How Camillo Golgi became “the Golgi”

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1. Black silhouettes

At the end of the nineteenth century Camillo Golgi, professor of General Pathology and Histology at the University of Pavia, was already internationally famous for his discoveries on the structure of the central nervous system and for his descriptions of the human malaria parasites development in the human blood [1].

Graduated in Pavia in 1865, he was trained in microscopy by Giulio Bizzozero, a Rudolf Virchow’s pupil and one of the pioneer of cell biology in Italy [2]. In 1873, while he was chief physician in a hospital for chronic patients at Abbiategrasso not far from Milan, Golgi developed a method, the “black reaction” (known nowadays as the Golgi stain or the Golgi impregnation), which allowed for the first time a full view of a single nerve cell. This histological method, which is widely still in use, was based on hardening blocks of nervous tissue in potassium dichromate, followed by impregnation with silver nitrate. The final result was a precipitate of silver chromate randomly distributed, and completely spares the others allowing the individual elements to emerge from the nervous puzzle.

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Aided by his black reaction method, Golgi described the complex arborisation of the dendrites, discovered the branching of the axons, analyzed several regions of the nervous system in detail and provided beautiful illustrations of them. Among the remarkable Golgi’s descriptions of different brain regions, particularly important were those of the cerebellum (where he described the so called “Golgi cells”), the olfactory bulb, the hippocampus, and the cerebral cortex. Taken together these investigations provided a remarkable contribution to the advancement of the knowledge on the structural organization of the nervous system.

Meanwhile he began to elaborate a general anatomic-physiological theory of brain organization, the “diffuse nervous net”, according to which the ramified axons were connected (through direct fusion or intimate contact) in a diffuse network along which the nervous impulse propagated. Actually, it dealt with an illusory network which resulted from a mistaken microscopic image created by superimposition and by interlocking of the axons of the diverse cells. Towards the end of the nineteenth century this concept

The great advantage of this technique is that, for reasons that are still unknown, the precipitate of silver chromate randomly but selectively stains in black only a small proportion of nerve cells (usually from 1% to 5%), and completely spares the others allowing the individual elements to emerge from the nervous puzzle.

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developed in polemical opposition to the neuron theory championed by the Spanish histologist Santiago Ramón y Cajal which affirms that the nervous system is anatomically and functionally composed of individual cells, like any other tissue, and that nerve cells act to each other through points of contact subsequently named synapses by the British neurophysiologist Charles Scott Sherrington.

Since the development of the black reaction in 1873, Golgi continued to modify the chemical and physical parameters of the reagents in order to improve the selectivity and the reproducibility of the method under standard condition. The goal was however never completely reached since an element of randomness remained, and still remains, in the Golgi stain. However by 1885, Golgi was able to describe in his book *Sulla fina anatomia degli organi centrali del sistema nervoso* (On the fine anatomy of the central organ of the nervous system) some modifications and variants of the black reaction[3]. Particularly important was the introduction of a osmium-dichromate solution as the first immersion step of the reaction which allowed a fast staining of the nerve cells (the so called rapid variant of the method).

Very interested in infectious diseases and concerned about public health, between 1886 and 1892 Golgi temporarily abandoned neurobiological research and concentrated on studying human malaria (see Fig. 2). Not only he did worked out the cycle of development of the malaria parasite *Plasmodium* in the red blood cells, but he also discovered the temporal coincidence between the recurrent fever of the infection, and the multiplication of the parasite in human blood. Between 1893 and 1896 Golgi was mainly involved in academic and administrative commitments as elected rector of the University of Pavia. However he never lost his interest for the nervous system. In 1897 he returned in the laboratory to perform original research and started an investigation on the structure of the spinal ganglia. The topic was at the centre of Golgi’s attention since the T shape of the spinal ganglion cells seems to contradict the “law of dynamic polarization” of Santiago Ramón y Cajal and Arthur van Gehuchten, one of the theoretical basis of the neuron theory.

2. A fine and elegant network hidden within the cell body

During this research Golgi noticed the occurrence of a strange reticular structure, hidden in the cytoplasm of the nerve cell body, which was clearly detached from the membrane and from the nucleus. Unfortunately this bizarre new formation was not constantly stainable. But Emilio Veratti (who in 1902 went on to describe the sarcoplasmic reticulum [4]), working in Golgi’s laboratory, was able to replicate and confirm the findings in the cell body of the fourth cranial nerve. Golgi then persevered in his neurocytological research and was able to obtain very good and reproducible impregnation of the intracellular apparatus in the cell body of the Purkinje cerebellar cells of the owl *Tyto alba* (see Fig. 3).
The apparatus was also detected in the cells of the sympathetic system by Veratti who added 0.1 platinum chloride to the fixative to facilitate the reaction [7].

Golgi continued to pursue with energy this line of research and on 15 July 1898 he described at the Medical–Surgical Society of Pavia the apparatus in cells of the spinal ganglia [8,9] and on 20 January 1899 he presented clear data on the age related variations of this structure [10]. He noticed that in adult and older animals the impregnation was only partial (see Fig. 5).

While he continued to perform research on the structure he had discovered [11–14] he stimulated the interest of his co-workers to search the structure in non-neural cell types (see Fig. 6).

3. Not only in the nervous system

At the turn of the century Golgi had organized in Pavia a very active laboratory of General Pathology and Histology. He was an effective mentor and supervisor for his co-workers and disciples as documented by the remarkable number of discoveries that they made under his direction. After the first observations of the internal reticular apparatus in the nerve cells, Antonio Pensa, in Golgi’s laboratory, succeeded in detecting this structure in the medullary cells of the adrenal glands and he presented his findings to the Medical–Surgical Society of Pavia in 1899 [15]. However, this first indication that the apparatus could not only be present in nerve cells was not considered conclusive given the common embryonic origin of neurons and adrenal medullary cells. While the paper was in press Pensa added a note to announce that “In our laboratory Mr. Negri … in these days … could detect in pancreatic gland cells and in the cells of some serous glands an endocellular apparatus with some analogies with what I have described in the medullary cells of the adrenal glands”. Negri, who was at the time a fifth year medical student, quickly succeeded in demonstrating the network in several non-neural cells, besides the pancreatic cell glands, i.e. thyroid, epididymis, salivary glands and ovary [16]. Meanwhile Edoardo Gemelli, another pupil of Golgi, described the apparatus in the pituitary gland cells [17]. It was becoming evident that this structure did not belong only to neurocytology, but was probably ubiquitous in various eukaryotic cell types.

4. Before Golgi

When the Spanish histologist Ramón y Cajal read of the new Golgi’s discovery, probably remembered a fact occurred some years before which caused one of his “most deplorable disappointments”: as he reported in his recollections [18]:

“In the years 1891 and 1892, I happened to immerse pieces of the cerebrum of a young rabbit in a certain mixture of equal parts of 3% potassium dichromate and 1% gold chloride solutions. A few days later, sections of the pieces showed a splendid selective reduction of the gold salt in the Golgi apparatus (then unknown) of the cerebral pyramids. Enraptured with the wonderful results, I devoted myself ardently to reiterated trials to determine the conditions of success. Well, the confounded reaction never appeared again! I was guilty on that occasion of excessive scrupulousness and timidity, since I did not dare to publish my rare discovery; it seemed to me that it would be an abuse to announce a fact of which confirmation was, at the time impossible. Had it not been for such considerations, the so called reticular apparatus of Golgi, which the neurologist of Pavia discovered in 1898 (by means of a formula, indeed, which is notably uncertain), it would figure today among my assets and under my name”.

In reality Golgi published his discovery only when, with the aids of his pupil Veratti, was able to constantly reproduce the results. But even before Ramón y Cajal (assuming that his vague and late
recollection refers to the same structure characterized by Golgi. Other histologists had observed cytoplasmic features that perhaps could be identified as the internal reticular apparatus. Among the others, the name of Adolphe von La Valette St. George (1867), Moritz Nussbaum (1882), Masanori Ogata (1883), Gustav Platner (1886) and Auguste Prenant (1887) are sometime mentioned in relation to early observations of the reticular apparatus. However it is uncertain that they had observed this structure or something else [19–21].

In any case it was Golgi and subsequently his school [22,23] who defined the apparatus morphologically as an organelle, a stable component of the eukaryotic cell, and clearly differentiated it from other cytological elements. Moreover the histologist of Pavia must be credited to have extended to general cytology the application of the metallic impregnation, previously used mainly in neurobiology.

5. Further contributions by the Golgi’s school

After the first demonstrations of its presence in non-neural cells, a number of students and researchers in Golgi’s laboratory investigated the presence and the morphology of the reticular apparatus in different conditions and in various cellular types. Among the relevant studies performed in the fifteen years after its discovery, important were those of Giuseppe Moriani, Ferruccio Marcora and Emilio Veratti who described it in various pathological processes [24–26], Antonio Pensà in cartilage cells [27] and in vegetal cells [28] Luigi Stropeni in hepatic cells [29], Giuseppe Carlo Riquier in the corpus luteum [30], Francesco Maccabruni in megakaryocytes [31] Ernesto Brugnatelli in renal tubules [32], Carlo Barinetti in various tissues [33] (see Fig. 7).

Golgi himself continued to pursue his investigations on the reticular apparatus and described a “photographic” method [34] derived by a technique introduced in 1903 by Ramón y Cajal. He was thus able to observe its variation in the shape and intracellular disposition during the secretory process in the mucus glands of the frog stomach. He found that the nucleus was located at the base of the cell and the apparatus projected towards the secretory

Fig. 6. Early protagonists of Golgi Apparatus research. We can recognise Golgi (fourth from right, first row), Pensà (second from left, first row), Veratti (second from right, first row), Negri and Gemelli (first and third from left, second row, respectively) and a young Perroncito (first from right, second row).

Fig. 7. Golgi Apparatus in the gastric mucosa cells of the frog. Original drawing probably of Emilio Veratti, Museum for the History of the University of Pavia.
surface [35]. One of his collaborators, Giuseppe D’Agata, extended the investigation to the reticular apparatus in the epithelium of the gastric mucosa [36]. One of the most important researches performed in Golgi’s laboratory at that time, was that of Aldo Perroncito who described the division of the apparatus, the so-called “dictyokinesis”, in living spermatocytes of Paludina vivipara [37,38]. According to Trautmann [19], this phenomenon had been already observed by Gustav Platner, Friedrich Hermann and Arthur Bolles-Lee but without understanding the meaning of the structure they describe (see also Ref. [21]).

6. Artefact or reality?

Golgi’s discovery spurred a wealth of investigations at the international level. However the difficulties in handling the original silver Golgi’s method, and its capriciousness, made the reproduction very difficult for non-expert histologists. So it was common to speak ironically of the “water of Pavia”, the miraculous water that made possible the reaction for the apparatus in Pavia while failed elsewhere.

There were however also important and precocious confirmations. One of the first was provided by Friedrich Kopsch in 1902 by using an osmium technique [39] followed by Ramón y Cajal, eternal rival of Golgi, but always along his tracks, who was among the first to study the reticular apparatus outside Pavia. He was able to demonstrate this structure in the nerve cells of the invertebrates [40] and then to extend his investigations to some other types of nerve and non-nerve cells [41–43] concluding in 1914 that “the reticular Golgi apparatus is an anatomical feature constant in the protoplasm of all living cells, both embryonic and adult” [43]. In fact it had been observed also in vegetal cells [28,44,45] while the demonstration of a structure equivalent to the reticular apparatus in the cardiac cells by Emeric Luna in 1911 allowed the differentiation of this organelle from the sarcoplasmic reticulum [4].

Thus, from the zoological laboratory of the Magdalen College, Oxford, came the important James Bronte Gatenby’s generalization according to which “every sort of metazoan cell carefully examined has been found to possess the typical apparatus of Golgi” [46]. The histological demonstrations and conceptualizations were however controversial. Beginning in 1899 the Swedish histologist Emil Holmgren described a system of ramifying “canals” in the cytoplasm of some types of cells, which he named “Trophaspongium”, that was in communication with ducts penetrating through the external cell surface from neighbour cells (the “trophocytes”) [47–50]. According to Holmgren this system of canals could play a nutritive role and included, as an important component, the reticulum described by Golgi. Also Ramón y Cajal agreed, at least in part, with Holmgren’s hypothesis, even though he firmly denied the communication of the Trophaspongium with the surface and with the structures outside the cell [43]. In the following years the problem continued to be debated [51]; however Holmgren’s system did not receive decisive confirmations and the term now designates only the axon of invertebrates and the invagination of glial processes around the cell body. Ramón y Cajal frequently referred in his publications on the subject to a “Golgi-Holmgren reticular apparatus”. Other researchers indicated the structure as “Golgi-Kopsch apparatus”, “Netzapparat von Golgi” or “réseau endocellulaire de Golgi”. In 1910 Carlo Besta designated this structure “Golgi apparatus” in the title of an article [52] and the term became increasingly more frequent in the subsequent years, especially after the publication of a seminal work by Jöell Nusbaum in 1913 [53] and its penetration in the English literature [51]. However, the supporters of the existence of the Golgi apparatus had to confront the heated opposition of a large part of cell biologists. The existence of the organelle was debated for years and many began to consider the Golgi apparatus as an artefact due to the fixation and/or metallic impregnation procedure [54–57]. Even the first studies with electron microscopy did not confirm the existence of the Golgi apparatus supporting the view that this structure was in reality a composition of “myelin figure” artificially induced in the cytoplasm during the preparation of the specimens [58,59]. At the end, however, this new revolutionary instrument was able to produce definite proof of the real existence of the Golgi apparatus, unravelling the reality and the various components of this organelle [60,61]. It is ironic that the electron microscope, the very instruments that had provided the existence of synapses between neurons, against Golgi’s concept of a continuous diffuse neural network, also supplied the final proof that his “internal reticular apparatus” was real [20,23,62–64]. A number of terms were introduced when the electron microscope began to reveal the complexity of this organelle, for example: Golgi bodies, Golgi zone, Golgi area. The designation of “Golgi complex” entered officially in the literature in 1956 with the seminal work by Dalton and Felix [65]. Both the terms Golgi apparatus and Golgi complex are currently interchangeable. However a quick “the Golgi” and the introduction of Golgi in adjectival form are now prevalent in the blooming scientific literature on the organelle [23,66]. Thus Camillo Golgi underwent his final transformation and, becoming the eponym of the organelle he had discovered, he found a way to immortality.

References
