

The Nervous System Histopathology Laboratory of the JAE: a historical overview from the perspective of the visiting researchers

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ABSTRACT

In late 1911, the Junta para la Ampliación de Estudios e Investigaciones Científicas created the Nervous System Histopathology Laboratory (LHPSN, for its Spanish initials). The laboratory was run by Nicolás Achúcarro Lund, a young Basque researcher who had recently returned to Spain from the United States.

Achúcarro continued directing the activities of the laboratory until his premature death in 1918. The laboratory constitutes the immediate antecedent to the microscopy school of Pío del Río-Hortega, conditioning its origin and the basis from which that school developed its scientific interests. These interests culminated in 1920 in the Laboratorio de Histología Normal y Patológica (LHNP), directed by Pío del Río-Hortega at the Residencia de Estudiantes.

This article presents a historical overview of Nicolás Achúcarro's LHPSN, based on the information available on its constitution and the biographical profiles of visiting researchers, of whom over 20 are addressed here, and places the laboratory in the historical context of the Spanish Histological School.

This information on the LHPSN and the students attending it reveals the basis and the legacy that gave rise to all the histopathological interests of the Spanish Histological School, which, beginning at this laboratory directed by Achúcarro, culminated with the scientific oeuvre of Del Río-Hortega.

KEYWORDS

Histopathology Laboratory, Junta para la Ampliación de Estudios e Investigaciones Científicas (JAE), Spanish Histological School, Nicolás Achúcarro, Pío del Río-Hortega

Introduction

The 1910-1911 report of the Junta para la Ampliación de Estudios e Investigaciones científicas (JAE; Council for the Extension of Studies and Scientific Research) announced the creation in late 1911 of a new laboratory, installed provisionally in a small space in the Museum of Natural History, in Palacio del Hipódromo in Madrid. It was there, at the JAE's Nervous System Histopathology Laboratory (LHSPN, for its Spanish initials) belonging to Santiago Ramón y Cajal's Laboratorio de Investigaciones Biológicas (Biological Research Laboratory), where

research would begin with the application of histological research methods to the normal and pathological nervous system.¹

The directorship of the laboratory was entrusted to Dr Nicolás Achúcarro Lund (1880-1918), a young Basque researcher of only 31 years of age, who had returned to Spain from the United States little more than a year earlier (Figure 1).

As president of the JAE, Cajal played a key role in promoting the creation of this new laboratory and in appointing Achúcarro its director.² Cajal, who was well

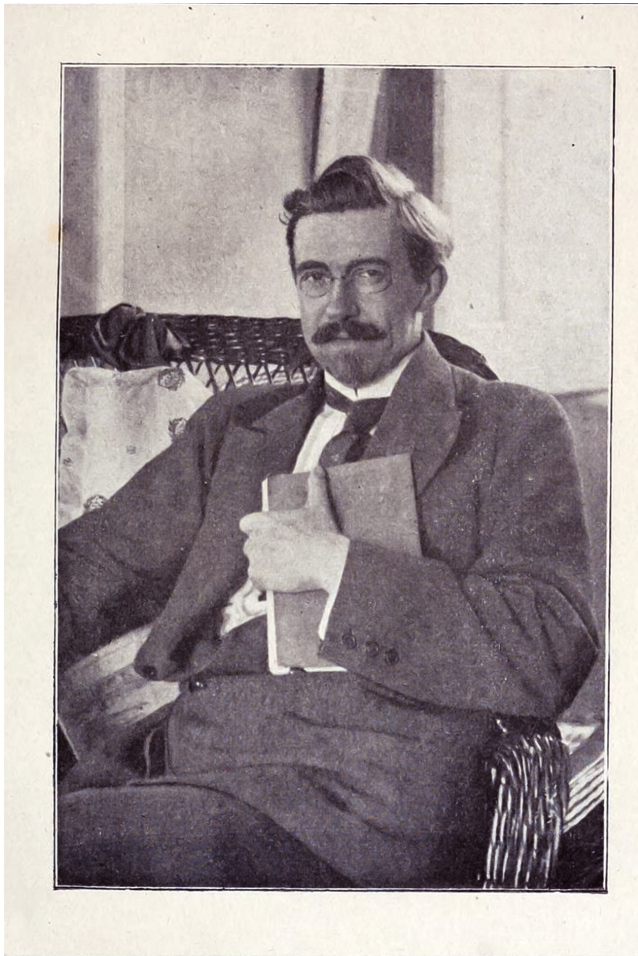


Figure 1. A portrait of Nicolás Achúcarro Lund (1880-1918) that was published in *Boletín de la Sociedad Española de Biología* (vol. VII, 1919), alongside an obituary by Cajal, read at the society's session of 26 April 1918.

aware of Achúcarro's value as a scientist and instructor, assigned him the specific task of providing technical training to physicians and researchers, who would later receive grants from the JAE to study abroad. Thus, from January 1911, Achúcarro was listed on the JAE's staff as an assistant instructor at Cajal's laboratory, with a monthly salary of 300 pesetas.³

Achúcarro remained as director of the LHPSN from late 1911 until his premature death in April 1918, before his 38th birthday. Thus, Achúcarro's brilliant career was truncated; it has been suggested that he might later have

succeeded Cajal as the leader of the Spanish Histological School.⁴

From October 1916, Achúcarro's absences from the LHPSN as a result of his disease became increasingly frequent. As a result, coordination of the laboratory was initially assumed by Miguel Gayarre y Espinal (1866-1936), the eldest researcher at the laboratory, and by Pío del Río-Hortega (1882-1945), who was the most technically skilled. Later, from 1918 until October 1920, the directorship was entrusted exclusively to Del Río-Hortega.

Pío del Río-Hortega was, without a doubt, the most important disciple at Achúcarro's laboratory. He quickly demonstrated that he was the individual who best understood the applicability of the tannin and ammoniacal silver method designed by his master Achúcarro in the summer of 1911 (Figure 2A)⁵; Del Río-Hortega was also the member of the laboratory with the most extensive and relevant scientific output.⁶

Two years after Achúcarro's death, Pío del Río Hortega established himself (completely independently from Cajal's laboratory) at the Residencia de Estudiantes, where he led a new laboratory, the Laboratorio de Histología Normal y Patológica (LHNP; Laboratory of Normal and Pathological Histology). The activities of the LHNP began with a small core group made up of Pío del Río-Hortega, Felipe Jiménez Asúa (1892-1973), and Carlos Collado Aguirre (1893-?), all of whom transferred from the LHPSN. The LHNP soon gained international recognition, and its fruitful scientific activity continued until the Spanish Civil War.⁶ The importance of the work conducted there under Del Río-Hortega, which remains relevant today, is such that he can be called the most important figure, after Cajal, in the Spanish Histological School.⁷

The LHPSN of the JAE, directed by Nicolás Achúcarro between 1911 and 1918, the main focus of this article, is therefore the immediate antecedent to the microscopy school of Pío del Río-Hortega, marking its chronological origin and laying the groundwork for the latter school's scientific interests. Today, more than a century later, knowing of the creation of the LHPSN and the personalities of the professionals working there is essential to understanding the foundations and the legacy upon which the histopathological work of the Spanish Histological School was built.

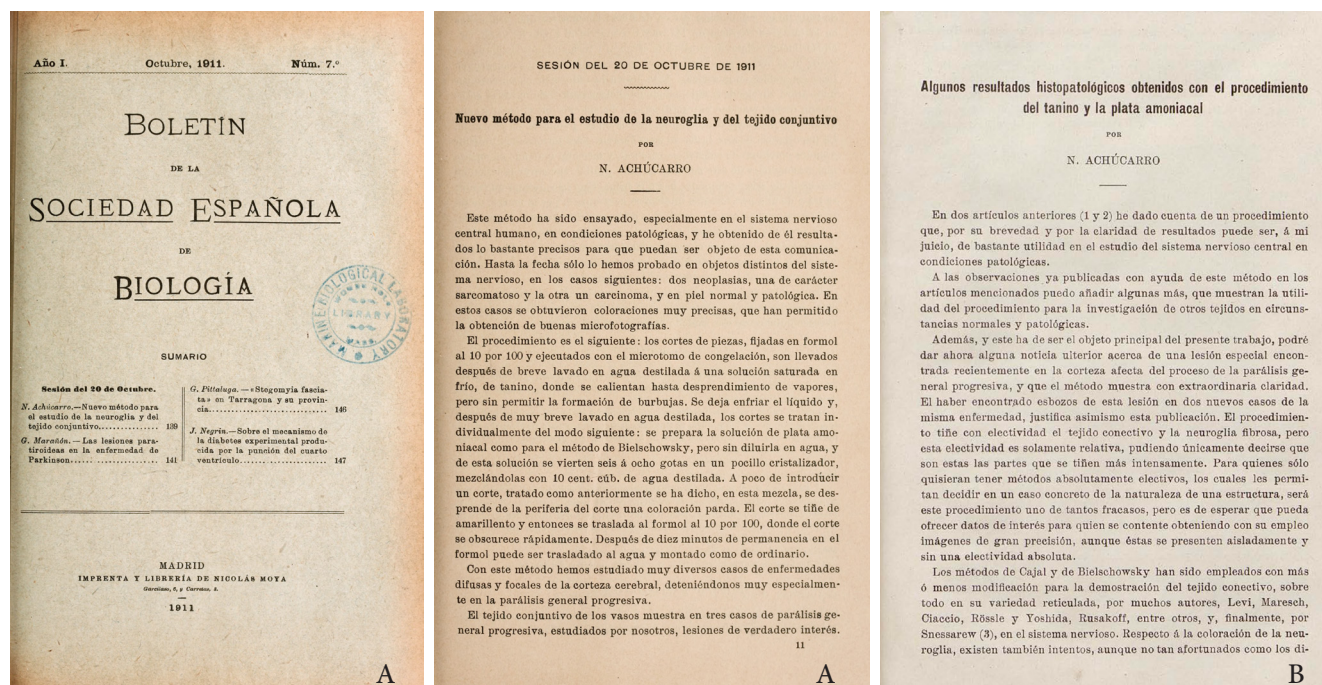


Figure 2. A) A communication presented by Nicolás Achúcarro to the Spanish Society of Biology on 20 October 1911, describing the tannin and ammoniacal silver method, in a brief text of three pages.⁵ B) The same year, Achúcarro published the first results obtained with his staining method in general paralysis of the insane, in Cajal's journal (*Trabajos del Laboratorio de Investigaciones Biológicas*). He reported the characteristics of rod-like cells and granulo-adipose bodies identified in the reticular perivascular tissue.²⁵

Objectives

To analyse the creation of the JAE's histopathology laboratory, directed by Nicolás Achúcarro Lund, within the general context of the Spanish Histological School. To give an overview of the biographical profiles of the researchers at the LHPSN, together with an overall assessment of the scientific contributions generated at the laboratory.

Documentary sources

The analysis is based on several documentary sources. The primary source consulted was the successive reports of the JAE,¹ as well as the personal files of the visiting researchers at the LHPSN in the JAE archives.⁸ Other sources include the autobiography of Del Río-Hortega,⁹ his correspondence,^{10,11} made available digitally by the Spanish Society of Neurology,¹² various monographs on Nicolás Achúcarro, and the original documents of many

of the publications produced at the LHPSN. In addition to the data compiled on the biographical profiles of the professionals at the LHPSN through the documentary sources mentioned above, online databases were also accessed to perform detailed searches on each of these figures.

Development

The Nervous System Histopathology Laboratory and the Spanish Histological School

This overview of the LHPSN requires, firstly, that we situate the laboratory within the general context of the Spanish Histological School.

As noted by López Piñero, the myth created around the figure of Cajal has blurred the distinction between different groups of researchers making up the Spanish Histological School.⁷ This mythification, which grew after the Spanish Civil War and especially after 1945,¹³

overshadowed the contributions of the various groups making up the school. Together, these contributions represent Spain's main contribution to scientific knowledge over the course of the first half of the 20th century.

Another event that contributed to the blurring of distinctions described above was the complete disintegration of the Spanish Histological School following the end of the Civil War.¹⁴ This disintegration affected many members of the LHPSN. Many of them, like Del Río-Hortega, had to take exile outside Spain.¹⁵ Others remained but were marginalised, sometimes dedicating their careers to subjects unrelated to microscopy research, and in some cases deleting all traces of their scientific biographies.¹⁶ Those who remained but did not face reprisals had to work in conditions of great scarcity, in an internationally isolated country that sought to rebuild itself institutionally through a complete rupture with its roots.

After the Spanish Civil War, knowledge of the scientific work conducted at the LHPSN, and later continued at the LHNP, was soon limited in Spain to the exclusive, restricted sphere of histology and histopathology, and did not translate to changes in the framework of public institutions; this situation persisted until the transition to democracy.

In consequence, conceptions of the Spanish Histological School have been clearly obscured. It is frequently described as the "Cajal school," a somewhat reductionist view. This simplification ignores the fact that, while the Spanish neurohistological school emerged around the work of this brilliant Aragonese researcher, in reality it included two clearly differentiated groups of researchers.^{7,17,18} The lines of research followed by these two groups were also clearly differentiated, but present points of intersection, with the main point of convergence being the use of microscopy techniques based on staining with silver salts.²

The first of these groups is made up of Cajal's direct disciples, who worked at his laboratory. This group's research was fundamentally devoted to the analysis of nervous tissue in normal biological conditions. This group of direct disciples of Cajal, in chronological order, included Pedro Ramón y Cajal (1854-1950), Domingo Sánchez (1860-1947), Francisco Tello (1880-1958), Fernando de Castro (1896-1967), and Rafael Lorente de No (1902-1990). With the exception of Cajal's brother, who always lived in other cities, all these researchers worked directly under their master, in the close setting of a single laboratory.¹⁷

The second group of researchers, who worked initially at the LHPSN and later at the LHNP, was successively led by Nicolás Achúcarro Lund and Pío del Río-Hortega. The two men have sometimes been described as a single scientific figure, successively embodied by two different persons.¹⁹ Achúcarro and Del Río-Hortega, unlike the direct disciples of Cajal, only occasionally collaborated with the latter in their neurohistological work.¹⁷ All members of the group were clearly influenced by Cajal's ideas and brilliant work, but their scientific interests were focused on the anatomical pathology study of the nervous system, working to identify and to perform cytological studies of neurodegenerative diseases.²

The activity of this second group of researchers took independent institutional form under the leadership of Del Río-Hortega, from October 1920.⁶ As a result, various disciples at the LHPSN, and especially members of the Del Río-Hortega school, never collaborated directly with Cajal. In fact, the publications produced, and especially those related to the Del Río-Hortega school, were often published in outlets other than the journal of Cajal's laboratory.⁶

Like Rodríguez Lafora (1886-1971), Achúcarro initially trained at the laboratory of the Valencian researcher Luis Simarro (1851-1921), who was the first master of both men. Simarro's teachings were passed on to the LHPSN through Achúcarro, and indirectly through Del Río-Hortega, whose autobiography mentions Simarro relatively often.⁹

Simarro was a Socratic master, who wrote little and whose teaching took place in the private setting of the microscopy laboratory he installed in his own home.^{2,20} Achúcarro and Rodríguez Lafora both passed through his laboratory in the first decade of the 20th century. Both men focused their research on the anatomical pathology of the nervous system, and both enjoyed considerable, almost consecutive training at international laboratories and clinics. Like Simarro, Achúcarro and Lafora both combined their microscopy research with neuropsychiatric practice. This combination of neurohistological research and clinical neuropsychiatric care is also observed in many other professionals at the LHPSN, as well as various disciples of the Del Río-Hortega school.⁶

In the early 1910s, Simarro's interests expanded greatly. In addition to his dedication to neurology and microscopy research, he began performing social and political activity, outside the clinic and the laboratory, which

marked the last decade of his life. In this context, most of Simarro's medical disciples (Achúcarro, Rodríguez Lafora, Gayarre y Espinal, and, to a certain extent, Villaverde) who frequented his home laboratory ultimately found themselves at Cajal's laboratory.^{2,20}

The arrival of Simarro's disciples led to an expansion of the scientific interests at Cajal's Laboratorio de Investigaciones Biológicas, as well as its institutional influence. Cajal, aware of this enrichment, contributed decisively to stabilising the careers of Achúcarro and Rodríguez Lafora, appointing them as the directors of two new laboratories created by the JAE.²

Thus, the LHPSN, to be directed by Achúcarro, was established in late 1911. Rodríguez Lafora, who initially also worked at Achúcarro's LHPSN, assumed the directorship of the Laboratorio de Fisiología Cerebral, in the Residencia de Estudiantes, in 1916. From October 1920, after the well-known dispute between Cajal and Del Río-Hortega,^{6,9,10} Lafora also joined Del Río-Hortega's laboratory at the Residencia de Estudiantes, which was subsequently renamed the Laboratorio de Histología Normal y Patológica.

Thus, the LHPSN, under the direction of Nicolás Achúcarro, represents the immediate scientific antecedent to the Pío del Río-Hortega school. This is demonstrated by the fact that various assistants and disciples of Achúcarro later joined the LHNP. Similarly, the scientific interests of the LHPSN were continued, culminating in the research activity conducted at the LHNP.

The location of the Nervous System Histopathology Laboratory and the arrival of Pío del Río-Hortega

We can confidently point to two locations of the LHPSN that was directed by Nicolás Achúcarro between 1911 and 1918, although some publications also mention a third, which, as we shall see, is not well defined.

The first location is described in the JAE report for 1910-1911, which mentions that the new laboratory directed by Dr Achúcarro was provisionally installed in a small room in the Museum of Natural History, in Altos del Hipódromo.¹

The second location of the LHPSN was in the old Velasco Museum, at number 13, Paseo de Atocha, where Cajal's Laboratorio de Investigaciones Biológicas was also located. Thus, the JAE report for 1914-1915 notes that "the Laboratorio de Investigaciones Biológicas, whose

director is Mr Ramón y Cajal, offered its hospitality to this Section and generously provided the inestimable support of its science."¹ According to data reported by Del Río-Hortega in his autobiography,⁹ the LHPSN was transferred to the Velasco Museum between October 1913 and August 1914, during which period Del Río-Hortega was abroad.

Del Río-Hortega first visited the LHPSN in October 1912, having been unsuccessful in attaining a suitable position at Cajal's laboratory.⁹ He attended Achúcarro's laboratory until October 1913, when he left first for Paris, and then for Berlin, with a grant from the National Cancer Institute. During his time abroad, Del Río-Hortega disseminated the tannin and ammoniacal silver method designed in 1911 by his master Nicolás Achúcarro,⁵ seeking to convince French and German scientists of the importance of using the methods of Cajal and Achúcarro.¹⁰ Thus, in 1913-1914, Del Río-Hortega published various studies conducted in Paris and Berlin in the journals *Trabajos del Laboratorio de Investigaciones Biológicas* (TLIB, for its Spanish initials) and *Boletín de la Sociedad Española de Biología* (BSEB) (Figure 3).²¹⁻²⁴ Due to the outbreak of the First World War, he returned hurriedly to Madrid, arriving in August 1914; Del Río-Hortega described how, upon his return, Achúcarro's laboratory was now located in the Velasco Museum on Calle Atocha, on the floor above Cajal's laboratory.⁹

Del Río-Hortega arrived at the LHPSN a year after Achúcarro communicated his tannin and ammoniacal silver method to the Spanish Society of Biology (SEB, for its Spanish initials), in October 1911.⁵ Just months later, Achúcarro reported in Cajal's journal (TLIB)²⁵ that he had applied his method in general paralysis of the insane, observing rod-like cells and granulo-adipose bodies in the perivascular region; he had been interested in these structures for years, and wished to elucidate their meaning and origin. Both subjects were brilliantly and definitively addressed by his disciple Del Río-Hortega. With regard to the tannin-ammoniacal silver method, in 1916-1917, Del Río-Hortega described four modifications or variants of his master's method, each with a specific application.^{26,27} Regarding the issue of the origin and significance of rod-like cells and granulo-adipose bodies, Del Río-Hortega masterfully solved the question between 1918 and 1920,²⁸⁻³⁰ applying a novel technique he had developed himself, the "ammoniacal silver carbonate solution," which he reported in Cajal's journal in 1918,³¹ a month before his master's death.

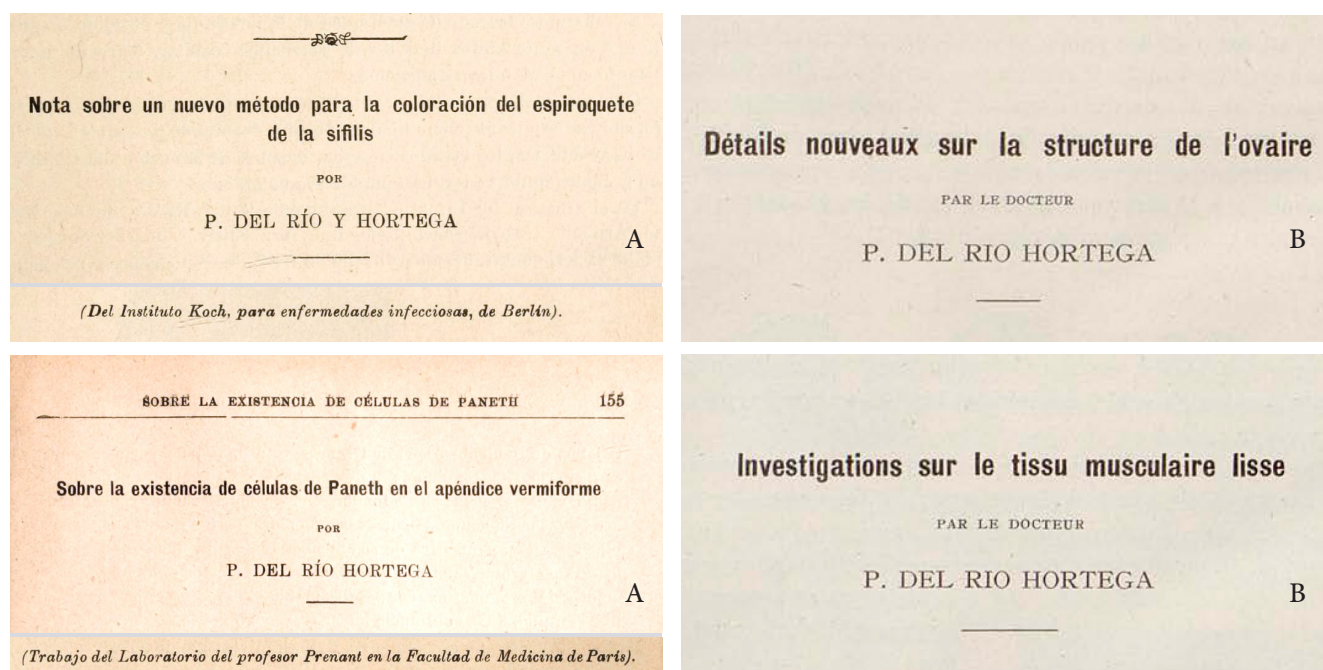


Figure 3. Studies performed by Del Río-Hortega in Paris and Berlin, which he published in Spain in the *Boletín de la Sociedad Española de Biología* (A)^{23,24} and *Trabajos del Laboratorio de Investigaciones Biológicas* (B),^{21,22} using the histological techniques of Cajal and his master Nicolás Achúcarro.

Therefore, Del Río-Hortega can unquestionably be considered the most important of Achúcarro's disciples, and the most outstanding figure of the LHPSN. Following Achúcarro's death in April 1918, Del Río-Hortega became director of the LHPSN until October 1920, when he transferred to the Residencia de Estudiantes to create the LHNP. The sheer scale of Del Río-Hortega's scientific oeuvre, first at the LHPSN and later at the LHNP, is such that it has been the subject of several historiographic analyses,^{6,7,10} which merit consultation to gain a complete picture of the importance of his work.

Returning to the subject of the different locations of the LHPSN, some imprecise references have been made to a possible third location, inside the Residencia de Estudiantes. It should be noted that the Residencia de Estudiantes was founded in 1910, with Achúcarro as a member of the board practically from the time of its creation.³² The Residencia was initially installed in a hotel rented by the JAE, on Calle Fortuny. The construction of

the Residencia de Estudiantes, at its definitive location at Altos del Hipódromo (called "Colina de los Chopos" by the poet Juan Ramón Jiménez) in Madrid, began in 1913, and the buildings were not inaugurated until 1915. Therefore, the hypothetical location of Achúcarro's laboratory within the Residencia de Estudiantes, if it ever really existed, would have to have been on Calle Fortuny.

However, it seems reasonable to suspect that this third location never did exist. The confusion arose and has sometimes been exacerbated due to several facts. Firstly, Achúcarro often frequented the Residencia de Estudiantes.³²⁻³⁴ For instance, he gave a series of technical lectures for students there prior to the installation of the LHPSN at the Museum of Natural History. In the words of his student Prados Such³³: "Mr Achúcarro gave us several lectures, some on general subjects, for all residents, and other more specialised lectures on the structure of the nervous system, prior to the installation of our little laboratory." These lectures are also mentioned

in the report of the JAE for 1911-1912.¹ The JAE report for the following academic year (1912-1913) notes that Achúcarro had been invited in September to deliver some lectures at Fordham University (New York).¹ Achúcarro also used the material from these lectures, as well as the slides he presented, for lectures to the students of the Residencia.^{1,32} These lectures at the Residencia during the 1912-1913 academic year were also mentioned by Wenceslao López Albo (1889-1944) in his biography of Achúcarro.^{35,36}

An additional factor that has contributed to the confusion is the fact that, at Achúcarro's request, a small new laboratory was installed at the Residencia de Estudiantes in the 1913-1914 academic year, which is also frequently confused with the LHPSN. Prados Such describes the creation of the laboratory: "in what had originally been a bike shed belonging to the Residencia de Estudiantes at the Fortuny hotel, a modest histology laboratory was created, where Luis Calandre taught histological techniques and Julio Blanco taught clinical analyses."³³ Both figures, Luis Calandre Ibáñez (1890-1961) of Cartagena³⁷ and Julio Blanco Sánchez (1888-1976) of Valladolid, were recent graduates and residents who had received grants from the JAE. They were soon joined by José Suredá Blanes (1890-1984), from Mallorca, who taught chemistry at the laboratory; Suredá was also a resident at the Residencia and was studying in Madrid for his doctorate.^{38,39}

This modest laboratory in the hotel on Calle Fortuny is mentioned in the JAE report for 1913-1914 as a histology and chemistry laboratory, with 16 students attending the histology laboratory and six attending the chemistry laboratory.¹ The histology laboratory, originally promoted by Achúcarro, was directed by his disciple Luis Calandre, who dedicated many years of his career to microscopy research. The laboratory was later named the laboratory of microscopic anatomy, and continued to be directed by Luis Calandre within the Residencia de Estudiantes until October 1931. Calandre Ibáñez, as we shall see, was effectively one of Achúcarro's earliest disciples at the LHPSN; he later shifted his focus to cardiology, publishing several works together with his master. From 1931, the microscopic anatomy laboratory at the Residencia de Estudiantes was directed by Manuel López Enríquez (1890-1968),⁶ a disciple of Del Río-Hortega who had attended the LHPSN throughout 1919.

Biographical notes on the visiting researchers at the histopathology laboratory

The reports of the JAE for the years 1912-1919 are today, more than a century later, the main documentary source to establish the identities of the professionals who attended the LHPSN to work with Nicolás Achúcarro.¹ These reports also list much of the scientific output of Achúcarro and his disciples at the LHPSN, globally considered a highly important body of work. Thus, if we analyse only the journal *TLIB*, the most important publication for the Spanish Histological School, practically half (44/96) of the works published in Cajal's journal in the period 1911-1919 were studies performed at the LHPSN (Figure 4A), with Pío del Río-Hortega being the most prolific author (Figure 4B).

The scientific publications of Nicolás Achúcarro have been addressed in several articles,⁴⁰⁻⁴² which have identified a total of 43 publications (in Spanish, French, English, and German) appearing between 1906 and 1916.⁴³ However, the most precise analysis of Achúcarro's scientific interests is the article by Fernando de Castro, who knew Achúcarro from his first year at medical school.⁴⁴ De Castro gives a clear, systematic summary of Achúcarro's scientific interests, in the following subjects: *a)* the problem of rod-like cells; *b)* the tannin and ammoniacal silver method; *c)* histological and histopathological research into the macroglia; *d)* the architecture of the neuroglia in the cerebral cortex; and *e)* superior cervical ganglion alterations in some mental disorders.⁴⁴

In compiling the list of professionals at the LHPSN, it is often difficult to establish the exact identities of these individuals. The JAE reports often list only one surname. Despite this, the reports show that between 1912 and 1919, more than 20 professionals attended the LHPSN, 60% of whom also received grants from the JAE for training placements, many of which were in other countries (Table 1).

Many of these visiting researchers had simultaneous or subsequent careers in neuropsychiatry, and several had previously studied at Simarro's laboratory.

There was also a group of researchers who were not physicians but rather graduates in natural sciences, some of whom had links with the Museum of Natural History of Madrid, the first location of the LHPSN. Furthermore, the list of professionals also includes some individuals from institutions independent of the JAE, such as the

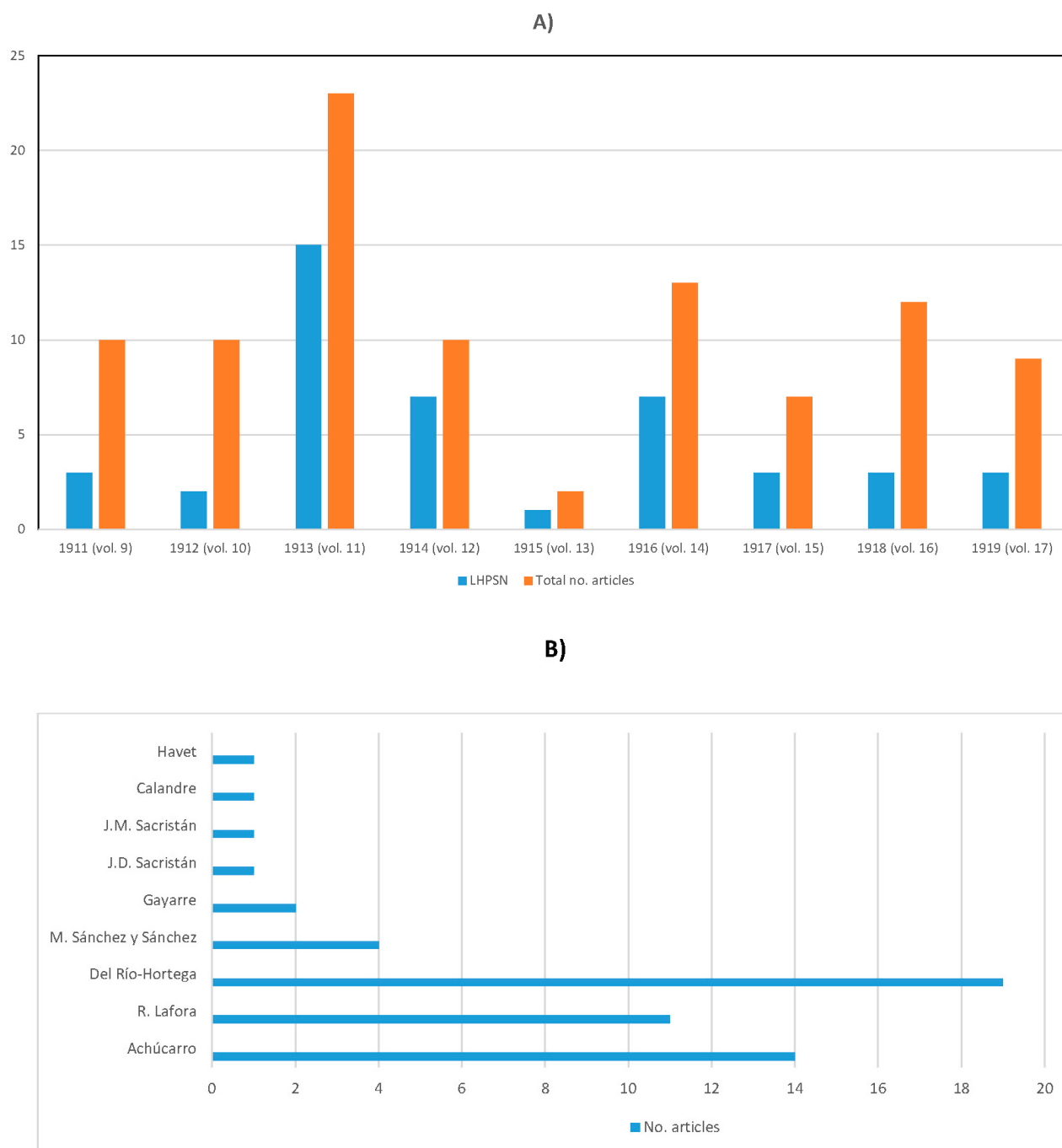


Figure 4. A) Scientific articles produced at the Nervous System Histopathology Laboratory and published in *Trabajos del Laboratorio de Investigaciones Biológicas* (1911-1919). B) Authors of articles produced at the Nervous System Histopathology Laboratory and published in *Trabajos del Laboratorio de Investigaciones Biológicas* (1911-1919).

Dominican brother Manuel Barbado, and from other countries, such as professor Havet.

We shall begin by considering the researchers who had previously studied under Luis Simarro. Such was the case of Gonzalo Rodríguez Lafora and Miguel Gayarre y Espinal, both of whom, like Nicolás Achúcarro, had received their initial training in histology at Simarro's laboratory in the first decade of the 20th century.

Gonzalo Rodríguez Lafora was one of the first visiting researchers at the LHPSN, after returning to Spain from the United States. Lafora had already received excellent scientific training, largely in parallel with Achúcarro, attending the best research centres and laboratories in Europe. Furthermore, during his medical studies, Lafora worked at Simarro's laboratory, where he performed histology research on the nervous system in fish.^{45,46} Thanks to this early study, he was one of the first to receive a JAE grant, in 1908,³² and completed training placements initially in Berlin and later in Munich and Paris. In 1910, Lafora travelled to the United States to work as a histopathologist at the Washington Federal Asylum, a position left vacant by Achúcarro.⁴⁵ He returned to Madrid in 1912, joining the LHPSN, and at the same time, together with Achúcarro, worked on the project to create a national school for children with disabilities. Lafora's scientific output after returning to Spain was prolific; for instance, in 1913 alone, he published nine articles on histopathological subjects in Cajal's journal (*TLIB*). The same year, Cajal founded a laboratory of experimental nervous system physiology at his institute, which was directed by Lafora for many years. Lafora's long scientific career, extensive body of publications (225 works), and the analysis of his neuropsychiatric practice are beyond the scope of this article; his scientific biography was analysed in detail by his disciple Luis Valenciano.⁴⁶

The other researcher at the LHPSN with links to Dr Simarro's laboratory was Miguel Gayarre y Espinal.⁴⁷ Gayarre was the eldest professional at the LHPSN. He performed numerous microscopy studies with Achúcarro, leading to the publication of a histopathological study of the cerebral cortex in general paralysis of the insane,⁴⁸ using the gold sublimate method designed by Cajal in 1913.^{49,50} Gayarre also analysed neuroglial alterations in Alzheimer disease, publishing his results together with Achúcarro in the *TLIB*.⁵¹ Gayarre's work at the LHPSN coincided with his time as director of the psychiatric hospital in Ciempozuelos (Madrid). He had attained

this role thanks to Simarro, who had recommended him to the centre's founder, the priest Benito Menni.⁴⁷ From 1919, another of Achúcarro's disciples became director of the psychiatric hospital in Ciempozuelos: José Miguel Sacristán (1887-1957), who had also attended the LHPSN.

Sacristán, as noted above, had also studied under Simarro at his laboratory, although his attendance was probably very sporadic.^{52(p35)} He also combined his histology research with psychiatric care, and attended the LHPSN from 1911-1912, as did his younger brother Juan de Dios Sacristán (?-1939). The Sacristán brothers are pictured in an iconic photograph of the Spanish Histological School taken in 1915 by the photojournalist Salazar at the laboratory on Calle Atocha; the image shows Cajal with several of disciples from the LHPSN (Figure 5).⁵³

The Sacristáns authored numerous publications during their time at the LHPSN. For instance, Juan de Dios Sacristán performed a study on the ganglion cells of the pineal gland, which appeared in German, with Achúcarro as co-author, in the *TLIB* in 1913.⁵⁴ A year earlier, José María Sacristán, together with Achúcarro, had published an analysis of the pineal gland,⁵⁵ based on studies using the tannin-ammoniacal silver method designed by Achúcarro in 1911 (Figure 2),^{5,25} which was well known and employed by all the researchers at the LHPSN.

Taking the advice of Achúcarro, José Miguel Sacristán obtained a grant to travel to Germany to work at Kraepelin's psychiatry clinic and at Rudolf Allers' neurochemistry laboratory.⁵⁶ There, Sacristán focused on researching the biochemistry of mental disorders, establishing a potential functional relationship between the neuroglia and endocrine glands, and specifically with hyperthyroidism. After returning to Spain in 1915, José Miguel Sacristán, together with Antonio Madinaveitia Tabuyo (1890-1974), became director of the laboratory of physiological chemistry, and later a collaborator at the physiology laboratory of Dr Negrín, both of which belonged to the JAE.⁵⁷

Overall, José Miguel Sacristán produced a very extensive body of scientific work, and is considered one of the leading figures in the institutionalisation of psychiatry as a differentiated medical specialty in Spain.⁵⁶ Despite his activity as a psychiatrist, Sacristán's interest in microscopy work is reflected in his biography until the time of the Spanish Civil War; for instance, in June 1938, when

Table 1. Visiting researchers at the Nervous System Histopathology Laboratory.

	Time at the LHPSN*	Grant from the JAE	Additional data on subsequent career
Brother Manuel Barbado Viejo (1884-1945)	1912-1913	ND	After the Spanish Civil War, he occupied Simarro's chair and directed the CSIC's Luis Vives Institute. ^{80,81}
Luis Calandre Ibáñez (1890-1961)	1912-1913	1912-1914 (Germany)	Directed the JAE's microscopic anatomy laboratory (1913-1914). Career in cardiology; directed Hospital de Carabineros. Suffered political persecution. ^{64,68}
Carlos Collado Aguirre (1893-?)	1917-1920	1923 (USA, Germany) – not used	Joined Del Río-Hortega at the LHNP in 1920. Rejected a neuropathology position in Boston in 1923. ^{9,10,96}
Luis Fortún Alcalá (1892-1928)	1912-1913 ^(s) and 1914-1917	1917-1918 (Switzerland)	Worked with Sacristán at the Ciempozuelos psychiatric hospital. Died in Switzerland due to tuberculosis. ^{74,75}
Francisco Ferrer Hernández	1917-1918	1909, 1911, 1919 ^(#)	Naturalist, assistant professor at the Faculty of Sciences in Madrid. Worked at the Museum of Natural History. ^{76,77}
Miguel Gayarre y Espinal (1866-1936)	1912-1919	ND	Direct disciple of Simarro. Director of the Ciempozuelos psychiatric hospital. ⁴⁷
F. Guerrero	1917-1919	ND	Published a study on the application of silver staining techniques in plant cells. ¹
Luis Guílera Molas (1895-1969)	1917-1918	1919 (Switzerland, Germany)	Chair of histology and anatomical pathology at the University of Granada. Cancer Institute of Hospital de la Santa Cruz y San Pablo, Barcelona. ^{90,93(p167-169)}
Felipe Jiménez Asúa (1892-1973)	1912-1913 ^(s) and 1919-1920	1917-1919 (Italy, Switzerland)	Joined Del Río-Hortega at the LHNP. Chair of histology and anatomical pathology at the University of Zaragoza. Died in exile in Argentina. ^{9,93 (p155-171, 263-264),94}
Jules Havet (1866-1948)	1914-1917	ND	Professor of anatomy and histology at the University of Leuven; disciple of Carnoy. Attended the LHPSN during the First World War. Was ordained a priest after the death of his wife. ^{9,82}
Felipe Hueto Zuluaga (1887-?)	1912-1915 and 1917-1918	Request for a grant was rejected.	Travelled to Munich, following Achúcarro's advice. Worked at the Ciempozuelos psychiatric hospital with Dr Sacristán. ⁵⁶
Manuel López Enríquez (1890-1968)	1919	1915-1919 (Switzerland, Netherlands)	Became coordinator of the LHNP after Del Río-Hortega's departure in 1937. ^{7(p72),84}
Emilio Luengo Arroyo (1898-1963)	1917-1918	ND	Specialised in parasitology with Pittaluga; received a grant from the Rockefeller Foundation, fought against malaria in the National Healthcare Institute. Suffered political persecution. ⁸⁹
Florencio Mozo	1917-1919	ND	
Augusto Navarro Martín (1897-?)	1918-1919	1920-1922 (France)	Worked on experimental syphilis with Sánchez Covisa, sat on the editorial board of <i>Actas Dermo-Sifiliográficas</i> . ⁸⁶⁻⁸⁸
Miguel Prados Such (1894-1969)	1918-1919	1920-1922 (United Kingdom, Germany)	Director of the Málaga psychiatric hospital. Evacuated to Valencia in 1936. Exiled to France and Canada. Professor at McGill University, died in Canada. ^{72,73}
Pío del Río-Hortega (1882-1945)	1912-1920	1913-1915 (France, Germany, United Kingdom) [†]	Directed the laboratory from 1918. Directed the LHNP from 1920. Evacuated to Valencia (1937); left Spain for Paris, Oxford, and Argentina, where he died. ^{6,9-12}
Gonzalo R. Lafora (1886-1971)	1912-1915	1908-1910 (Germany)	Director (1913) of the brain physiology laboratory. Took exile in Mexico in 1938, returning in 1947. ^{32,45,46}
José Rodríguez Valderrama	1918-1919	ND	Wrote an apparently unfinished study in 1919 on the histopathology of the neuroglia and its correlation with endocrine glands. ¹
José Miguel Sacristán Gutiérrez (1887-1957)	1912-1915	1912-1914 (Germany)	Director of the Ciempozuelos psychiatric hospital. Evacuated to Valencia in 1936. Several months' exile in France. Persecuted and took self-imposed exile after returning to Spain. ^{56,58}
Juan de Dios Sacristán Gutiérrez (?-1939)	1912-1919	ND	Abandoned microscopy research after winning a competitive examination to enter the postal administration. Took exile in France, where he died following a psychotic process. ⁵⁶
Manuel Marcelo Sánchez Sánchez (1899-?)	1914-1919	1915 (marine biology station, Santander) 1920-1921 (France)	Lived at the Residencia de Estudiantes. Naturalist, worked at the Museum of Natural History. ⁷⁹
José María Villaverde Larrar (1888-1936)	1917-1919	1916-1917 (Switzerland)	Psychiatrist at the Hospital General (men's ward). Killed in Madrid in 1936. ^{59,60,63}

CSIC: Spanish National Research Council; JAE: Junta para la Ampliación de Estudios e Investigaciones Científicas (Council for the Extension of Studies and Scientific Research); LHNP: Laboratorio de Histología Normal y Patológica (Laboratory of Normal and Pathological Histology); LHPSN: Nervous System Histopathology Laboratory.

(*): Visiting researchers at the histopathology laboratory between 1912 and 1920, listed in the successive reports of the JAE; (s): visited the histopathology laboratory as student; (#): received a grant to work at the marine biology stations in the Balearic Islands; ND: no data included in the JAE archives; †: received a grant from the National Cancer Institute.

he was evacuated to Valencia with Del Río-Hortega and Prados Such, the Faculty of Medicine of Valencia proposed that he be appointed an associate professor in the anatomy department to conduct studies into neurobiology and the architecture of nerve cells (Figure 6).⁵⁸

Unlike his brother, Juan de Dios Sacristán's interest in microscopy was less enduring. After winning a competitive examination for a position in the postal administration, Juan de Dios left behind his histology research; he died years later due to a psychotic process that he developed during his exile in France.⁵⁶

Another researcher with some links to Simarro is José María Villaverde Larrar (1888-1936). Villaverde was from Valladolid, and was initially treated by Simarro as his patient. He later became acquainted with Simarro during the experimental psychology course taught by the latter,^{59,60} and the pair later published a work together based on research conducted at Simarro's laboratory in 1913.^{61,62} Prior to his time at the LHPSN, Villaverde had travelled to Switzerland (1916) with a JAE grant.⁶³ Villaverde attended the LHPSN later in his career (1917-1919), as noted in the autobiography of Del Río-Hortega,⁹ and from 1920 his name no longer appears among the visiting researchers at the LHNP, as he maintained links only with Cajal's laboratory. Villaverde, who held a conservative ideology, had many differences of opinion with Lafora, for example because the former had opposed Del Río-Hortega's admission to the Spanish National Royal Academy of Medicine in 1934. Regarding these disputes between Villaverde and Lafora, in which ideology clearly played a role, a little-known detail is the fact that it was Lafora himself who had submitted a favourable report of Villaverde's work to the JAE in order that he be classed as proficient after receiving his grant⁶³; this enabled him to enter competitive examinations for university positions. Following significant controversy, Villaverde was eventually selected for the open position in the Royal Academy; however, he never took his place, as he was tragically killed in Madrid in 1936.^{59,60}

One of the first professionals to visit the LHPSN was Luis Calandre, of Cartagena, whom we mentioned earlier. Since 1910, Calandre had been a recipient of a JAE grant to live at the Residencia de Estudiantes. The grant, worth 225 pesetas, was awarded thanks to a favourable report by Luis Simarro,^{37,64} whom Calandre sent a box of histological preparations he had made, with a report and a study he had published in *Revista Clínica de Madrid*,

still a medical student (Figure 7A).^{64,65} After receiving the grant, Calandre attended Achúcarro's laboratory, where from 1912 to 1913 he analysed the application of his master's tannin and ammoniacal silver method in the study of cardiac muscle.^{66,67}

Subsequently, with financial support from the JAE, Calandre travelled to study under the cardiologist Georg Friedrich Nicolai and the pathologist Carl Benda, performing electrocardiography studies at La Charité, after obtaining an extension of his time in Berlin thanks to a report submitted to the JAE by Achúcarro (Figure 7B).⁶⁴ In 1914, Calandre was appointed as a physician at the Residencia de Estudiantes, and became director of the microscopic anatomy laboratory at the Residencia.^{37,68}

This laboratory, under the directorship of Calandre, was always in close scientific contact first with Achúcarro and later with Del Río-Hortega. In fact, after Calandre, the role of director was held first by Enrique Vázquez López (1907-1951) and after 1933 by Juan Manuel Ortiz Picón (1903-1995), both of whom were disciples of Del Río-Hortega.⁶ Between 1912 and 1919, Calandre published six studies in the *BSEB*, the *TLIB*, and *Revista Clínica de Madrid*; all six were based on Achúcarro's staining method.⁶⁵ The last of these publications, in which he collaborated with Mier,⁶⁹ appeared in the *BSEB* in 1919; in that study, Calandre used the silver carbonate method described by Del Río-Hortega.³¹

Another researcher, who arrived later at the LHPSN (1818-1819), was Miguel Prados Such (1894-1969). Miguel Prados, from Málaga, lived at the Residencia de Estudiantes with his brother and participated in studies conducted at the LHPSN, working with Rodríguez Lafora at the laboratory of experimental nervous system physiology. He collaborated with Lafora on two studies on the cerebrospinal fluid.^{70,71} In 1920, Prados Such received a grant to travel to England, where he worked with Frederick Mott; later, he worked under Spielmeyer and Kraepelin in Munich.⁷² From 1923 to 1932, Prados was director of the San José psychiatric sanatorium in Málaga, where he implemented a series of improvements to the care provided. In November 1936, he was part of a group of scientists and intellectuals evacuated from Madrid to Valencia, which also included Pío del Río-Hortega and Miguel Sacristán. From Valencia, Prados travelled to Barcelona and subsequently took exile in France and Canada, where, with the support of Del Río-Hortega, he achieved a stable research and teaching

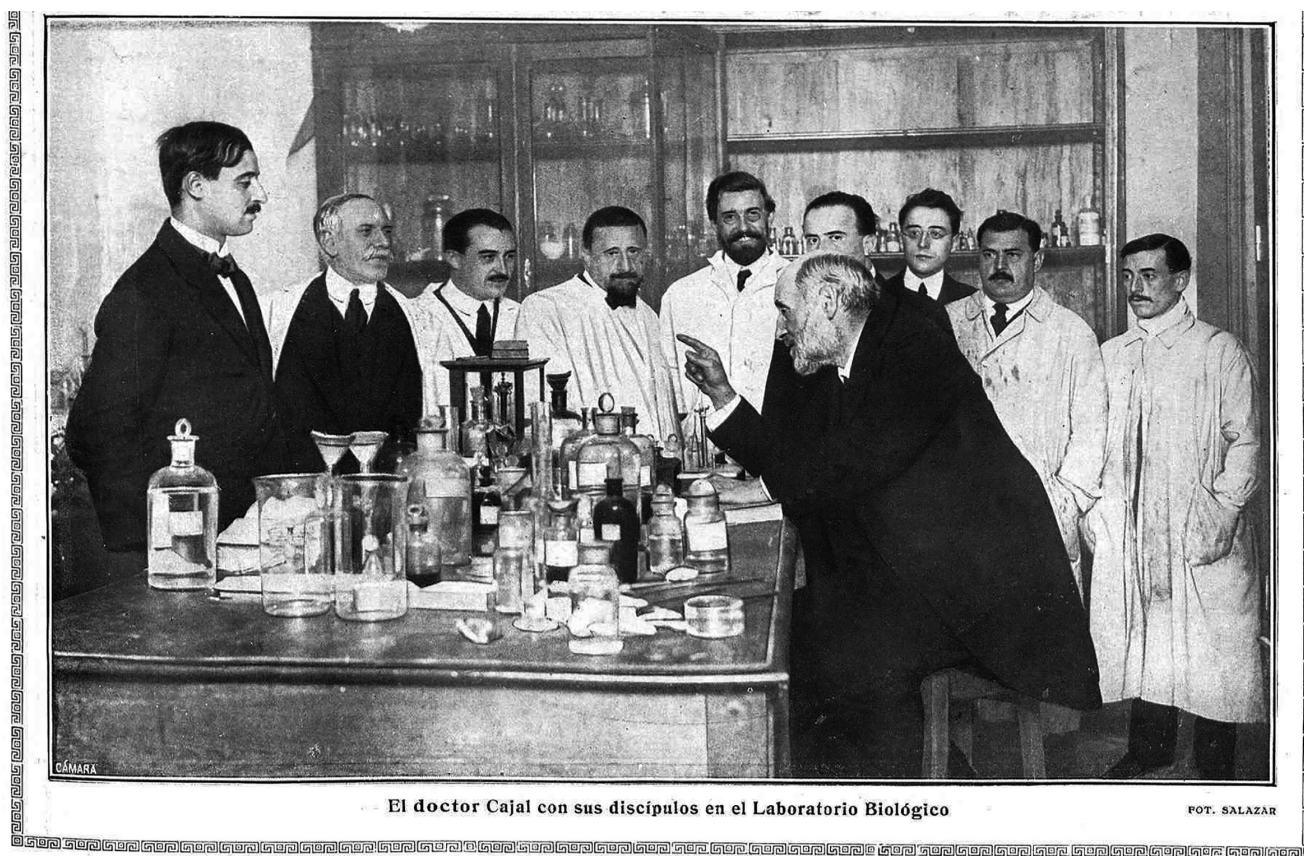


Figure 5. A photograph taken at the Laboratorio de Investigaciones Biológicas on Calle Atocha in 1915, which was published in the illustrated magazine *La Esfera*.⁵³ Listening to Cajal, the image shows, from left to right: Gonzalo Rodríguez Lafora, Domingo Sánchez Sánchez, José Miguel Sacristán y Gutiérrez, Miguel Gayarre y Espinal, Nicolás Achúcarro Lund, Luis Rodríguez Illera, Juan de Dios Sacristán y Gutiérrez, the porter Tomás García de la Torre, and the laboratory assistant Jerónimo. With the exceptions of Domingo Sánchez and Luis Rodríguez Illera, all the physicians shown in the photograph belonged to the Nervous System Histopathology Laboratory directed by Achúcarro. Source: Photograph by Salazar, published in *La Esfera: Ilustración Mundial*, 1915, year II, no. 56, 24 January. Creative Commons 4.0.

position at McGill University; he also privately practised psychiatry, focusing on psychoanalysis, until his death in 1969.⁷³

Fewer data were found on some other visiting researchers at the LHPSN, who were also linked to neuropsychiatry. Such is the case of Felipe Hueto Zuluaga (1887-?) and Luis Fortún Alcalá (1894-1928), who was a student at the time. After their time at the LHPSN, both are known to have worked with Sacristán at the Ciempozuelos psychiatric hospital. Fortún is also known to have published four studies based on Achúcarro's tannin and ammoniacal silver method, and was awarded a JAE grant to travel to Switzerland,⁷⁴ where he worked with von Monakow in the field of neuropathology and with Bleuler in clinical

psychiatry. Subsequently, Fortún completed his neurological training with Bing, in Basel; after returning to Spain, he worked with José Miguel Sacristán at the Ciempozuelos psychiatric hospital, where he was part of the so-called Spanish biological psychiatry.⁷⁵ Years later, Fortún contracted tuberculosis, which led him to conduct numerous studies on the disease; he died in 1928 in Switzerland, where he had travelled to attempt to recover from his disease.

As noted above, not all visiting researchers at the LHPSN were graduates in medicine. According to the reports of the JAE, at least four graduates in natural sciences attended the laboratory, several of whom belonged to the Museum of Natural History. Two examples are Francisco

Ferrer Hernández and Manuel Marcelo Sánchez y Sánchez. The first is known to have been an assistant professor in the Faculty of Sciences, and worked at the Museum of Natural History. Ferrer's presence at the LHPSN is mentioned in the JAE report for 1917-1918¹; he had received grants from the JAE on several occasions to work at marine biology stations in Santander and the Balearic Islands, as well as a grant to study marine zoology in England.^{76,77} Thanks to this experience, Francisco Ferrer became a distinguished specialist in sea sponges, and identified a considerable number of new species at the Museum of Natural History.⁷⁷ Ferrer conducted microscopy work alongside Del Río-Hortega at the LHPSN, using Del Río-Hortega's three variants of Achúcarro's tannin and ammoniacal silver method. He applied these microscopy techniques to an extensive collection of sponges conserved in alcohol at the Museum of Natural History. The results of the study were published in the *Boletín de la Real Sociedad Española de Historia Natural (BRSEHN)* of 1917,⁷⁸ one of the few works that Del Río-Hortega published with a co-author.⁶

In turn, the naturalist Manuel Marcelo Sánchez y Sánchez had lived at the Residencia de Estudiantes, studying initially at the microscopic anatomy laboratory at the Residencia and subsequently at the LHPSN, in the period between 1914 and 1919. Sánchez was awarded JAE grants⁷⁹ first at the marine biology station in Santander, and later to travel to France to study the fish nervous system. His scientific output was very noteworthy: his file in the JAE archives includes a document drafted in France in 1922 (file 134/248),⁷⁹ in which he reports that he had authored a total of 10 publications on microscopy, which were published in the *BRSEHN*, *BSEB*, and *TLIB*.

Fewer data are available on the other two naturalists who attended the LHPSN, Florencio Mozo and F. Guerrero, who are mentioned in the JAE report for 1917-1918. Regarding Guerrero, the JAE report only mentions that he performed a study on the application of silver staining techniques in plant cells.¹ However, neither of the two is subsequently mentioned as the recipient of a JAE grant.

We should also mention some professionals at the LHPSN who came from institutions independent of the JAE. The first of these is brother Manuel Barbado (1884-1945). Barbado was a Dominican brother from the monastery of Almagro, where he had created a biology laboratory. His presence at Achúcarro's laboratory is recorded in the JAE report for 1912-1913.¹ Subsequently,

he left for Rome, to teach experimental psychology at the Angelicum international college, run by his own Dominican Order. Years later, after the Spanish Civil War, Manuel Barbado played an important role in the institutions created under the new regime. For instance, in the academic context, he occupied the famous chair of experimental psychology created for Simarro at the Complutense University of Madrid. From the chair, he promoted an Aristotelian/Thomist personal view of psychology, serving at the same time as the first director of the Spanish National Research Council's Luis Vives Institute, established in the months following the end of the war.^{80,81}

Another visiting professional at the LHPSN was the Belgian professor Jules Havet (1866-1948). Havet was a lecturer at the Catholic University of Leuven, where he taught histology and embryology. His time at the LHPSN (1914-1917)¹ coincided with the First World War, and Del Río-Hortega^{9(p56)} notes that he came to the laboratory fleeing the horrors of the conflict. Havet had been a disciple of Jean Baptiste Carnoy; after the end of the war and the death of his wife, he was ordained a priest, and held the title of emeritus professor in Leuven from 1936 until his death in 1948.⁸² Havet's work focused on the histological analysis of the nervous system of invertebrates, studying neuroglia in earthworms using Achúcarro's method and Cajal's gold chloride technique.⁸³

We should also mention some researchers who attended the LHPSN during the final period of its activity, after Achúcarro had died and Del Río-Hortega had succeeded him as director. This group includes Manuel López Enríquez (1890-1968), Augusto Navarro Martín (1897-?), Emilio Luengo Arroyo (1898-1963), and Lluís Guílera Molas (1895-1969).

The first of these, Manuel López Enríquez, focused on ophthalmology, and was awarded a JAE grant to travel to Switzerland in 1915.⁸⁴ He prepared his doctoral thesis in 1926 under the supervision of Del Río-Hortega, evidencing the presence of microglia in the retina and optic pathways.⁸⁵ His attendance at the LHPSN is reported in 1919, a year after Achúcarro's death; therefore, we can consider him fundamentally to have been a disciple of Del Río-Hortega. Subsequently, and until 1937, he also attended the LHNP, and was appointed coordinator of the laboratory when his master was evacuated to Valencia.^{7(p72)}



Figure 6. Official letters from June 1938, from the dean of the Faculty of Medicine (Luis Urtubey) and the rector of the University of Valencia to the minister of public education, nominating José Miguel Sacristán for selection as interim associate professor at the Anatomy Institute of the Faculty of Medicine, to conduct studies on neurobiology and nervous system architecture. Source: Arxiu Històric de la Universitat de València, file 984/1.⁵⁸

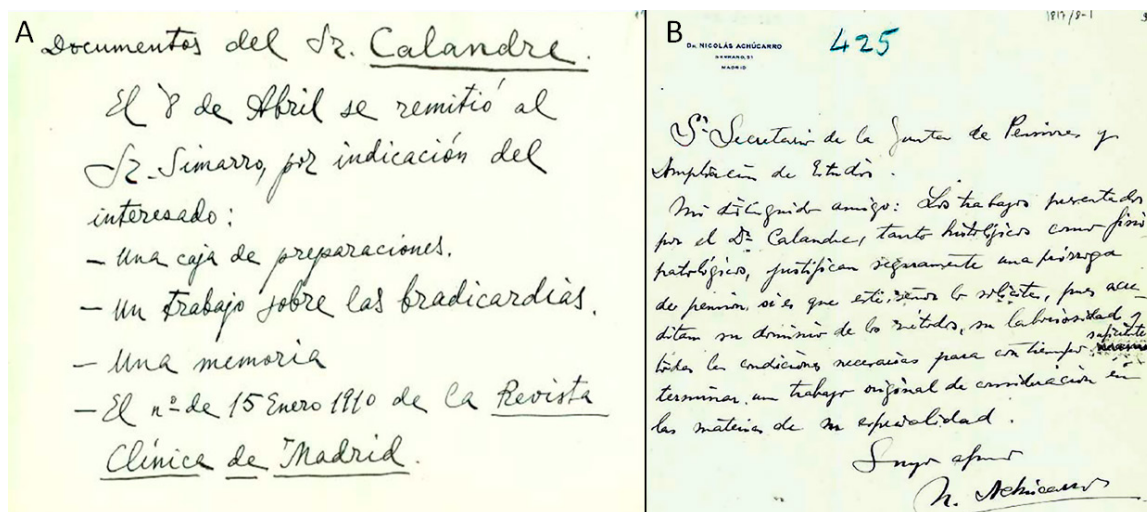


Figure 7. A) A handwritten document from 1910, held in the archives of the JAE, listing the documents sent to Dr Luis Simarro in order that he report the request by the medical student Luis Calandre Ibáñez for a grant (225 pesetas per month) to live at the recently created Residencia de Estudiantes. B) A letter from Nicolás Achúcarro to the JAE endorsing Luis Calandre's request to renew his grant to stay in Berlin. Source: Archivo JAE, expediente de Luis Calandre Ibáñez, file JAE 27-85, folder 1817.⁶⁴

Augusto Navarro Martín was born in Torrecilla de la Orden, in the province of Valladolid. During his studies in Madrid, he lived at the Residencia de Estudiantes, where he attended Dr Calandre's microscopic anatomy laboratory (1913-1916) and Antonio Madinaveitia's biological chemistry laboratory (1916-1917). He is mentioned as a visiting researcher at the LHPSN in 1918, and was taught the silver staining methods of the Spanish Histological School by Del Río-Hortega. During the period 1920-1922, he received a JAE grant to travel to the Institut Pasteur in Paris,⁸⁶ where he worked with Levaditi, studying experimental syphilis and its treatment with bismuth salts. At the same centre, he also performed numerous experimental studies with Fournier, researching the treponemicidal action of pentavalent arsenic derivatives.⁸⁷ After his time in Paris, Navarro Martín worked with Lafora at the Laboratorio de Fisiología Cerebral in Madrid, in the experimental neurosyphilis section, at Hospital de San Juan de Dios, and with the chair of dermatology, José Sánchez Covisa. Subsequently, he dedicated his career to dermatology and laboratory diagnostic techniques. He later worked at Casa Salud de Valdecilla in Santander, and was an active member of the editorial board of the journal *Actas Dermo-Sifiliográficas* from 1925.^{87,88}

Emilio Luengo Arroyo was born in Navalmoral de la Mata, in the province of Cáceres, a historically endemic area for malaria. After completing his medical studies, he attended the LHPSN in 1918-1919 to gain skills in histological techniques,¹ later specialising in parasitology with Gustavo Pittaluga and Dr Sadí de Buen. He received a grant from the Rockefeller Foundation in 1925 to travel to the United States, where he conducted studies on malaria. Subsequently, after his return to Spain, he, Pittaluga, and Sadí de Buen worked together in the fight against malaria in his home town; at the same time, he was working in the National Healthcare Institute. He was sanctioned in the political purges five years after the Civil War, but eventually returned to his post at the National School of Healthcare.⁸⁹

Lluís Guilera Molas, who earned his medical degree at the University of Barcelona, attended the LHPSN in the period 1917-1918 with a grant from the Pedro Esquerdo private foundation, and worked with Del Río-Hortega on the Graafian follicles, using the three variants of Achúcarro's method described by Pío del Río-Hortega, as well as the lithium carbonate technique. These studies were published in the *BSEB*,⁹⁰⁻⁹² and formed the basis

for his doctoral thesis. Guilera received JAE grants to travel to Germany, where he worked under the founder of gynaecological pathology, Dr Robert Meyer (1864-1947).⁹⁰ In 1929, he was selected for the chair of histology and anatomical pathology of Granada, immediately requesting a leave of absence. His professional activity focused on cancerology and gynaecological radiotherapy at the Cancer Institute of Hospital de la Santa Cruz in Barcelona. In 1941, he was appointed to the chair of histology in Seville, once more requesting a leave of absence to return to Hospital de la Santa Cruz.^{93(p167-169)}

Finally, we should mention two more researchers at the LHPSN, Felipe Jiménez Asúa (1892-1973) and Carlos Collado Aguirre (1893-?), who in 1920 left for the Residencia de Estudiantes with Del Río-Hortega to form the initial core group at the LHNP.

The former, Felipe Jiménez Asúa, attended Achúcarro's LHPSN while he was still at medical school.¹ There, he met Pío del Río-Hortega, and the pair eventually became scientific collaborators and close friends. In 1914, Jiménez Asúa had been studying abroad, and met Del Río-Hortega on his return trip to Spain, through the Netherlands; both men were fleeing the outbreak of the First World War.^{9,10} Three years later, with a grant from the JAE (1917-1919), Jiménez Asúa left for Italy and Switzerland to conduct studies on diseases of the blood.⁹⁴ Jiménez Asúa's scientific output was extensive, with the majority of his works focusing on subjects related to haematologic pathology.^{93(p263-264)} In 1926, he was selected for the chair of histology in Zaragoza, although he set off for Argentina a few months later, remaining there practically uninterrupted until 1934, when he returned to Spain. In 1937, he returned once more to Buenos Aires, now in exile, and died there in 1973.^{93(p155-157)}

In turn, Carlos Collado Aguirre travelled to Madrid from the faculty in Valladolid, where he had worked in histology with Leopoldo López García, the former master of Del Río-Hortega. He attended the LHPSN from 1917¹ and, like Jiménez Asúa, left with Del Río-Hortega for the Residencia de Estudiantes in October 1920, obtaining a grant to work there. In 1919, under the directorship of Del Río-Hortega, he published a study in the *BSEB* on the role of the microglia in the pathological substrate of rabies.⁹⁵ In 1925, he was awarded his doctorate, writing his thesis on the origin and evolution of myofibrils, supervised by Del Río-Hortega. However, Carlos Collado's scientific career was cut short, apparently after

he obtained a position in an insurance company, and he never came to use the grant he had been awarded by the JAE to travel to the United States and Germany.⁹⁶ He also declined an offer of a remunerated position in Boston (at Peter Bent Brigham Hospital¹⁰); Del Río-Hortega criticised this decision in his autobiography.⁹

The details on these two men are the last of the data compiled on the visiting researchers at the LHPSN, a subject that today, more than a century later, enables better historical consideration of Dr Achúcarro's laboratory, the birthplace of the basis and the legacy of histopathological research by the Spanish Histological School.

Conflicts of interest

The author has no conflicts of interest to declare.

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