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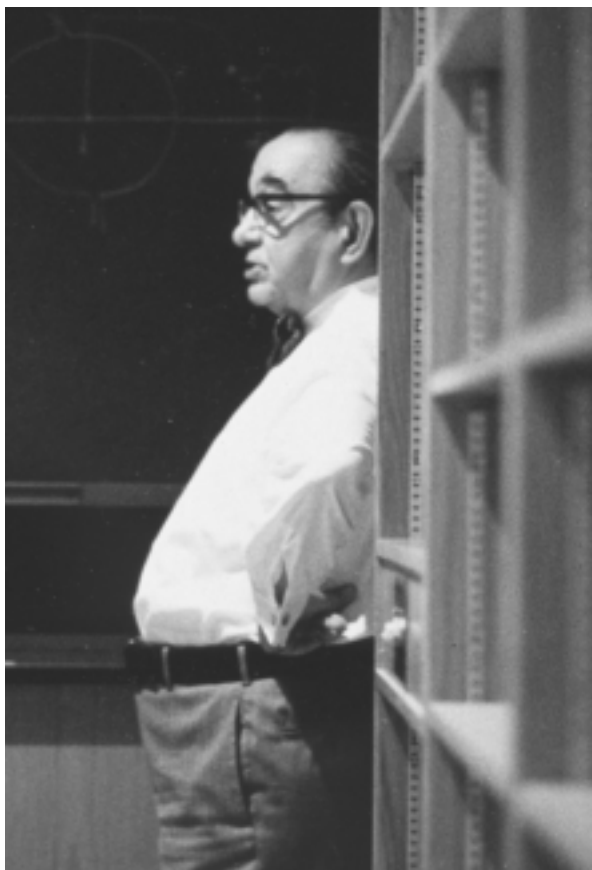
RAFAEL LORENTE DE NÓ
1902—1990

A Biographical Memoir by
THOMAS A. WOOLSEY

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Biographical Memoir

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Rafael Lorente de No

RAFAEL LORENTE DE NÓ

April 8, 1902–April 2, 1990

BY THOMAS A. WOOLSEY

AT THE BEGINNING OF the twentieth century, studies of the nervous system were still in their infancy. After much difficulty, the principal elements of the nervous system were known to be separate cells—neurons and glia, the components for communication identified as synapses and substrates for simple behaviors understood through electrical stimulation, reflex activity, and careful analysis of brain lesions. The mechanisms by which these elements work were not known. How these elements work together to perform complex behaviors is the question still facing scientists in the new millennium. For most of the twentieth century, Rafael Lorente de Nó was a significant figure in crucial areas of what is now called neuroscience and neurobiology.

When he was elected to the National Academy of Sciences in 1950, Rafael Lorente de Nó was one of the premier neurophysiologists in the United States. While Lorente de Nó pioneered discoveries in many areas, he wished foremost to be remembered for his work in neurophysiology. He contributed to understanding mechanisms of nerve cell communication, potassium channel function, functional organization of the brain stem, neuronal activation through multiple reentrant and parallel pathways, the hippocampus, and

modular organization of the cerebral cortex. The breadth of Lorente de Nó's contributions is extraordinary. Today their importance is testified to everywhere; his discoveries are standard textbook information, taken for granted without attribution.

PERSONAL HISTORY

Rafael Lorente de Nó (called Lorente, Dr. Lorente, or Don Rafael by his colleagues, students, and friends, respectively) was born into the well-to-do country family of Francisco Lorente and Maria de Nó (de Lorente) on April 8, 1902, in Zaragoza, Spain. He matriculated in the medical school in Zaragoza at the age of 15. At 18 he transferred to the University of Madrid, where he completed his medical studies in 1923. He was an assistant in the Cajal Institute from 1921 to 1929. Lorente took postdoctoral training in Uppsala from 1924 to 1927 with several months in Berlin in 1925. Beginning in 1927 he trained in otolaryngology in Madrid and several centers in Germany prior to practicing otolaryngology in Santander from 1929 to 1931. In 1931 he returned briefly to Madrid, where he married the vivacious Hede Birfeld, daughter of the professor of German at the University of Madrid.

Shortly thereafter, Lorente and Hede sailed to the United States, where he became the head of the Neuro-Anatomical Laboratory at the Central Institute for the Deaf (CID) in St. Louis. He was appointed lecturer in the Washington University School of Medicine in 1935. Lorente moved to the Rockefeller Institute in 1936 and became a member in 1941. He was naturalized in 1944. When the Rockefeller was re-organized as a university in 1953 Lorente's title was changed to professor. Lorente de Nó retired in 1970, and in 1972 was appointed professor emeritus in the departments of surgery and anatomy and in the Brain Research Institute

at the University of California, Los Angeles, where he remained active into the 1980s. Progression of his emphysema and other ailments necessitated a move to Tucson, where his devoted daughter, Edith, as she had in New York and in Los Angeles, supported him until he died from cancer on April 2, 1990.

Lorente de NÓ was long an active member of the American Physiological Society and the American Association of Anatomists. In addition to the National Academy of Sciences, he was elected to the American Academy of Arts and Sciences and was awarded honorary degrees by the University of Uppsala, Clark University, and Rockefeller University. Lorente won the Karl Spencer Lushly Award from the American Philosophical Society in 1959. He received the Award of Merit in 1986.

PROFESSIONAL HISTORY

Chronology. Lorente's first paper, a mathematical treatment of thermodynamics, was published when he was 15 (1917). He began his lifelong investigations of the nervous system in Zaragoza, where he undertook independent studies of spinal cord responses to injury with a compression model in tadpoles (1921) under the guidance of Pedro Ramón, professor of obstetrics and gynecology. Ramón had studied the nervous system under the guidance of his illustrious older brother, Santiago Ramón y Cajal. Lorente was a voracious reader and an exceptionally energetic student who was invited to transfer to the University of Madrid to work with Cajal. In 1920 Rafael first met the great Cajal, who was then 68 and far and away the most important and adulated scientist in Spain, having received the Nobel Prize in 1906 (with C. Golgi "in recognition for their work on the structure of the nervous system"). While Cajal continued to work vigorously until his death in 1934, Lorente was his last and

arguably most distinguished student. In Madrid, Lorente used silver staining and impregnation methods first to study the cerebral cortex and then the brain stem.

In 1923, his last year of medical school, Lorente returned to Zaragoza expressly to hear Professor Robert Bárány of the University of Uppsala, who served as a visiting professor for several weeks at the medical school. (Bárány won the 1914 Nobel Prize “for his work on the physiology and pathology of the vestibular apparatus.”) According to Lorente, Bárány was astounded to find such a knowledgeable young man in Spain. In 1924 Lorente by invitation joined Bárány in Uppsala. In 1925 Lorente briefly interrupted his work in Sweden on the physiology and behavior of the vestibulo-ocular reflexes to study the architecture of the human cerebral cortex with Oskar and Cécile Vogt at the Berlin Brain Research Institute.

Back in Madrid in 1927, lack of funding forced Lorente to seek clinical training. Based on his research experience, otolaryngology was the natural clinical field for Lorente. He trained first with Professor García Tapia in Madrid and then with leaders at centers in Königsberg, Frankfurt am Main, and Berlin. When he became chief of otolaryngology in the new Valdecilla Hospital in Santander in 1929, the stage was set for him to become Spain’s leader in otolaryngology. He shouldered an enormous clinical load, yet somehow continued his research activities. He was paid by impoverished patients with kittens, which provided the material for studies of the structure of the vestibular and auditory brain stem. A large practice and an insufficient staff lead him to seek opportunities to return to pure research. Lorente had been highly recommended by Bárány and the Vogts to Alan Gregg of the Rockefeller Foundation, who contacted Max Goldstein. Goldstein, founder of the CID in St. Louis, offered Lorente a position as director of the Neuro-

Anatomical Research Laboratory. Lorente arrived with his new bride (who was not expected by the CID) in St. Louis in the fall of 1931.¹

St. Louis in the early 1930s was an exciting place for studies of the nervous system. Pioneering work on the auditory system put the CID in the forefront of hearing research.¹ At the CID Lorente published studies on the structure of the cerebral cortex that he had begun in Berlin. He also fully analyzed materials collected while in Santander. Major works on the VIIIth nerve and the vestibular nuclei were published. A large paper describing the acoustic nuclei of the cat brain stem was accepted by the *Journal of Comparative Neurology*, but it was not published because of the costs of the numerous illustrations. In St. Louis, he instructed James Lee O'Leary in the Golgi methods, which O'Leary used in important studies of the cat visual system.^{2,3} Lorente's anatomical papers from the CID are classical (see below), but what really captivated him was the emerging electrophysiology. Discoveries using the cathode ray oscilloscope (termed the "inertia-less smoke drum" by William Landau) in the late 1920s by Joseph Erlanger, Herbert Gasser, and George Bishop, later joined by Peter Heinbecker, O'Leary, and Helen Treadway Graham, were exploding at the Washington University School of Medicine.^{1,4}

Funding for science during the Great Depression was especially tight, and Lorente considered the possibility of returning to Spain. Herbert Gasser (1944 Nobel laureate with Erlanger "for their discoveries regarding the highly differentiated function of single nerve fibers") had been appointed chair of physiology at Cornell Medical College in 1931, moving to become the head of the Rockefeller Institute in 1935. Fortunately, just as Lorente's Rockefeller Foundation support at the CID ended, Gasser invited Lorente to join him in New York. Their daily luncheon conversa-

tions about science, which often crescendoed into vociferous debates, were a prominent feature of the Rockefeller experience for trainees and colleagues for many decades.

As a scientific loner, Lorente never built a large laboratory and was the sole author of most of the work he published. Nevertheless, he was sought after to mentor training in neurophysiology. At the Rockefeller he collaborated with T. P. Feng on the action of barium in rhythmic activity of nerves, A. Gallego on monovalent ions in nerve conduction, Yves Laporte on synaptic function in sympathetic ganglia, and G. A. Condouris on decremental conduction in peripheral nerves. He published a long series of papers with V. Honrubia on experimental observations and theoretical aspects of transmission in nerves. He supervised K. E. Åstrom's anatomical studies on the cranial nerve nuclei in the mouse brain stem.

Neuronal Integration, Synaptic Transmission, and Axonal Conduction. Until 1972, first in St. Louis and then with new oscilloscopes and better amplifiers in New York, Lorente de Nó studied neuronal activation, nerve conduction, and synaptic transmission. Lorente de Nó's conversion to electrophysiology is evident in his April 10, 1934, letter to Cajal. He justified this to Cajal: ". . . estoy dedicando la mitad de mi tiempo a experimentos fisiologicos" ("just now I dedicate half of my time to physiological experiments"). Further on, he argued for this change in emphasis saying that structure is illuminated by function. Lorente predicted that a mutual colleague would have the same headache in interpreting his experiments "que yo tuve hasta que conseguí montar mi oscilógrafo de rayos catódicos" ("that I had until I made my cathode ray oscilloscope").

Approximately 15 years of work culminated in the publication of the two volume *A Study of Nerve Physiology* (1947). This monograph included detailed mathematical models initiated during a visit in 1940 with Leverett Davis, Jr., at

the California Institute of Technology. In the end, Lorente concluded incorrectly that electrical conduction did not depend on the cations sodium and potassium, but he correctly surmised that this process ultimately depended on oxidative metabolism. These two volumes were known to physiology students of the time as the “telephone books,” which they resembled in size, color, and readability.⁵

At the CID and the Rockefeller, his early microelectrode studies of the central vestibulo-ocular system extended Sherringtonian principles of synaptic activation to new levels of precision. Lorente developed a profound understanding of the features of spatial and temporal summation and synaptic delay, perhaps because he had an accurate picture of the complexities of the underlying structures. He participated in the debates concerning the nature of synaptic transmission (1940). A number of papers evaluated acetylcholine and other putative neurotransmitters for which he could not establish a specific role. He also could not rule out direct electrical activation of post-synaptic cells. He favored, as did Eccles at the same time, the hypothesis that synaptic transmission was electrical rather than chemical (1953).

Lorente studied impulse conduction in vertebrate peripheral nerves for three decades. As part of this effort, Lorente de Nó first synthesized a series of quaternary ammonium compounds, including tetramethylammonium (TEA), which he substituted for monovalent cations (especially sodium) in his studies of the ionic basis of the nerve impulse (1949). Although not appreciated at the time, TEA is now a crucial standard tool in modern neurobiology as it selectively blocks K^+ channels.⁶ Synthesis and application to excitable tissues of this compound were Lorente’s great practical contributions to modern neuroscience.

Lorente’s attempts to understand the excitability of axons in vertebrate nerves, principally from frogs with and with-

out coverings (“sheathed” and “desheathed”) ultimately lead him into direct contradiction with Alan Hodgkin and Andrew Huxley (who shared the 1963 Nobel Prize with Eccles “for their discoveries concerning the ionic mechanisms involved in the excitation and inhibition in the peripheral and central portions of the nerve cell membrane”).^{5,7} Their elegant experiments on the squid giant axon and the clean model of how this works are the basis for today’s textbook descriptions of axonal conduction. Lorente’s quixotic battle against this formulation (which he derisively referred to as “the so-called sodium hypothesis”) consumed enormous energy for at least 30 years of his life (1963).⁸ These views did not help to keep his earlier significant contributions to neurophysiology in perspective; one imagines, however, that Lorente might have been pleased that, using TEA, K⁺ channels in squid and frog axons were shown to differ.⁹

Vestibular Reflexes, VIIIth Nerve, and the Vestibular and Auditory Brain Stem. As a medical student in Madrid, Lorente began experiments on the vestibulo-ocular pathways in rabbits (1925). In 1924, when he went to the laboratory of Robert Bárány (perhaps best known for developing the caloric test of vestibular function) and subsequent to his return to Madrid in 1927, he combined functional (reflex), anatomical, and selective lesion studies to understand the vestibulo-ocular reflex arc. Rafael published a number of studies in German (1927), French (1930), and Russian on the VIIth nerve and the vestibular nuclei. After coming to the United States, he published a 56-page paper synthesizing the findings in English (1933). The paper illustrates progress in his thinking on complex circuits in the brain stem. (This work stood for nearly two decades as the authoritative source about the organization and function of brain stem vestibular nuclei.) He observed persistence of vestibular activation of eye movements after midline section of the brain stem to cut inputs

from the opposite side. He correctly inferred that there were multiple pathways mediating this response. He also published two long papers on the origins and targets of the VIIIth (vestibulocochlear) nerve suggesting that there was preservation of topography and function from the end organs in the target nuclei (1933).¹⁰ The importance of Lorente's understanding of the role of the brain stem reticular formation was emphasized by Ann Graybiel at a 1978 tribute held at the Rockefeller (see Goodhill's foreword to *The Primary Acoustic Nuclei* [1981]).

With Helen Treadway Graham, he developed electrophysiological skills in studies of cranial motor neurons in the oculomotor, trochlear, and abducent nuclei, which lie just below the floor of the IVth ventricle. The results clearly demonstrated convergent synaptic activity and supported his hypotheses about integration by single neurons. Confirming studies in other neurons were not published by others until nearly 20 years later.

Lorente published a monograph *The Primary Acoustic Nuclei* (1981) with strong support from Victor Goodhill, head of the Department of Otolaryngology at UCLA. This work was originally completed over 50 years earlier and was accepted for publication, but it went unpublished for want of funds during the Great Depression. (Lorente nearly threw the manuscript and exquisite drawings away when he moved from St. Louis to New York in 1936.) This work demonstrates many of Lorente de Nó's best scientific characteristics: a focused approach to an important problem; a clear appreciation of the function and anatomy of his subject; concise, accurate drawings of the material; and a thorough summary of the pertinent literature.

Cerebral Cortex. In 1920 Santiago Ramón y Cajal was approaching the end of his exceptional career. He was the pre-eminent scientist of the Spanish-speaking world. (As a

medical student in Zaragoza, Lorente de Nó had read the two-volume *Histologie du Systèm Nerveux de l'Homme et des Vertébrés* (*Histology of the Nervous System of Man and Animals*) or more likely Cajal's earlier three-tome Spanish original *Textura del Sistema Nervoso del Hombre y de los Vertebrados* (*Texture of the Nervous System of Man and the Vertebrates*) and the *Recuerdos de Mi Vida* (*Recollections of My Life*). Cajal had considered from time to time morphological correlates relevant to the human intellect and advanced the idea, from his comparative work, that these could lie in the greater complexity of cell types in the human cortex. The young Rafael did not accept this proposal and challenged Cajal directly with a vigor that typified his career. To make his point, he chose to investigate the brain of the mouse. In this little animal, the lowliest available creature with a neocortex, Lorente found and described neuronal cell types in the mouse cortex with Golgi's method that were at least as rich as described in Cajal's earlier account of the human cortex. Cajal took Lorente's work for publication in his journal without making any changes. In style and in substance, this paper set a tone for Lorente's subsequent prodigious output. The premise (now termed hypothesis) was clearly stated, the results copiously illustrated and their meaning considered in light of the appropriate literature. The work on the mouse cortex described in "La corteza cerebral del ratón," which appeared in the *Trabajos del Laboratorio de Investigaciones Biológicas de la Universidad de Madrid* (1922), is a classic.¹¹ Published when Lorente was only 20, it included the first Golgi description of the distinctive region of the somatosensory cortex now known as the "barrel" field.¹²

The great Cajal and the combative young rascal (as Rafael described himself) maintained a cordial yet somewhat argumentative relationship that is rare in the hierarchical struc-

ture of science, even today. (However, in later life, Rafael Lorente de Nó chose not to accept many offers to reminisce about Cajal.)

During his stay in Berlin in 1925, work with the Vogts acquainted Lorente with the issues surrounding the identification of different architectural (functional) regions of the human brain including its blood vessels (1927). After he got to St. Louis, Lorente de Nó published the cellular architecture and Golgi stained cells of the entorhinal cortex (1933) and the hippocampal formation (1934). From the dates on the drawings, the work was obviously begun just after Lorente's sojourn to Berlin. He applied his good eye and brain to the analyses of cell bodies (cytoarchitecture) and cells as seen with the Golgi stains in several animals from mouse to man. Evidently Cajal kept up with Lorente's work and queried him on specifics. The first line of Lorente's April 10, 1934, letter to Cajal obviously answers a question: "Las figuras a que V. [Cajal] se refiere en su carta (figuras 19, 20 y 21 de mi trabajo sobre el area entorrinal) son esquemáticas. . . ." ("The figures that you refer to in your letter (figures 19, 20 and 21 of my paper on the entorhinal area) are schematics. . . .")

Lorente subdivided the hippocampus proper into regions, which he abbreviated CA1, CA2, etc., (CA = cornu ammonis = Ammon's horn), based on an appreciation of the correlation of different connections with architecture. These designations are now in wide use.¹³ It is likely that Lorente's thinking was guided by his work on the brain stem.¹⁴ He ended his second paper (1934) with a model that he described as follows:

The only possibility for . . . [a neuron] . . . using all the impulses seems to be, first, that each synapse sets only a subliminal (chemical or other) change able of summation and, second, that the conduction through the synapses is not followed by a refractory period. The subliminal changes are sum-

mated first in the dendrites then the surrounding of the axon. When the change reaches threshold value, an explosive discharge through the axon takes place. The axon . . . enters in a refractory state, but the cell body and dendrites do not do so, they continue receiving and adding subliminal changes until the threshold value is reached again and the axon has recovered. . . .

If this conception of the neurone is right, then it becomes easy to understand that impulses arrived at different dendrites or at two points of a dendrite can be summated. As far as I can see this the greatest problem of the physiology of the nerve cell.

His studies of the simpler entorhinal and hippocampal cortices gave him insights about the patterns of neuronal articulation in the cortex. These papers became widely known when his chapter in the cerebral cortex first appeared in Fulton's *Physiology of the Nervous System* (1938). This masterly review of his own and others' works is a remarkable synthesis of information: accurate, broad, insightful, crisply written, and clearly illustrated. It is significant that he actually looked at all of the material again as indicated in Fulton's footnote

The first three sections (pp. 291-325) of this chapter have been written by Rafael Lorente de Nó. The extent of my debt to him will be obvious to those who peruse it. Dr. Lorente de Nó states in a letter: "One of the reasons why writing it has been so laborious is that I have verified in my collection of brain sections the truthfulness of every statement in the text and of every line in the drawings."¹⁵

Lorente used his experience with the vestibulo-ocular system to put functional meaning to the cortical neurons he saw. Perhaps the key that he had, and his mentor Cajal lacked, was direct experience with the physiology of the brain. He clearly articulated the idea that the cells of the cerebral cortex are arranged in vertical modules that include interneurons and parallel and reentrant pathways. The organi-

zation of cortex into functional columns that Mountcastle demonstrated in 1957 has been extended widely and is one of the central tenets of neurobiology. The importance of Lorente's synthesis was summarized by Mountcastle in the last paragraph of his landmark paper

The hypothesis that such a vertically linked group of cells is the elementary unit for cortical function is not new. Such a conclusion was reached by Lorente de N6 from his extensive studies on synaptic linkages of cortical neurons.¹⁶

Raphael Lorente de N6: The Person. Lorente de N6's scientific career spanned seven decades. His contributions were profound and diverse. With the passage of time it is easier to step back and view his whole corpus of work, to sort through it and glean the significant essentials free from the heat of argument. Lorente de N6 was independent and energetic. His early successes surely made him confident. A quick mind and voracious, intelligent reading pointed him in new and tractable directions. His energy drove him through an enormously productive professional life. He trained and collaborated with the best scientists of his time: three Nobel laureates, in three distinctively different areas of "neuroscience," in three different lands. His impressions on them and his capacity for hard work opened doors with each of them and they in turn opened doors for Don Rafael. He was a neurobiologist long before the word was coined.

I first came across Lorente's work in the summer of 1966 as I was reading the literature on the architectonics of the mouse brain.¹⁷ Lorente's paper figured prominently in the discussion of M. Rose's study of the cytoarchitecture of the mouse cortex,¹⁸ a copy of which I had at the University of Wisconsin. The library in Madison did not have the *Trabajos*, so in innocent desperation I wrote Lorente at the Rockefeller

to request a reprint of the 1922 article. I promptly got back a note, in a hand I would later recognize well, thanking me for the request but politely indicating that the reprint supply had been exhausted many years before. One month later, back at Johns Hopkins, I read the elegant paper in the library of the Phipps Clinic. What wonderful illustrations!

It is thanks to Lawrence Kruger at UCLA that I actually got to meet Lorente in Los Angeles nearly nine years later. Short in stature, Lorente was an urbane, charming, and inquisitive man excited about science and life. His faculty for language was obvious; his English was perfect. It was difficult to reconcile the man with the reputation for pugnacious polemics that consumed so much of his later career. At this and subsequent meetings he shared what questions drove his choices for investigation and the conditions that surrounded the answering of those questions. This was fascinating stuff.

Lorente traveled to New York in May 1978 for Rockefeller University's celebration of Lorente and David P. C. Lloyd's contributions and the conferring of honorary degrees. I invited him to stop in St. Louis on his way to present the work on the acoustic nuclei that I knew he was preparing for publication. He would be pleased to come and discuss that subject, he said, but only if he could give three lectures concerning the neural sheath and the sodium hypothesis first. We made the deal and he came. The lectures on the sheath and sodium were fascinating on several levels, but cellular physiologists in the audience reacted strongly with their feet to the speaker's data and his interpretations of them. The last lecture, given in the traditional Saturday neuroscience series, concerned the acoustic system. A large, rapt audience was convinced by the speaker's data and his interpretations of them. Throughout his visit Lorente listened to and engaged many different colleagues at Washington

University whose work in some way or another related to areas he had touched.

There was another and possibly more astounding aspect to this visit. In our earlier discussions I had learned from Lorente that, when he was at the CID, he had introduced Nancy Blair to his colleague and pupil O'Leary, and they were subsequently married. The O'Learys were mentors and friends to my wife and me. Although O'Leary died in 1975, it occurred to us that there might be others in St. Louis who were Lorente's friends from the 1930s. As I drove him in from the airport he responded to my question about them saying that he doubted very much whether his friends were still living. I pressed him, and he finally recalled, ". . . the most intelligent and interesting woman I ever met." On further interrogation it was clear that he was speaking of our neighbor Natalie Grant (Mrs. Samuel B.) across the street.¹⁹ In short order Lorente was reminiscing with her and Dr. Grant. My wife, Cindy, as she elegantly and so often does, quickly expanded the planned dinner party to include acquaintances from Lorente's St. Louis days and other colleagues of long standing then living in St. Louis. Other than C. C. Hunt, his wife, Marion, and ourselves, all were septuagenarians at the very least. The evening was fascinating, as Lorente was obviously stimulated by and stimulating to all with whom he reminisced in our living room almost to dawn. It was obvious that he and his wife, Hede, had formed an integral part of an exceptional, lively, and ultimately very distinguished "crowd" whose interests ranged widely to most areas of human endeavor.

In summary, Lorente was the last and most acclaimed student of Ramón y Cajal. Lorente de NÓ was the first Spaniard to become a neurophysiologist. His lasting contributions were (1) defining the organization of brain stem vestibular and auditory systems; (2) synthesis of TEA, a com-

pound that is now a standard tool for analysis of potassium channel function; (3) distinction between non-refractory spatio/temporal summation in neuronal dendrites and somata and refractory all-or-none action potential in the axon; (4) provocative involvement in the quest to understand the basis of axonal conduction and synaptic transmission; (5) recognition of and naming the principal divisions of the hippocampal formation; and (6) formulation of the basic idea of the anatomical (and functional) columnar organization of the cerebral cortex.

The list is indeed diverse and impressive. Perhaps it is for this reason that it is so difficult to fully comprehend Rafael Lorente de Nó's extraordinary impact on science.

I THANK Javier de Filipe of the Instituto Cajal in Madrid for a copy of Lorente's letter dated April 10, 1934, to Cajal in response to Cajal's letter of March 26, 1934, to him (items 1135-1139 in the Museo Cajal Madrid). Renee D. Mastrocco kindly provided information from the archives at Rockefeller University and Jenny S. Mun furnished information from the National Academy of Sciences. Much of the information was gathered for a previous article on Lorente de Nó by Lawrence Kruger and me. I thank Larry W. Swanson for his photograph of Lorente during his first lecture on April 26, 1978, during a visit to St. Louis, which is reproduced here with his permission.

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