of their patients. In fact, one of the early reformers of American psychiatry, Benjamin Rush, in his book *Medical Inquiries and Observations upon the Diseases of the Mind* (1812), defended the scientific spirit and abolished the whip and chains in the Pennsylvania Hospital in Philadelphia where he practiced medicine. Later, in June 1844, *The Journal of Insanity* was first published in order to deal exclusively with mental illness and its treatment. That same year a group of hospital directors meeting in Philadelphia founded the Association of Medical Superintendents of American Institutions for the Insane, which would later be named the American Psychiatric Association.

Achúcarro pointed out that by the beginning of the twentieth century, American psychiatry was trying to improve its scientific standards and become more specialized in patient treatment and care. Many students were sent to Europe for training in neuropsychiatry and the hospitals were establishing new places for study and scientific research on mental illness.

In addition to the efforts of William A. White and collaborators to promote scientific research at Saint Elizabeths, Achúcarro especially praised the Swiss-born psychiatrist Adolph Meyer (1866-1950), who in October 1909 became the director of the future Henry Phipps Psychiatric Clinic at Johns Hopkins Hospital in Baltimore (Lief, 1948). Achúcarro probably visited Johns Hopkins during his stay in Washington, DC, and we know that Henry M. Hurd (1843-1927), the hospital's director, showed him the plans of the new clinic, as he wrote:

The future psychiatric clinic (already in construction), dependent on Johns Hopkins Hospital, is called to be one of the most important institution of mental medicine. *Ad. Meyer ... happens to be the most prominent man in this kind of studies. The director of the Johns Hopkins Hospital, Dr. Hurd... showed us the plans of the new clinic. Space for 80 beds and a lot of space for laboratories of histology, chemistry, psychology, etc. I have the impression that this facility will be something like Kraepelin's psychiatric clinic in Munich* (Achúcarro, 1909b, pp. 9-10).

We also know that in March 1913 Meyer invited Achúcarro to attend the inauguration of the Phipps Clinic and Achúcarro declined the invitation, and that in September 1912 the two met in New York on the occasion of the honorary doctorates awarded by the University of Fordham at the beginning of the International Extension Course in the Science of Medical and Nervous Diseases (Sánchez, 2011, pp. 119-121).

Achúcarro also praised the construction in cities of "psychopathic hospitals" for the diagnosis and treatment in a relatively short time

of acute psychotic persons, and the early care and observation of chronic cases, as well as the teaching of psychiatry. Among them was Bellevue Hospital of New York, where of the 2,500 patients admitted each year, 250 were treated at the hospital without being referred to a madhouse.

Achúcarro did not want to end the article without mentioning the religious psychotherapies carried out by Christian Science and Emmanuelism, the latter being the most recent and important religious movement in terms of neurology and psychiatry. After describing the origins and characteristics of religious psychotherapies, he recognized that they were progressing rapidly because of the ability of their leaders and the ease with which mystical ideas were implanted in the United States. But they were facing stern opposition from psychiatrists and neurologists and would probably could not hold out for long.

If Achúcarro devoted so much space to religious psychotherapies it was because he believed that they expressed the great social interest that psychiatry had generated in America. This was in sharp contrast to the lack of interest in his own country, as he wrote at the end of the article:

We have tried here to talk about the millions of dollars spent in psychiatry, the hundreds of thousands of patients and hundreds of hospitals, not to discourage anyone in view of the limited resources in our country. This is just to show what a country has done in a short time for the development of psychiatry, and to evoke the awareness of our inferiority in psychiatry, not in connection with what is done outside Spain, but in relation to what our country is doing in other parts of medicine. Let us compare any operating room in Madrid General Hospital with the department of mental patients and say if the difference of effort for the two kind of patients isn't manifest. Psychopathic rooms and public psychiatric hospitals should not be considered at all as if they cared for a lower category of patients. Of course, it is up to psychiatrists to get a greater scientific effort and philanthropic attention for their patients, anything less than that provided to other patients (Achúcarro, 1909b, pp. 11-12).

The article was clearly an invitation to Spanish psychiatrists to try to improve the conditions in their mental hospitals and raise them to the level of other hospitals in the country.

### Honorary Doctor from Fordham University

At age thirty, Achúcarro returned to Spain with well-deserved esteem for work in one of the most prestigious psychiatric hospitals in America. He joined the staff of the neurology ward at the Madrid General Hospital as an associate doctor, but received no payment until a year later, and therefore had to open a private practice as neuropsychiatrist. Cajal was also unable to offer him a remunerated position in the Biological Research Laboratory at Madrid University, which left him in a precarious financial situation during the first year.

After marriage on January 25, 1911, finances began to improve with the first payment from the General Hospital, and on

February 1st the Gazette of Instruction and Fine Arts published his appointment as interim assistant to the chair of practical and experimental teaching at the Medical School (Lain Entralgo, 1968; Vitoria Ortiz, 1977). During his summer vacation he visited Munich again and, working at Alzheimer's laboratory, discovered the silver tannin method known as the "Achúcarro technique" (Achúcarro, 1911a, 1911b).

His scientific contributions began to be recognized when Fordham University of New York invited him to participate in the International Extension Course in Medical and Nervous Diseases offered by the School of Medicine from September 9 to 28, 1912 (Gannon, 1967). The organizers of the course, including his old friend Smith E. Jelliffe, wanted to present in three weeks a complete overview of cutting-edge work by international and national experts in brain and behavior disorders for an audience of practicing physicians (Mattson, 2015).



Fig. 5: Instructors and participants in the Fordham International Course. Achúcarro is in the first row, fourth from the left. Seated to his left are William A. White and Henry Head (Photo courtesy of Fordham Archives)

The first of them, Dr. Henry Head (1861–1940), of the London Hospital, was a fellow of the Royal Society, editor of *Brain*, and one of England's most respected neurologists. He lectured on how sensation is affected by nerve lesions and presented the case of a partially paralyzed patient suffering from a lesion of the optic thalamus, which for the New York Times was "unique" in the world ("Famous Doctors Get Fordham Degrees", 1912). With him arrived Dr. Gordon Holmes (1876–1965), an Irish neurologist who specialized in the visual system and the cerebellum and was lecturer of the physiology of the nervous system at London University.

The psychoanalyst Carl Gustav Jung (1875–1961), associate professor in psychiatry at the university of Zurich, delivered nine lectures in which his theoretical differences with Freudian libido theory became public. He also gave a two-hour seminar for a small group each day for the last two weeks of the course (Mattson, 2015).

Achúcarro received the honorary degree of Doctor of Science. His lectures on histological microscopic observation and pathology, along with Saturday laboratory sessions, were followed with interest, as reported by the *Journal of the Michigan State Medical Society* (Hitchcock, 1912).

Participation in an international course alongside such prominent figures, together with the honorary degree and the echo the course

had in the press, were a boost for Achúcarro's career. Back in Madrid, he developed an intense teaching activity under the guidance of Cajal, who considered him the most brilliant of his collaborators. Achúcarro taught Cajal's university classes when he was absent, although he did not become associate professor until January 1914. He also collaborated in the Madrid University biological research laboratory, giving new impetus to pathological histology by renewing lines of investigation and exploring new methods and techniques of nervous tissue staining (López Sánchez, 2012).

## Conclusion

In 1912, on Cajal's recommendation, Achúcarro was appointed director of the laboratory of normal and pathological histology of the Board of Extension Studies (Junta para la Ampliación de Estudios), an institution dedicated to training young students planning to complete their scientific training abroad. There he met many of his disciples, including Pío del Río-Hortega (1882–1945), Felipe Jiménez de Asúa (1892–1973), José Miguel Sacristán (1887–1957), Luis Calandre (1890–1961) and Miguel Gayarre (1886–1936). It could be said that he was the master of the first generation of Cajal's disciples (López-Muñoz et al., 2008).

Achúcarro combined histological research and university teaching with providing social and philanthropic assistance of handicapped people. On October 26, 1914, he took office as secretary, and in fact technical director, of the National Patronage for the Handicapped (Patronato Nacional de Anormales). One year later, with the help of Rodríguez Lafora, he organized the first elementary course on mental disability celebrated in Spain for an audience of teachers (Monteagudo-Soto & Chisvert-Perales, 2017), and in September the Patronage opened special consulting rooms for children with learning disabilities. His health, however, began to fail with the first symptoms of what was thought to be a tuberculosis, but was actually Hodgkin's lymphoma. Unable to continue with his work, on June 1916 he moved to the town of El Pardo and one year later returned to Bilbao to die in his homeland on April 23, 1918.

Achúcarro's death was followed by a host of obituaries in the national press written by authorities like Cajal, and philosophers Miguel de Unamuno (1864–1936) and José Ortega y Gasset (1883–1955). They not only praised his scientific contributions but also his respect for patients, his kindness, good humor, wit, empathy and love of nature (López Albo, 1926).

His work, although unfinished, opened new ways to neuropsychiatry and pathological histology. In addition to his early research on the functional role of "Stäbchenzellen", and the histological technique of tannin and ammoniac silver known as the "Achúcarro Technique," he investigated the arrangement of glia in cortical and other brain structures (Achúcarro, 1913a, 1913b). His studies on dementia confirmed what he had already discovered in Washington, namely, that added to the neural changes described by Alzheimer should be other fibrillary neuroglial alterations, which in the final stages had a curly or reticular appearance. In his opinion, they were regressive processes of the neuron (Achúcarro & Gayarre, 1914).

He explored the glia architecture in the Ammon's horn and the *fascia dentate* of man, as well as in different nerve areas of several experimental animals and found that the topography on the Ammon's horn and the *fascia dentate* corresponds to the arrangement of layers of neurons in these regions (Achúcarro, 1914b). He also noted that in man and ape the neuroglial cells are more differentiated, both in protoplasmic and fibrous variety. By contrast, in the dog, cat and rabbit, neuroglia tissue is fibrous tissue in both regions.

His research on alterations of the sympathetic cervical ganglion in some mental illness (Achúcarro, 1914a) took as a starting point the recently discovered relationship between the sympathetic system and emotional life. In his opinion, the hormones secreted by the hypothetical protoplasmic glia reinforced the action of other endocrine manifestations essential for emotions, such as hyperthyroidism and hyperadrenalinemia.

One of his last research projects was a comparative study of the glia in the phylogenetic series from the perspective of its relationship with the vascular system (Achúcarro, 1915). He believed that the protoplasmic glia had a glandular function, discharging into the bloodstream the substance made in the cytoplasm. Although the hypothesis was abandoned, Achúcarro contributed to the knowledge of many structural characteristics of glia. His work on neuroglial cells and his research on the physiological connection between the nervous system and endocrine glands made him one of the earliest representatives of the current histophysiology.

Let us conclude this study of the American stage of Achúcarro's career with this text written by Smith E. Jelliffe, an American who knew him well:

Doctor Achúcarro was a man of broad culture which was infused by an enthusiasm and a special ability to impart knowledge and inspiration as a teacher, so that his work still continues through the pupils he gathered around him. His intellectual brilliancy and his keen judgment were combined with a vigor and independence of ardor in his scientific pursuits and a nobility of character which won him both love and admiration from his associates and acquaintances (Jelliffe, 1919, p. 272).

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