Montpellier : Colloque de la Société des Neurosciences

SANTIAGO RAMÓN Y CAJAL BETWEEN SPAIN AND FRANCE.

CHAIRED BY F. CLARAC (MARSEILLE), J.G. BARBARA (PARIS)

S10 - 24/05/07, 13:00 - 15:00

Cajal and the birth of modern neuroscience.

De Felipe J. (Madrid)

The appearance of Santiago Ramón y Cajal in the world of neuroscience provoked a radical change in the course of its history. The studies of Cajal into the microanatomy of virtually the whole of the central nervous system, his observations regarding degeneration and regeneration, together with his theories about the function, development and plasticity of the nervous system had a profound impact on researchers of his era. Numerous investigators followed the example set by Cajal, confirming and extending his theories in practically all fields of neuroscience. These studies represent the roots of what are today some of the most exciting areas of discovery in terms of the structure and function of the brain in both sickness and health.

Cajal's degeneration studies.

Ferrer I. (Barcelona)

Santiago Ramón y Cajal was born in Petilla de Aragón (Navarra) in 1852. He was enrolled in the army with destination to Cuba in 1873, and back to Spain he started his medical career as Assistant Professor at the University of Zaragoza, and then as Professor of General and Descriptive Anatomy at the University of Valencia in 1883. Four years later, he obtained the position of Professor of Histology and Pathologic Anatomy of the Faculty of Medicine at the University of Barcelona. The city was splendid as it was the place of the "Exposición Universal" and the nest of a new cultural and artistic renaissance. Ramon y Cajal worked aside absorbed by fruitful inspiration that culminated in the theory of the functional unity of the neuron, the theory of the neuronal polarity, and the neurotropic theory. It is still possible to have a visit to the different places were Ramon y Cajal and his family used to life at this

time. It is interesting to note the severity and restrictions that Ramon y Cajal imposed to himself and his family to the point to pay the publication of his discoveries in journals edited at home. The vast majority of his creative mind was born and was elaborated in Barcelona. Yet opportunities were better in Madrid than in Barcelona, and Ramon y Cajal moved to Madrid in 1892 after obtaining the position of Professor of Normal Histology and Histochemistry, and Pathologic Anatomy of the Faculty of Medicine at the University of Madrid. There, he continued his very constructive work and he published in 1899 "Textura del Sistema Nervioso del Hombre y de Vertebrados", one of the most comprehensive and illuminated books in Neuroscience ever written. This was followed by the publication of "Estudios sobre la degeneración y regeneración del sistema nervioso" in 1913-14. Francisco Tello, Nicolás Achúcarro, Pío del Rio Hortega, Rafael Lorente de Nó, Fernando de Castro, among many others, were solid disciples and further collaborators who conformed the Spanish School of Neuroscience. Ramon y Cajal deserved numerous nominations and prices including the Nobel Price in 1906. The Cajal Institute was founded in 1920, but it was not inaugurated until 1932. At the same time, Ramon y Cajal published, with F. de Castro, "Técnica micrográfica del sistema nervioso" which included all the histological methods employed during his life. "¿Neuronismo o reticularismo?" was published in 1933. Silveria Fañanas, his wife, died in 1930. Santiago Ramon y Cajal died in Madrid in 1934. It is not necessary to stress the importance of the tremendous bequest of Ramon y Cajal. Some of his discoveries needed the arrival of technical advances to be fully corroborated, and his shade has covered the neuroscience of the last century. Ramón y Cajal employed the Golgi methods to study of the normal nervous system. This method has been substituted by other methods in the study of diseases of the nervous system. Yet, the Golgi method was transiently used for two decades by several scientists who discovered important aspects of human developmental abnormalities and degenerative diseases of the nervous system. M. Marin-Padilla, C. Sotelo, D.P. Purpura, V.S. Caviness, R.S. Williams, M.S. Schiebel and A.B. Scheibel were the pioneers of this adventure. Their work is with no doubt one of the late legacies of Santiago Ramon y Cajal.

Cajal and the regeneration of the nervous system.

Sotelo C. (Paris)

Cajal started to work on the degeneration and regeneration of the nervous system to challenge the results obtained by Bethe, who claimed that the trophic bases for the neuron doctrine were obsolete because the distal nerves stumps separated from their parent cell bodies were able to regenerate. Thus, Cajal worked hard to innovate a reliable silver staining (the reduced silver method), and during 10 years of work (1903-1913) he demonstrated that, opposite to peripheral neurons whose axons are able to regenerate, in central neurons the regeneration is always abortive. He published the results of his pupil Francisco Tello, who using grafts of peripheral nerves implanted in the forebrain, revealed the reason for this abortive regeneration: the nonpermissive environment offered by the lesioned CNS, because central axons can regenerate within the grafted nerves.

The study of the peripheral nerve regeneration offered Cajal an optimal material to search for evidences in favor of his "neurotropic hypothesis" (1892). The major contribution of Cajal was to show that the sources of neurotropic substances released by distal stumps were neither contained in remnants of the myelin nor in degenerated axons, as advanced by

Forssman (1900), but in Schwann cells. This important result was obtained by transplanting a piece of peripheral nerve untreated (living stage) or treated with chloroform to kill all the Schwann cells. The growth of regenerating axons was oriented towards the grafted nerve only when living Schwann cells were present. These experiments clearly illustrate that the guidance of regenerative growth is not the result of mechanical or physical interactions. It is solely conditioned by the release of substances by living cells in the distal amputated or transplanted aneural nervous stumps, which are particularly rich in Schwann cells. Therefore, Cajal investigations in axon regeneration opened a new era in this field, because today it is generally accepted that axonal regeneration in the CNS is the results of the interplay between a permissive environment and the intrinsic properties of the axotomized neurons.

Ramón y Cajal's hypothesis and the unknown territory of dendritic arborizations.

Tyc-Dumont S. (PARIS)

The shapes of dendritic arborizations is a unique property which differentiates the nervous tissue from all other tissues of the organism. The neuron doctrine which we owe to Santiago Ramón y Cajal was established fifty years after the cellular theory proposed by Schwann in 1839. This period of trial and error is simply explained by the great difficulty of recognizing a nerve cell on histological preparations. It was only after the discovery of the Golgi method that Ramón y Cajal established the first fundamental concepts of neuroscience. He observed an immense number of neurons stained with the Golgi method in a variety of species. The comparison of dendritic morphologies of neurons located in homologous regions of the brains of different animals led him to formulate what I call the shape hypothesis. It was in the darwinism context of the time and tuned with the comparative phylogenetic approach. No other cells can compete with neurons for sheer complexity of dendritic forms.

His genius must be recognized not only because his magnificent anatomical skills but also his will of finding a functional explanation of his anatomical descriptions. He already predicted the modern view of the role of a functional dendritic field in his early writings. Even though the modern current terminology is lacking in Ramón y Cajal wording, notions of neurons as independent units, dendritic spines as the main point of contact between axons and dendrites, integrative properties of the dendrites based on the structural dendritic complexity, dendritic processing as a system of communication between internal and external world be found in his powerful predictions. These ideas, one hundred years later, are still central to the study of the function of dendritic arborizations.

Time came for electrophysiology with its numerous crucial discoveries that have dominated the neuroscience field for fifty years. It was accompanied by dogma considering dendrites as negligible structures for neuronal operations that have postpone the study of dendritic function for many decades. Actual verification of Ramón y Cajal’s hypothesis are now progressing with new technological tools and new concepts.

Ranvier, Cajal and the French reception of the neurone doctrine.

Barbara J.G. (PARIS)

French histologist Louis Ranvier (1835-1922) is not included among the prominent XIXth c. histologists involved in the foundation of the neurone theory. However, his name remains known for the nodes in nerve fibres myelin sheaths, he described in the 1870s. Ranvier was a student of Claude Bernard, specialized in microscopic anatomy, which he created as a new discipline in France, when he obtained a Chair of Anatomie Générale at the Collège de France (1875). Although Ranvier and Ramon y Cajal (1852-1934) never met, some relations between them may be described. Ranvier was an expert histologist using chromic acid and silver staining to visualize the minute structures of isolated nerve fibres. These skills not only allowed him to see nodes and interpret them in a bernardian perspective, but they were essentials for later Ranvier's studies on nerve degeneration and regeneration, which were acclaimed by Cajal several decades later. Ranvier's techniques were published in a Treatise published in 1875 and translated worldwide. The Salpêtrière hospital in Paris showed great interest in Ranvier's techniques, which were adopted by Babinsky and Déjerine, replacing former techniques by Vulpian and Charcot. Ranvier's course at the Collège de France was attended by foreign students, including Luis Simarro Lacabra from Spain, who learnt Golgi staining there. Back in Madrid, he performed public demonstrations of it, which Cajal joined. Cajal acknowledged the great value of Ranvier's Treatise and of Golgi reaction he probably learned from him. However, Cajal noticed French histologists did not make great use of the new method, as Ranvier himself, who felt it wasn't reproducible enough. The next generation of French histologists, among whom Matthias Duval and Dr. Azoulay, Cajal's translator, used the method extensively. The introduction of Golgi reaction in French histology was made possible with the acceptance of cell theory and the neurone doctrine in part thanks to the Strasburg school of the Alsacian physiologist Prof. Küss, and to its best student, Matthias Duval, when he moved to Paris.

Cajal and the retina: "El más antiguo y pertinaz de mi amor de laboratorio".

Piccolino M. (FERRARA)

In 1888 Cajal published his first studies using the method ("reazione nera") invented by Golgi in 1873. Cajal learned about the technique in 1887 as a consequence of seeing some histological preparations brought from Paris by Luis Simarro Lacabra (a Spanish neurologist who had worked with Charcot and Ranvier). Among the first nervous structures investigated by Cajal with this powerful staining method was the retina. It was the beginning of an interest in the structure of the retina that lasted throughout his life. From his retinal studies Cajal drew important conclusions about the basic principles of the organization of the nervous system, which led to the theories of the 'neuron doctrine'and the 'dynamic polarization of nerve cells'. In spite of his declared 'love' for retina, Cajal encountered, however, many difficulties in interpreting the basic organization of retinal circuits and particularly in establishing the role of horizontal and amacrine cells. This he acknowledged in his last published article on this subject, where he discussed the "paradox of retinal horizontal cells" and of "the enigma of amacrine cells". The manner in which Cajal dealt with these difficulties revealed fascinating aspects of his scientific personality and also shed light on the mechanisms underlying the progress of understanding in science.