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Review

Cajal's debt to Golgi

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We are accustomed to thinking of Camillo Golgi and Santiago Ramón y Cajal as contemporary scientists at war over the neuron doctrine. This is certainly how Cajal in his biography and later writings portrayed their relationship and Golgi did not help matters by his most unfortunate Nobel acceptance speech of 1906 (Golgi 1907) in which he emphasized in a contentious way his continuing belief in an outmoded view of the nervous system. Cajal's speech (Cajal, 1907), by contrast, was of a kind typical of that of any modern neuroscientist in which he outlined his past achievements in neurohistology and then proceeded to describe his ongoing experiments in nerve regeneration. The contrast between the two speeches is a reflection of the fact that Golgi's work on the organization of the central nervous system had essentially ended by 1883 when he turned mainly to investigations of malaria, while Cajal's which had commenced only in 1888 was still in full flight. As neuroscientists, therefore, they cannot be seen as contemporaries. In what follows, I shall attempt to present the case that Golgi's observations, made on tissue stained by his black reaction represented a fundamental breakthrough in the way in which the nervous system was viewed and that his observations provided a firm basis upon which Cajal was later able to build. While it would be wrong to say, as some have, that Cajal stood on the shoulders of Golgi, there can be little doubt that a number of Golgi's observations on the structure and organization of nerve cells not only transformed the way

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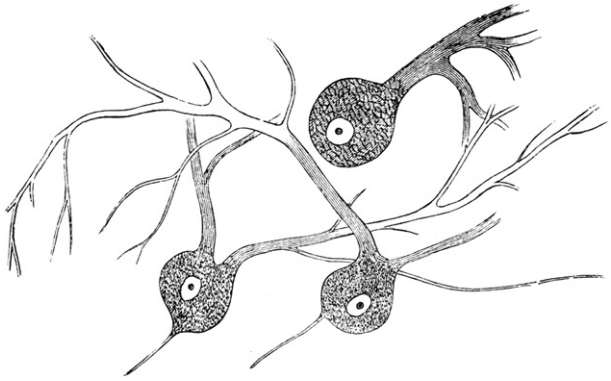

Fig. 1 – Drawings of Purkinje cells from the human cerebellum, showing the extent of detail that could be visualized in material fixed in chromium or osmium salts and stained with carmine. From Kölliker (1863).

in which contemporary scientists perceived nerve cells but also represented the starting points for Cajal's work in which in a few years he unraveled the intrinsic circuitry of just about every region of the nervous system.

Prior to Golgi's discovery of the black reaction (Golgi, 1873) and his publication of the first images of nerve cells obtained with it, knowledge of the form of nerve cells was remarkably primitive. Purkinje did not visualize the cells that now bear his name as the magnificent structures with their elaborate planar set of dendrites that we know today but as no more than globules that represented only the cell body. The later introduction of chromic acid as a fixative and carmine as a stain extended somewhat the knowledge of the nerve cell, notably in the hands of Deiters who identified branching dendrites (which he called protoplasmic processes) and the axon (called the axis cylinder). But the forms of the dendritic trees demonstrated by Deiters and others were incomplete and the collateral branches of axons had not been discovered. Kölliker's (1863) drawings of Purkinje cells (Fig. 1), while definitely an advance on what Purkinje himself had seen, are still primitive when compared with what we have subsequently learned about the structure of that neuron. Prior to his discovery of the black reaction, Golgi's drawings of nerve cells which he had observed in tissue fixed in potassium dichromate, chromic or osmic acid (Fig. 2) are little different from those of other contemporary histologists, sometime showing branching dendrites but often with no more than stumps of dendrites emerging from the soma and perhaps the axon hillock and initial segment.

The first images of neurons impregnated with the Golgi stain heralded the beginning of a revolution in how nerve cells were viewed. Those early drawings of Golgi (e.g. Golgi, 1875) present neurons for the first time in the form in which we are still accustomed to portraying them (Fig. 3). Golgi's disappointment at the slow recognition in print of the importance of his findings was real but it seems clear that this was less on account of disbelief than on the fact that few scientists could successfully employ his method to obtain similar results. It was only after Cajal much later, in 1888 and 1889, applied the stain in repeated impregnations, with longer immersion times and more concentrated reagents, and in infant animals in which myelination was less advanced than in adults, that others were able successfully to use it (DeFelipe and Jones, 1992). But at the time of Golgi's first publications no one with any eye for the nervous system could fail to appreciate the manner in which his stain had dramatically extended anatomical knowledge of the nerve cell, its dendrites and its axon. Outside the world of scientific publishing there were many who early on recognized that a revolution had occurred and attempted to implement the Golgi methods themselves. Fritjof Nansen in 1887, traveled to Pavia to learn the secrets of the method (Jones, 1994), and Luis Simarro who in 1887 was to give Cajal his first glimpse of a Golgi preparation (Cajal, 1917) applied while in Ranvier's laboratory in Paris. Neither of them published the results of their investigations, however, and others such as Kölliker, who also visited Pavia in 1888, after earlier correspondence with Golgi, were unable to get the stain to work. To the scientific establishment, the new revelations about nerve cells seemed to have come as the result of a freakish accident by a little known Italian. That other Italians, notably Tartuferi in his study of the retina (1887) could make preparations as compelling as those of Golgi made it clear that, given the correct application of the stain, nerve cells could be revealed in far greater detail than before. When Cajal reported his first observations in short communications in 1888 (Cajal, 1888a,

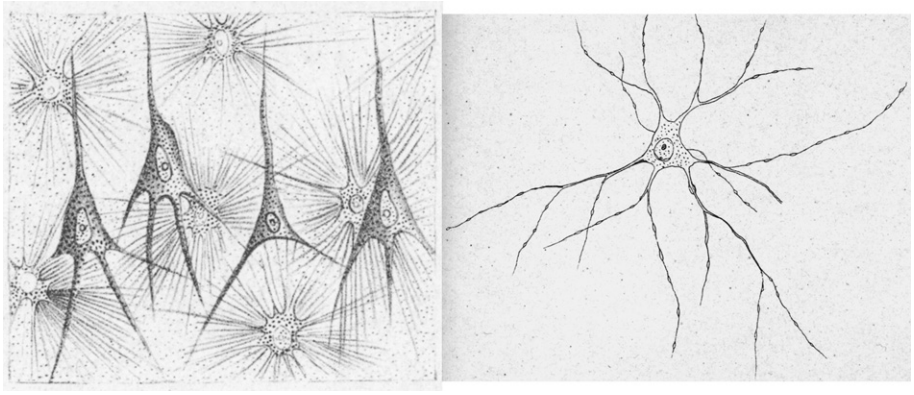

Fig. 2 – Drawings of nerve cells made by Golgi in the years before his discovery of the black reaction. Left: pyramidal cells and neuroglial cells from the human cerebral cortex sectioned after fixation in osmic acid. From Golgi (1871). Right: Ganglion cell from the retina of a horse, from a whole mount fixed in potassium dichromate and osmic acid. From Golgi (1872).