

The Nobel Prize of 1906

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December 2006 marked 100 years since the Nobel Prize in Physiology or Medicine was awarded jointly to 2 pioneers in the cellular anatomy of the central nervous system (CNS), Camillo Golgi and Santiago Ramon y Cajal. Golgi developed the silver impregnation method for studying nerve cells, a technique that clearly showed entire cells with their arborizing dendrites and axons for the first time. Ramon y Cajal seized on the method for a series of groundbreaking studies that provided convincing support for what came to be known as the neuron theory, in opposition to the reigning model of the time, the reticular theory. The retina was one of Ramon y Cajal's favorite tissues for study. Although he was perplexed by the horizontal and amacrine cells, he was remarkably prescient in his analysis of retinal and CNS cellular anatomy. Few scientists have cast such a long shadow in their field, but Ramon y Cajal did not establish the neuron theory single-handedly, and the real tale is much more complicated.

NEURON THEORY

The main elements of the neuron theory as it evolved a century ago were these:

- The neuron was a discrete entity and the physiologic unit of the CNS.
- There are 2 main types of cells, the glial and ganglion types, and specialized subtypes within each group. Dendrites and axons are elongations arising from the nerve cell body.
- The nerve cell body, that part of the cell that contains the nucleus, provides nutrition and support to these outgrowths.
- There is usually a single direction of impulse in the CNS, from dendrites to cell body to axon.
- There is physical discontinuity (called "synapsis" by Sherrington¹ in 1897) between the processes of one neuron and that of another.
- Nerve impulses can pass across synapses in only one direction; they then travel along pathways that are a concatenation of discrete neurons.

These concepts are so much a part of our mental baggage today that it startles

one to realize that at the turn of the 20th century some of these elements were still a matter of debate.²

In the mid-19th century, histology was still struggling to be accepted as a useful discipline. Because of the primitive technique of the time, some scientists held the microscope in contempt, thinking it detrimental to progress in biology and microscopic anatomy as "pure fancy," "stargazing," or "celestial anatomy."³ Specimens were whole mounts, thick sections, or perhaps laboriously teased-apart preparations, either unstained or poorly and undependably stained. This became an acute problem when one studied nervous tissue. When in 1839 Schwann proposed that the entire body was made up of cells, this cell theory was accepted for all organs with the lone exception of the CNS.⁴ Early anatomists recognized that the CNS was made up of fibers, and nerve cells could be seen with the early microscopes, but how exactly the fibers and cells were related could not be seen directly and caused one anonymous anatomist of the 1840s to lament that "the anatomy of the intimate structures of the brain is and remains apparently a book sealed with 7 seals and written, moreover, in hieroglyphics."³

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However, by the 1860s, achromatic lenses and oil immersion had been introduced and most anatomists were convinced that a nerve fiber was an outgrowth of the cell body, suggesting that the combination was the functional unit of the CNS, termed "neurone" by Waldeyer in 1891.^{2(p160)} But there was no unanimity as to whether these units were independent of each other, with their nerve processes contacting the contiguous processes or cell bodies of other nerves but not fusing with them, or whether nerve trunks arose from fusions of chains of cells or from protoplasmic bridges between cells.

To the clinician, some of this may seem like arguing about the number of angels that can fit on the head of a pin, but seldom has a controversy dealing with such a seemingly recondite detail of cellular anatomy had such large implications. How exactly one conceived of the connection between nerves influenced how one thought of the way the CNS operated. If the fibers were separate and distinct from one another with autonomous nerves communicating with each other in some unknown way but not actually fusing, such independence promoted the localization of CNS pathways and functions. However, if the fibers were fused with each other, interconnected in an intricate network, syncytium, or reticulum, with one fiber, in effect, connected to all others and with nerve cell bodies providing only support and nutrition, this reticular theory promoted the idea that the brain acted as a whole in producing its effects.

Camillo Golgi (**Figure 1**), in 1873, as a resident in a chronic disease hospital, and working after hours in a converted kitchen space, decided to combine silver nitrate with potassium dichromate to yield silver dichromate, and which, when used to stain brain tissue, more easily penetrates the nerve fiber. He then sometimes found a strange and unexpected effect. Most cells and fibers failed to stain at all, but those few that did stained black with the arborizing dendrites and axons standing out in fine detail against a pale yellow background. The Golgi stain was undependable and difficult to reproduce, and was not much



Figure 1. Camillo Golgi (1843-1926).

used between 1880 and 1885 when Golgi reported on it.^{4(p45)} Golgi became so discouraged that even though he had discovered the Golgi apparatus in nerve cells (one of the basic features of all cell structures), he turned from neurohistology to the study of malaria, during which he identified different species of *Plasmodium* as responsible for the tertian and quartan forms of the disease, which made him famous.

In 1887, however, the Golgi stain came to the attention of a young pathologist working in Spain, Santiago Ramon y Cajal (**Figure 2**). He had chosen histology for his field of study, in part because of practical economics; once one had a decent microscope, histology required little in the way of expensive equipment. This was a necessity because he had to pay all laboratory expenses out of a small academic salary. What histology did require was tremendous patience and an artistic bent, which he had shown as a child and that had horrified his country-physician father.

Ramon y Cajal experimented with variations on the Golgi stain and made improvements (mainly repeated impregnations of the tissue) that made it more reliable in his hands. The tenacity required in tracing parts of a cell through a multitude of levels, the accuracy and detail of his observations and the artistic skill in rendering what he saw, the imagination to pick important problems to study, and the meticulousness of his work (that bor-



Figure 2. Santiago Ramon y Cajal (1852-1934).

dered on obsession) are so admired by neuroanatomists today that his name is still invoked with reverence in the contemporary literature, where the modern paper is considered as only commentary on Ramon y Cajal.⁵ Even the late renowned neuroembryologist Viktor Hamburger wrote that "Indeed it is very difficult to be original in histogenesis without Cajal looking over one's shoulder."⁶

Ramon y Cajal's drawings were syntheses of what he saw in many different views of different cells in different sections. He had no peer in grasping the interrelationships between neurons rarely seen together in a single view through the microscope. His forte was not in tracing long tracts through the CNS but rather in examining the connections between cells in particular regions such as the cerebellum and retina. He was not above drawing a space between the fibers at each side of a synapse to emphasize the discontinuity there, although such a space was invisible to him and remained so until the electron microscope demonstrated it in the 1950s (**Figure 3**).⁷ He did not hesitate to apply his insights widely and occasionally was inspired with such ideas as neurotropism in the development of fiber tracts^{6,8} and the plasticity of the CNS.¹⁰

Ramon y Cajal had a deep-seated aversion to the reticular theory, recognizing that it led nowhere in trying to understand the CNS. Only the neuron theory, with its autonomous neurons following

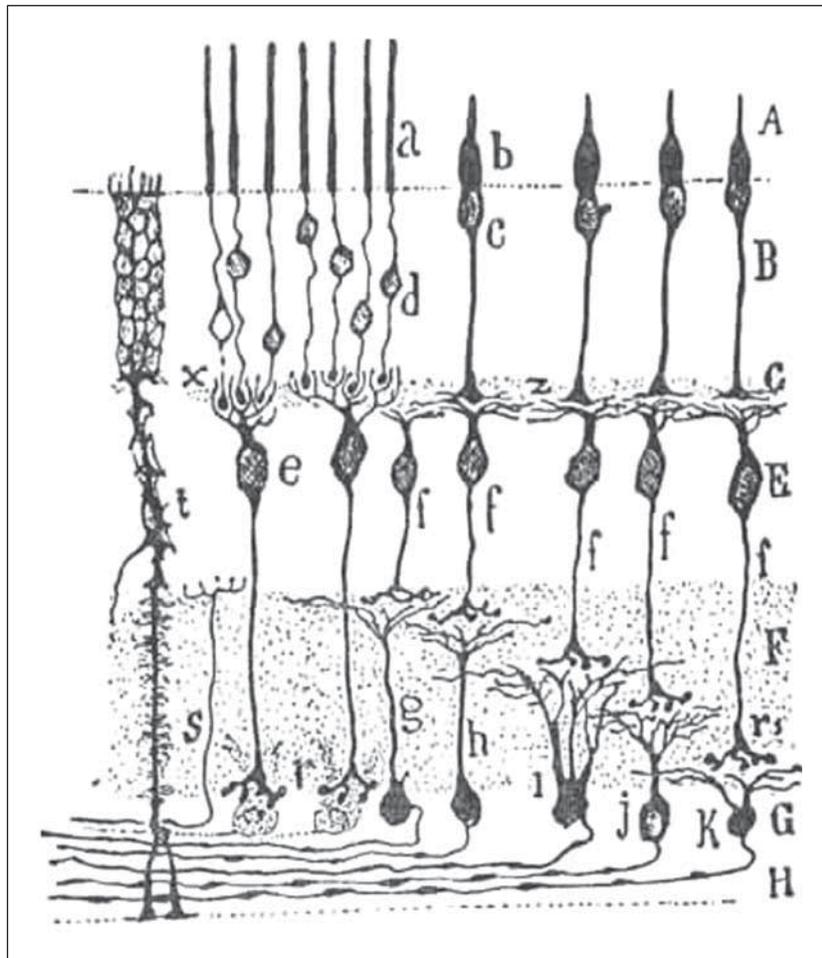


Figure 3. A section of mammalian retina in Golgi preparation as drawn by Ramon y Cajal in 1893.⁹ RB marks rod bipolar cells. The space between the distal processes of the rods and the dendrites of the rod bipolar cells could not have been actually seen by Ramon y Cajal but were drawn in this way to promote the idea of a discontinuity between sensory cells and neurones as well as between different neurons.

circumscribed conduction pathways through the CNS, could account for such phenomena as the reflex arc and the rapidly emerging evidence of localization of functions in the spinal cord and brain.

Ramon y Cajal's uncompromising advocacy helped to achieve an eventual consensus in favor of the neuron theory, but he was by no means the only significant contributor to this consensus.^{2,11} It was the product of many minds, and several approaches were important. Wilhelm His (1831-1904) observed the axon growing directly out of the embryonic nerve cell, indicating that the two were manifestations of the same unit and that the axons have free endings before they make connections (1886-1889). August-Henri Forel (1848-1931) showed that after enucleation of the eye or lesions of the visual cortex, the injured neurons exhibited de-

generation that did not extend to neighboring cells (1887). The underappreciated Ross Granville Hamilton (1870-1959) invented tissue culture and transplanted embryonic tissue (1910) to demonstrate nerve cell growth independent of any other elements in a tissue.⁶ (He failed to receive the Nobel Prize he deserved because the Nobel Committee wrongheadedly believed there was little general utility to the technique of tissue culture.) Charles Scott Sherrington (1857-1952) elaborated on the delay in transmission of the spinal reflex in comparison with the speed of the nerve impulse in a peripheral nerve, making the concept of the synapse a credible reality independent of any histologic findings (1906). The neuron theory then proceeded to have such great explanatory and predictive power in the physiology and pathology of the 20th century that it be-

came an accepted foundation of modern neurobiology.

RAMON Y CAJAL'S USE OF THE RETINA

Ramon y Cajal realized that the nerve fiber resisted staining once it became myelinated, and therefore, he concentrated on the fetal or neonatal brains of birds and small mammals, in which myelination is less dense or often absent altogether. The retina was a favorite tissue for him, and he wrote that "the retina has always [been] shown to be generous to me . . . the retina [is] the oldest and most tenacious of my laboratory loves. . . ." ^{12(p130)} It was only lightly myelinated and, thus, allowed better penetration of the silver stain into its cells.¹³ Furthermore, its precise organization in layers of alternate cell bodies and fibers made orientation easier for the microscopist, who also would have no doubt about the direction the nerve impulse was traveling through the tissue. This was important for Ramon y Cajal because his scheme of dynamic polarization held that nerve impulses travel in a single direction from dendrites to cell bodies to axons.

The retina at the time was something of a puzzle to histologists and, although most of its cell types had already been recognized, the reason for the orderly layering of cells and fibers, obviously important in some way, was obscure. Ramon y Cajal made the retina an understandable nervous structure that clearly illustrated the neuron theory.

His preconceptions sometimes determined what exactly he observed (Figure 3). He believed that Max Schultze's analysis of the rods and cones as distinct systems in the retina meant that the nerve impulse from the rods had to be separate from those from the cones, all the way through the bipolar cell layer to the ganglion cells. Ramon y Cajal thought that a single ganglion cell receiving converging transmissions from both rods and cones would be contrary to the duplicity theory. Therefore, he saw no such converging pathways, although they are there. Even with the cone system itself, if there was to be retention of spatial information inherent in the retinal image, he believed

there had to be point-to-point transmission from the cone to the ganglion cell, with minimal convergence, and this is what he drew.

This became a problem when it came to interpreting the function of the horizontal cells in the bipolar cell layers because he could see quite well that they appeared to connect noncontiguous areas. He had, after all, studied these cells carefully, naming one type of cell an amacrine cell. Piccolino, who has commented in detail about Ramon y Cajal's retinal ideas, also points out that

Cajal ignored in a systematic way the presence in the retinas . . . of an axonless type of horizontal cell [reported by other authors]. One is led to believe that Cajal saw exclusively axon-bearing horizontal cells because these conformed well to the principle of dynamic polarization.^{13(p525)}

Other writers¹⁴ agree that his faith in the neuron doctrine was sustained even when he saw contradictory evidence, such as a process of a bipolar cell occasionally appearing to fuse with the terminal spherule of a rod. With the standard microscope, this appeared to be an obvious syncytium; only the resolution of the electron microscope could show that the fusion was more apparent than real. Ramon y Cajal also showed that the axons of all rod bipolar cells in mammals end on the dendrites of ganglion cells, whereas they mainly synapse with amacrine cells.^{2(p14)}

Ramon y Cajal conceived of no function for the synapse except to excite the next cell in line; he had no idea of its valvelike action or of the receptive field of a ganglion cell as encompassing both inhibitory and excitatory synapses, that is, of there existing a coding of the image within the retina and not simply a transmission up the line of a photographic image. Not until a half-century later did Hartline, Kuffler, and Barlow present this concept on the basis of their electrophysiological findings. Not living long enough to see this, Ramon y Cajal wrote, in the year before he died (1934, at the age of 82), of the "paradox" and "enigma" of the horizontal and amacrine cells.¹²

THE NOBEL PRIZE

Although the Nobel Prize is an award for work in physiology or medicine, from the start it was largely limited to contributions in physiology, or what is now termed "basic science." When the award consultants wished to recognize advances in the understanding of the CNS, they were unanimous in considering anatomists, not clinicians. One wonders at their options at this early point. Who else still alive at the time could have been honored for purely clinical advances? This was still the golden age of British neurology; John Hughlings Jackson would have been a name to conjure with just as much as Ramon y Cajal. But it was not to be. Five of 6 advisors to the Karolinska Institute were anatomists, and the predilection was a foregone conclusion.

Golgi was proposed as a recipient when the first awards were given in 1901.¹⁵ Ramon y Cajal was considered soon afterward, and by 1906, opinion was swinging in his favor as the stronger candidate. The decision to award the prize jointly set a precedent and soon became standard.

At the award ceremony in Stockholm, each recipient had the opportunity to speak about his work. Neither touched on the clinical implications of their work. Golgi spoke first. He still felt that recovery of function of the brain after injury, as well as its great capacity for coordination and integration of functions, upheld the reticular theory.

However opposed it may seem to the popular tendency to individualize the elements, I cannot abandon the idea of a unitary action of the nervous system, without bothering if . . . I approach old conceptions.^{16(p216)}

Ramon y Cajal's speech was longer, going into more detail about his reasons for supporting the neuron theory. He acknowledged the contributions of His and Forel in formulating the neuron theory and gave credit to many others. He then went on to discuss his newest work on nerve degeneration. But, he could not resist a sarcastic slap at the reticularists:

True, it would be very convenient and very economical from the point of view

of analytical effort if all the nerve centers were made up of a continuous intermediary network between the motor nerves . . . and sensory nerves. Unfortunately, nature seems unaware of our intellectual need for convenience and unity, and very often takes delight in complication and diversity.^{17(p240)}

RAMON Y CAJAL, THE PERSON

Ramon y Cajal was, by nature, a born polemicist, unafraid of confrontation, a loner by inclination,¹⁸ and adept at promoting his own position. (He was still defending it in his last paper, in 1933.¹⁹) Jacobson,² who has made the most thorough and thoughtful commentary to date on Ramon y Cajal, warns us that his autobiography should be approached with caution, since he was not above dramatizing himself and putting his ideas at the center of the scientific world, even to the point of claiming priority over Golgi for discovery of the Golgi complex and over others for the discovery of passive immunity (and even for the invention of the phonographic recording disk before Edison). There are passages that read like a caricature of the egotistic scientist in the throes of a demonic possession. For example, on the death of his 3-year-old daughter:

Poor Enriqueta—her pale and suffering image lives in my memory, associated, by a singular and bitter contrast, with one of my most beautiful discoveries, the axis-cylinders of the cerebellar granule cells and their continuity with parallel fibers of the molecular layer . . . one ill-starred night, as the shadows began to fall on an innocent being, the splendor of a new truth suddenly illuminated my mind.^{2(p49)}

Jacobson comments, "We have no right to expect a genius to be amiable. The majority of them are singularly unamiable characters, and Cajal was no exception."^{2(p50)}

Ramon y Cajal is certainly a major figure in the history of biology, but a large halo effect has augmented his reputation to the point where even such an important modern embryologist as Viktor Hamburger could make the following parochial and exaggerated claim:

[Ramon y Cajal] is the founder of modern neurology, which is also the basis of

neurophysiology, neuropathology, and physiological psychology. Almost single-handedly, he unraveled the design of the central nervous system . . . and traced its structure to the most intricate details.⁶

Jacobson² gives a much more nuanced and realistic opinion. He points out that when Sherrington wrote his definitive book about the synapse,²⁰ published in 1906, the same year the Nobel Prize was awarded to Ramon y Cajal and the reason for Sherrington receiving the Nobel Prize in 1932, he referred to Ramon y Cajal's work several times but gave no credit to him for his work on the connections between neurons. That work could not actually visualize the synapse and did not help physiologists when they observed delay, summation, and inhibition at the synapse.

And the synapse was now to be a crucial structure. Anatomists had occupied center stage in the 19th century, but pure morphology could take one only so far. The 20th century would belong to the physiologists.

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