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THE CONTRIBUTION OF CAMILLO GOLGI TO OUR UNDERSTANDING OF THE STRUCTURE OF THE NERVOUS SYSTEM

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A century ago Camillo Golgi (1843-1926) and Santiago Ramón y Cajal (1852-1934) were awarded the Nobel Prize for Physiology or Medicine for their investigations on the structure of the nervous system. While the work of Cajal is universally acknowledged, Golgi's contribution is less well known. The anniversary of the award provides a good opportunity to review the work of Golgi and introduce it to young investigators.

There is no doubt that the main contribution of Golgi to our understanding of the structure of the nervous system is his invention of the black reaction (5). As Koelliker (1817-1905) wrote in 1887, the invention marked the beginning of a new era in the study of the microscopic anatomy of the nervous system (1). In a previous article the characteristics of the black reaction were described in detail (18). Here it seems sufficient to emphasize that the technique was greatly superior to those used up to that point. Previously the two procedures available for the histological investigation of nervous tissue were: 1) fixation, embedding, and cutting of the tissue, followed by staining of the sections with hematoxylin or carmine; 2) immersion of nervous tissue blocks in reagents which served both to fix and harden the material followed by mechanical isolation of individual nerve cells using needles under the microscope. These techniques made it possibile to reveal only certain parts of nerve cells, whereas the black reaction made it possibile to see individual nerve cells in their entirety, i.e. with all their processes.

Before examining some of the results obtained directly by Golgi on the nervous system it should be noted that the black reaction made it possibile for many other researchers to make important contributions to our knowledge of nervous system structure. In particular, several findings obtained using the black reaction were important for framing the neuron theory. The belief widely held at the time was that nerve cells were in protoplasmic continuity with each other; by contrast, the neuron theory affirmed that nervous tissue consisted of distinct units [called neurons by Waldeyer (1891)], that are connected by surface contacts. Several authors were involved in establishing the neuron theory; important among these are W. His (1831-1904), B.A. von Gudden (1824-1886), A.H. Forel (1848-1931), and H.W.G. Waldeyer (1836-1921), who worked independently of each other. The most forceful and effective advocate of this conception was certainly Ramón y Cajal. Paradoxically, with the invention of his black reaction Golgi provided researchers with one of their most valuable tools

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Fig. 1. – *Camillo Golgi ca. 1875.*

for establishing the theory that he fought against obstinately throughout his career. Furthermore, the use of the black reaction, both by Golgi and his pupils, and by other researchers, resulted in a radical change of ideas about how the central nervous system was organized. In Golgi's time it was widely believed that nerve cells were embedded in an amorphous ground substance, considered to occupy more than 50% of the volume of the gray matter. The systematic use of the black reaction revealed, on the contrary, that the central nervous system consisted mainly of cells.

The black reaction produced a wealth of significant new findings in the decades around the turn of the 20th century, but continued to bear fruit for many years afterwards. During the second half of the 20th century it was used as follows: 1) to quantitatively analyze the branching pattern of neuronal dendritic trees in studies concerned with the evolution and ontogeny of the nervous system; 2) to determine the number and distribution of dendritic spines, and hence of corresponding synapses, in several types of neuron under normal and pathological conditions, and after experimental manipulation; 3) in association with electron microscopy to identify, for any particular synapse, the two participating neurons. In this way the black reaction proved to be one of the most useful tools for studying the structure of the nervous system for over a century. It was only at the end of the 1960s that the black reaction started to be replaced, in uses 1) and 2) above, by the injection of individual nerve cells with markers (e.g., biocytin, and Lucifer yellow) using intracellular electrodes. This new technique made it possible not only to visualize a nerve cell in its entirety, but also to record its electrical activity.

Golgi's personal contributions to our understanding of the structure of the nervous system are summarized in what follows. 1) A view popular in Golgi's time was that the axis cylinder (now called the axon) was unbranched for its entire length (see, e.g., 4). Golgi (11) showed, however, that the axon gives off lateral branches. 2) Another commonly held belief was that the protoplasmic processes (now known as dendrites) of one nerve cell anastomose with those of other nerve cells. Golgi (11) established that dendrites end freely. 3) Golgi also revealed the previously unsuspected variety of nerve cell types. Today morphology is rather unfashionable and is often somewhat ignored. However, it is worth remembering that knowledge of the morphology of a neuron can be very useful in interpreting its functional role, particularly when its connections are known in detail. In the central nervous system, Golgi (11) distinguished two types of nerve cell on the basis of the configuration of their axons. Type I cells have an axon which sends out few collateral branches, retains its distinct identity, and is usually myelinated. Type II cells have an axon which usually remains unmyelinated and divides repeatedly shortly after leaving the soma, thus giving rise to an arborization in the neighborhood of the cell body. This simple classification is still valid today and the differing morphologies of the two types of nerve cell reflect their different functional roles. 4) Golgi (10, 12, 13) recognized a thin envelope covering the body and the dendrites of nerve cells. This envelope, which often appears as a meshwork, was initially called the pericellular net and later the perineuronal net. The existence of this structure was repeatedly confirmed by other workers. In the second half of the 20th century it became evident that the perineuronal net results from condensation of components of the extracellular matrix of the central nervous system (3). 5) Golgi (11) elucidated the morphology of astrocytes and their relations to blood vessels. 6) He also carried out detailed investigations of several brain regions [the cerebellum (6), the olfactory bulb (7), and the hippocampus (11)]. 7) Golgi (13) discovered within nerve cells the internal reticular apparatus that now bears his name. Later it became clear that this organelle is not confined to nerve cells, but is present in nearly all eukaryotic cells. The discovery of the Golgi apparatus had a great impact on cell biology, and was commemorated by several authors on the occasion of its centenary (e.g., see 2). Golgi obtained the results listed above using his black reaction. Using other techniques (e.g., gold impregnation, osmium tetroxide) he obtained the following additional important results. He (8, 9) discovered the mechanoreceptors located at the junction between muscles and tendons; these receptors were later called Golgi tendon organs. Furthermore, he demonstrated the presence of sensory corpuscles in the peritendinous connective tissue and perimysium of human muscles (8, 9). Later Mazzoni (17) described these receptors, now known as corpuscles of Golgi-Mazzoni, in greater detail.

Golgi's neuropathological investigations and his important studies on malaria lie outside the scope of this article. Information on these aspects as well as on the life and personality of Golgi can be found in Mazzarello (16).

The findings listed above have been repeatedly confirmed by other researchers. They are major achievements that form important bases for modern neurohistology.

They demonstrate that Golgi was a first rate scientific observer. However, the morphologist's task is not simply to observe and describe however carefully, but also to interpret his observations and put forward hypotheses regarding the functional significance of the structures discerned. It is here that Golgi shows his limitations. In fact several of his interpretations have not stood the test of time. To interpret results obtained studying the gray matter, he formulated the theory that nervous processes form a continuous network that he called the diffuse neural network (11). Golgi maintained this theory unbendingly till the end of his life, notwithstanding the fact that it could not to be reconciled with most of the physiological and other evidence that became available during his lifetime. In particular, neurophysiological results in evident contrast to his theory were published while he was still engaged in active research, but he systematically neglected these findings. Other erroneous interpretations that Golgi imputed to his results were the consequence of his convinction of the reality of the diffuse neural network, as the following examples show. He thought that the lateral axonal branches, which he discovered, contributed to the diffuse neural network (11). Furthermore, although he demonstrated that dendrites end freely, he did not consider them to be part of the conduction pathway of the nerve cell, and assigned them an exclusively trophic role (11, 12, 14). Finally, Golgi attributed an insulating function to the pericellular net which he discovered; in fact, he maintained that this net prevented the contact between nerve cells proposed by the neuron theory (12, 13).

Jones (15) has suggested that the errors of interpretation made by Golgi induced many young investigators to neglect his findings or underestimate their importance. It is probably for this reason that Golgi's contribution to our understanding of the structure of the nervous system is often considered to be confined to his invention of the black reaction. However, this disparaging interpretation of Golgi's lifework does not accord him the merit he deserves. The achievements reviewed in this article, irrespective of Golgi's erroneous interpretations, stand as major landmarks in the progress of our understanding of nervous system structure.

SUMMARY

A hundred years ago Camillo Golgi and Santiago Ramón y Cajal were awarded the Nobel Prize for Physiology or Medicine for their investigations on the structure of the nervous system. The work of Cajal is universally acknowledged, whereas Golgi's contribution is less well known. This article reviews the main achievements of Golgi in that field. In addition to Golgi's most important results, the errors he made in interpreting his own findings are examined. These errors contributed notably to a widespread neglect and underestimation of his important contributions to our understanding of the structure of the nervous system.

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