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Guest Editorial

A CENTURY OF "UNITY IN CONTIGUITY"

Camillo Golgi (1843-1926)

Santiago Ramon y. Cajal (1852-1934)

Hundred years is a very small time span in the history of mankind, but the last one hundred is by no means small. Tremendous progress has been made in many fields of science including Neuroscience. Probably it was recognized that this would be the case exactly a century ago when the Nobel Prize in Physiology/Medicine for the year 1906 was awarded to two eminent neuroscientists, namely Camillo Golgi and Ramon y. Cajal. It was also a landmark in the history of the Nobel Prize in that this was the first time that a Nobel Prize was shared.

The knowledge about the nervous system was very vague and full of contradictory theories till the late 19th – early 20th Century. At the same time, research was being done to address these issues. Prof. K A H Morner aptly summed up the scenario in his Nobel Presentation speech.

"It should be remembered in particular that almost nothing was known for certain of the relationship between nerve fibres and nerve cells. The central nervous system appeared as a confused mass of filaments, each as fine as the thread of a spider's web, and of microscopic cells armed with cellular processes. It was impossible to isolate the individual components of tissue specimens. Nor was it possible to resort to known staining methods by which, for example, a single nerve cell with its processes could be distinguished as an entity.

For these reasons Golgi's method of silver impregnation, which met these requirements, must be considered as a fundamental discovery in the field of nerve anatomy. Using his original method, Golgi was also able to demonstrate a number of essential points of the architecture of the central nervous system, as well as many important structural details.

It was only after many years, however, that attention was paid to his work and its importance recognized. When at last this happened, many scientists began to work in the field of action which Golgi had opened up. One could mention the names of a number of eminent scientists from far and near who, by their important contributions in the field of original studies of the anatomy of the nervous system, have done a great deal for science. First among these we must place someone whose extraordinarily active and successful work in

this field has revealed both fundamental factors of great importance and many essential details and who therefore, more than anyone else, has contributed to the recent extensive development of this branch of science. I refer to Mr. Ramón y Cajal.

By their achievements, which have been briefly described here, Professors Camillo Golgi and Ramón y Cajal must be considered as the principal representatives and standard bearers of the modern science of neurology, which is proving so fertile in results. In recognition of their achievements in this field, the Staff of Professors of the Caroline Institute has decided to award to them this year's Nobel Prize for Medicine."

Camillo Golgi was born at Corteno near Brescia on July 7, 1843, the son of a physician. He studied medicine at the University of Pavia under Mantegazza, Bizzozero and Oehl. Golgi himself stated that Bizzozero greatly influenced him and his methods of scientific research; Bizzozero introduced Golgi to experimental research and histological techniques, and established with him a lifelong friendship.

After graduating in 1865 Golgi continued to work in Pavia at the Hospital of St. Matteo. He started his scientific career in 1869, with an article in which, influenced by Lombroso's theories, he stated that mental diseases could be due to organic lesions of the neural centers. However, convinced that theories had to be supported by facts, Golgi soon abandoned psychiatry and concentrated on the experimental study of the structure of the nervous system. Histological techniques, such as fixation procedures and tissue stainings (hematoxylin or carmine) had been introduced in the middle of the 19th century. However, these procedures were inadequate and unsatisfactory for the investigation of the structure of the nervous system, due to its relative complexity in organization as compared to other tissues.

In 1872, due to financial problems, Golgi had to interrupt his academic commitment, and accepted the post of Chief Medical Officer at the Hospital of Chronically Ill in Abbiategrasso. In the seclusion of this hospital, he transformed a little kitchen into a rudimentary laboratory, and continued his search for a new staining technique for the nervous tissue. In 1873 he published a short note ('On the structure of the brain grey matter') in the *Gazzetta Medica Italiana*, in which he described that he could observe the elements of the nervous tissue "studying metallic impregnations... after a long series of attempts". This was the discovery of the 'black reaction' (*reazione nera*), based on nervous tissue hardening in potassium bichromate and impregnation with silver nitrate. Such revolutionary staining, which is still in use nowadays and is named after him (Golgi staining or Golgi impregnation) impregnates a limited number of neurons at random (for reasons that are still

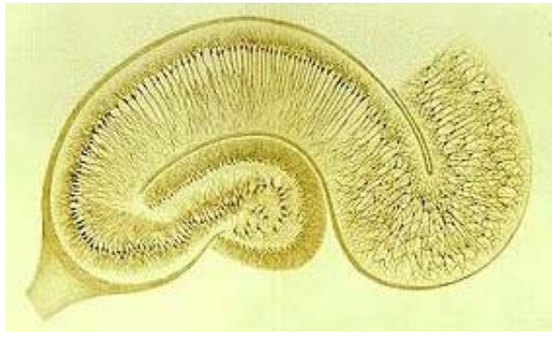

Fig. 1: Golgi's drawing of the hippocampus impregnated by his stain.

mysterious), and permitted for the first time a clear visualization of a nerve cell body with all its processes in its entirety. Golgi himself was extremely modest and reticent about his work and it is not known when exactly he made this invention. All through his life, however, he continued to work on these lines, modifying and improving this technique.

In 1875 Golgi published, in an article on the olfactory bulbs, the first drawings of neural structures as visualized by the technique he had invented. In 1885, Golgi published a monograph on the fine anatomy of the central nervous organs, with beautiful illustrations of the nerve centers he had studied with his method.

This turned out to be the turning point in the life of the other Nobel laureate of 1906, Ramon y Cajal.

Santiago Ramón y. Cajal was born on May 1, 1852, at Petilla in Aragon, Spain. As a boy he was apprenticed first to a barber and then to a cobbler. He himself wished to be an artist. His father, however, who was Professor of Applied Anatomy in the University of Saragossa, persuaded him to study medicine. He enrolled in the medical school at Zaragoza, and as a young student, Cajal was very fond of philosophy and gymnastics, restless, energetic, shy and solitary. He graduated in medicine at the University of Zaragoza in 1873. Shortly after his degree he was drafted into the army and dispatched to Cuba, at that time under Spanish rule, as a medical officer. Cajal returned to Spain very sick as he had contracted malaria in Cuba, and then tuberculosis, and at the end of 1875 he started his academic career as “Auxiliary Professor” of Anatomy at the University of Zaragoza.

In Zaragoza, Cajal purchased in 1877 with his own funds an old-fashioned microscope and started his scientific activity. His first studies were devoted to inflammation and to the structure of muscle fibers. In 1885, during his tenure as Professor at the University of Valencia, the Provincial Government of Zaragoza, in recognition of his labor during a cholera epidemic, awarded him with a modern Zeiss microscope, which helped him a lot in his research.

The key event for Cajal’s scientific career and for the development of modern neuroscience took place in Madrid in 1887. In this year, Luis Simarro Lacabra, a brilliant psychiatrist interested in histological research, showed to Cajal, who had traveled from Valencia to get an update on technological advances, material impregnated with the Golgi staining. Dr. Simarro had just returned from Paris, and had brought specimens stained by the new technique of silver impregnation (the *reazione nera*), that had been discovered earlier by Camillo Golgi. Cajal wrote in his autobiography “it was there, in the house of Dr. Simarro...that for the first time I had an opportunity to admire...those famous sections of the brain impregnated by the silver method of the Savant of Pavia.”

At that time, Cajal had only been studying the nervous system for one year, mainly to collect suitable illustrations for a book of histological techniques, and he had realized how inadequate the ordinary methods were to study the nervous tissue. The observation of preparations impregnated by the Golgi stain was a flash of lightning:

"a look was enough" and Cajal was enraptured. Nerve cells appeared "coloured brownish black even to their finest branchlets, standing out with unsurpassable clarity upon a transparent yellow background. All was sharp as a sketch with Chinese ink," Cajal wrote in his autobiography. In a feverish burst of activity, Cajal worked on the retina, the cerebellum and the spinal cord, applying to the tissues the Golgi stain, of which he worked out some modifications.

In October 1889, Cajal went to Berlin, to the Congress of the German Anatomical Society, to show his slides to the leading authorities in the field, in order to convince them of the importance of his observations. On this occasion, he obtained the recognition of several qualified professors, including the eminent Swiss histologist Rudolf Albert von Kölliker (1817-1905), who from there on became a supporter of Cajal and of the "neuron doctrine," which would be officially enunciated by Wilhelm Waldeyer (1836-1921) in 1891.

Golgi's discovery of the black reaction and his subsequent investigations provided a substantial contribution to the advancement of the knowledge on the structural organization of the nervous tissue. The theory that tissues are composed of individual cellular elements "the cell theory" had been enunciated in 1838-1839 by Matthias Jacob Schleiden (1804-1881) and Theodor Schwann (1810-1882), but had not been extended to the nervous tissue. However, Golgi believed that his own observations of ramified nerve fibers could support the 'reticular theory', which postulated that the nervous system was a syncytial system, consisting of nervous fibers forming an intricate network, and that the nervous impulse propagated along such

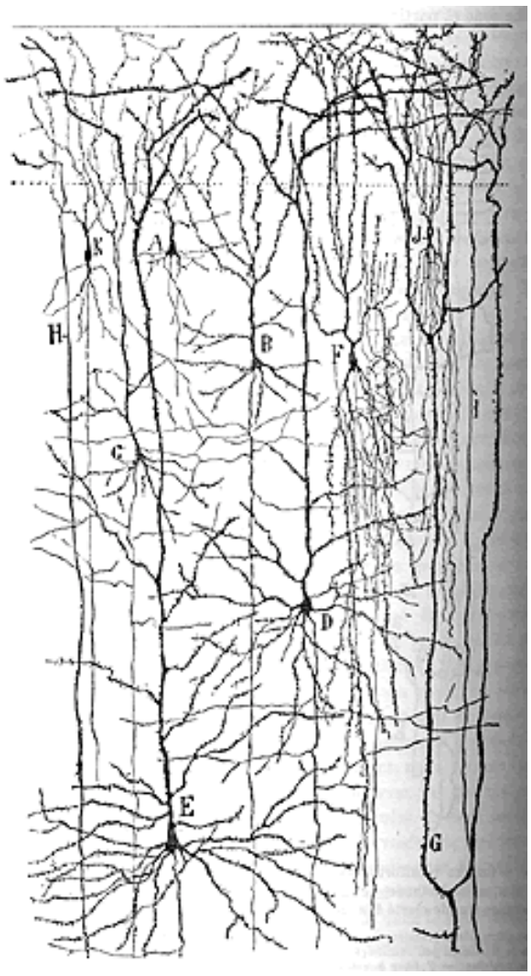

Fig. 2: Superficial layers of the human frontal cortex drawn by Ramon y. Cajal based on Golgi staining.

diffuse network. In the meantime, the theory that the nervous system as the other tissues was composed of cells, which were christened as 'neurons' by Wilhelm Waldeyer in 1891, was receiving wide support, also from studies pursued in other laboratories by means of the Golgi's new staining. Cajal was the main supporter of the 'neuron theory'.

Cajal was fiercely opposed to the idea

that the nervous system was made up of a network of continuous elements, as had been stated by Joseph von Gerlach (1820-1896) and supported by Golgi himself. Camillo Golgi had believed to have found in his own preparations the demonstration that the nervous system was made of a widespread network of filaments in continuity one with the other (the *rete nervosa diffusa*, 'diffuse neural network'). On the contrary, since the first observations and in his subsequent studies, Cajal's imagination was fired by the idea that the nervous system is made up of billions of separate nerve cells. Cajal's work led to the conclusion that the basic units of the nervous system were represented by individual cellular elements, the "neurons". This conclusion is the modern basic principle of the organization of the nervous system.

Golgi and Cajal, who shared the Nobel Prize in 1906 for their studies on the nervous system, met only in Stockholm, to receive the award. Golgi gave his Nobel lecture first, in which he tied to his belief in "reticular" neural networks. He said "What I have just said of the network, on its structure and, above all, on the fact that all the parts of the central nervous system make up a part of it, proves the anatomical and functional continuity between nerve cells. And that is the reason why I have not been able to accept the idea of this independence of each nerve cell which is the essential basis of the neuron theory.... I have never had reason, up to now, to give up the concept which I have always stressed, that nerve cells, instead of working individually, act together, so that we must think that several groups of elements exercise a cumulative effect on the peripheral organs through whole bundles of fibres."

This was entirely contradicted by Cajal's Nobel lecture. Cajal, a strenuous supporter of the contiguity (and not the continuity) of individual cells representing the basic units of the nervous system, said "The pericellular baskets and the climbing plexuses, and other morphological structures, whose form varies according to the nerve centres being studied, confirm that the nerve elements possess reciprocal relationships in contiguity but not in continuity. It is confirmed also that those more or less intimate contacts are always established, not between the nerve arborizations alone, but between these ramifications on the one hand, and the body and protoplasmic processes on the other.... From the whole of these facts, the neuronal doctrine of His and of Forel, accepted by many neurologists and physiologists, is derived as an inevitable postulate."

Golgi and Cajal certainly shared the same passion for science and dedication to science but their personalities were very different. Cajal, impetuous, burning with enthusiasm, dedicated his life to the study of the organization of the nervous system, on which he made fundamental discoveries with his peculiar talent and intuition. Golgi, a "cooler" academic, discovered the tool used by Cajal in his studies and provided outstanding contributions in many fields of cell biology and of pathology, and important contributions also on the structure of the nervous system.

Golgi was an exceptionally acute and prolific investigator, who provided a number of outstanding observations. Although he misinterpreted the overall view of the organization of the nervous system, he contributed highly to the modern knowledge

of its structure. Among other findings, Golgi described the morphological features of glial cells and of the relationships between glial cell processes and blood vessels. He also described two fundamental types of nerve cells, 'Golgi type I' and 'Golgi type II' neurons. Among his other discoveries, in 1878 Golgi described the tendinous sensory corpuscles that bear his name (the Golgi tendon organs). In the years 1886-1892, Golgi provided fundamental contributions to the study of malaria: he elucidated the cycle of the malaria agent, the *Plasmodium*, in red blood cells, and the temporal coincidence between the recurrent chills and fever with the release of the parasite in the blood. In 1897, studying the nervous system with his black reaction, Golgi noticed in neurons an intracellular structure, the "Golgi apparatus". The discovery of this cell organelle was a real breakthrough in cytology and cell biology. However, the existence of the Golgi apparatus was debated for decades (many scientists believed that it only represented a staining artifact) and was only confirmed in the mid-1950s by the use of the electron microscope.

Cajal's contribution is no less than that of Golgi's. Cajal defined "the law of dynamic polarization," stating that the nerve cells are polarized, receiving information on their cell bodies and dendrites, and conducting information to distant locations through axons, which turned out to be a basic principle of the functioning of neural connections. Cajal also made fundamental observations on the development of the nervous system and its reaction to injuries. In addition Cajal was also an accomplished photographer and he wrote several books destined to a not strictly scientific wide audience, including his autobiography "Recollections of My Life".

Going back to the Nobel Prize nominations, this was the first time (1906) that the Nobel Prize was shared between two laureates and it had its share of controversies as to whether Cajal deserved it more than Golgi. But it seems Cajal had the final word about this when he wrote (from the English translation of his autobiography, 1989, p. 546): "The other half was very justly adjudicated to the illustrious professor of Pavia, Camillo Golgi, the originator of the method with which I accomplished my most striking discoveries."

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